IHE Report

Determinants and Prevention of Low Birth Weight: A Synopsis of the Evidence

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Determinants and Prevention of Low Birth Weight: A Synopsis of the Evidence

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Foreword

Low birth weight (defined as a birth weight of less than 2500 grams) is associated with fetal and neonatal morbidity and mortality, impaired cognitive development, and the advent of chronic diseases in later life. The incidence of preterm birth is increasing, particularly in developed countries such as Canada. The reported rate of low birth weight births in Canada was 5.9% in 2003; an increase from the 2001 rate of 5.5%. While the rising incidence of multiple births has been cited as the main contributor to this trend, there are many other interrelated factors that play a role.

In Alberta, the rate of low birth weight births has consistently exceeded both provincial targets and the reported national rate. For example, in 2003, 6.3% of births in Alberta were classified as low birth weight, compared to the national average of 5.9%. Despite ongoing research and health strategies aimed at addressing contributing factors, the rate of low birth weight births in Alberta has been resistant to change. This problem, therefore, continues to be of particular interest to the Alberta Perinatal Program. The Program, which is funded by Alberta Health and Wellness, set a goal for change in 2007. Through the collaborative efforts of a number of provincial partners, plans were initiated for a provincial conference that would help guide public health initiatives in addressing the issue of low birth weight births in Alberta.

The Institute of Health Economics, Alberta, Canada sponsored the writing of a report by Dr. Arne Ohlsson and Dr. Prakeshkumar Shah in preparation for the May 2007 Consensus Development Conference on *Healthy Mothers-Healthy Babies: How to Prevent Low Birth Weight*, which was held in Calgary, Alberta. The report produced for the Institute of Health Economics was one of the selected references considered by the panel at the conference. The intent for producing this book is to share the information that was presented in the report with a wider clinical audience.

This book is a synopsis (an overview of summaries and individual studies) of the evidence on the determinants related to low birth weight births and the effectiveness of strategies and interventions to prevent them. It consists of 16 chapters. The first two chapters provide general background information on the incidence, survival rates, and consequences of low birth weight births and a summary of the approach used to identify and synthesize the extensive literature on the subject. Chapters 3 to 15 provide succinct overviews of the evidence-base for the myriad determinants and interventions for low birth weight births addressed in the literature. The final chapter provides a useful reference guide to the contents of the book in the form of tabulated summaries of the evidence and conclusions.

We are honoured to have Dr. Ohlsson and Dr. Shah co-author this book. Dr. Ohlsson is renowned as a clinician, administrator, academic, and researcher, with numerous publications and awards. Dr. Shah, also from Mount Sinai Hospital, Toronto, Ontario, is a staff neonatologist who shares Dr. Ohlsson's enthusiasm for conducting systematic reviews to advance best practices in perinatal and neonatal health.

This book, to the best of our knowledge, represents the most comprehensive compilation of the literature on the factors associated with low birth weight births, including preterm, small for gestational age, and intrauterine-growth-restricted births, and the various interventions and strategies used to prevent them. It is a valuable resource for clinicians wishing to understand the multifaceted issue of low birth weight births, as well as a starting point for ascertaining areas where further research may help ameliorate the problem. It should be noted that this book is not a comprehensive systematic review, but a synopsis of the evidence.

We greatly appreciate the significant contribution of Dr. Ohlsson and Dr. Shah. Without their dedication, this book would not have been possible.

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Professor, University of Alberta, and University of Calgary
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Production of this document has been made possible by a financial contribution from Alberta Health and Wellness.

The views expressed herein do not necessarily represent the official policy of Alberta Health and Wellness.

Abbreviations

AEP – alcohol-exposed pregnancy
AGA – appropriate for gestational age
AHR – adjusted hazard ratio
AMP – adenosine monophosphate
AOR – adjusted odds ratio
ART – assisted reproductive technology
BMI – body mass index
BV – bacterial vaginosis
BW – birth weight
CI – confidence interval
CMI – contingency management intervention
CO – carbon monoxide
COX – cyclo-oxygenase
CRH – corticotropin-releasing hormone
DNA – deoxyribonucleic acid
EF – etiologic fraction
ELBW – extremely low birth weight
GenDB – genealogy database
HIV – human immunodeficiency virus
HUAM – home uterine activity monitoring
IL-6 – interleukin-6
IUGR – intrauterine growth restriction/restricted
IVF – in vitro fertilization
KB test – Kleihauer-Betke test
LBW – low birth weight
MD – mean difference
MMP – metalloproteinase
ns – not significant
OR – odds ratio
PAH – polycyclic aromatic hydrocarbon
PDE5 – phosphodiesterase 5
PG – prostaglandin
PI – pulsatility index
PROM – prelabour rupture of membranes
RCT – randomized controlled trial
RR – risk ratio
SD – standard deviation
SGA – small for gestational age
STD – sexually transmitted disease
TNF-α – tumour necrosis factor alpha
UTI – urinary tract infection
VLBW – very low birth weight
WHO – World Health Organization
WMD – weighted mean difference

CHAPTER 1:

Introduction

Main Summary Points

- Low birth weight and preterm births are indicators of potential lifelong consequences to individuals, families, and communities at large.
- The incidence of low birth weight is higher in the developing world compared to the developed world; however, the incidence is on the rise in the developed world.
- The survival rates of preterm and low birth weight infants have increased in recent years.
- In this book, we will review the available literature on the determinants and primary preventive strategies for preterm and low birth weight births.

Burden of Illness

Birth weight (BW) is the most important determinant of perinatal, neonatal, and post-neonatal outcomes.[1,2] Poor growth during the intrauterine period increases the risks of perinatal and infant mortality and morbidity throughout life.[2-6] An adverse intrauterine environment may result in either low birth weight (LBW) or preterm births. LBW (defined as BW <2500 g) is a multifaceted problem that may result in a wide spectrum of diseases in later life such as hypertension, ischemic heart disease,[7] stroke, metabolic syndrome, diabetes, malignancies, osteoarthritis, and dementia.[3,4] Preterm birth is of significant public health importance because of its association with an increase in mortality and childhood morbidities such as developmental problems, cerebral palsy, learning difficulties, hearing and visual impairments, and an increased risk of sudden infant death.[1,6] LBW can result from preterm or intrauterine-growth-restricted (IUGR) birth, or a combination of the two. Owing to the difficulty in ascertaining gestational ages and the relative simplicity, accuracy, validity, and reproducibility of measurement of BW, it is the most commonly used indicator worldwide to compare population characteristics. Preterm birth is defined as an infant born at <37 weeks (259 days) gestation.

Global Situation

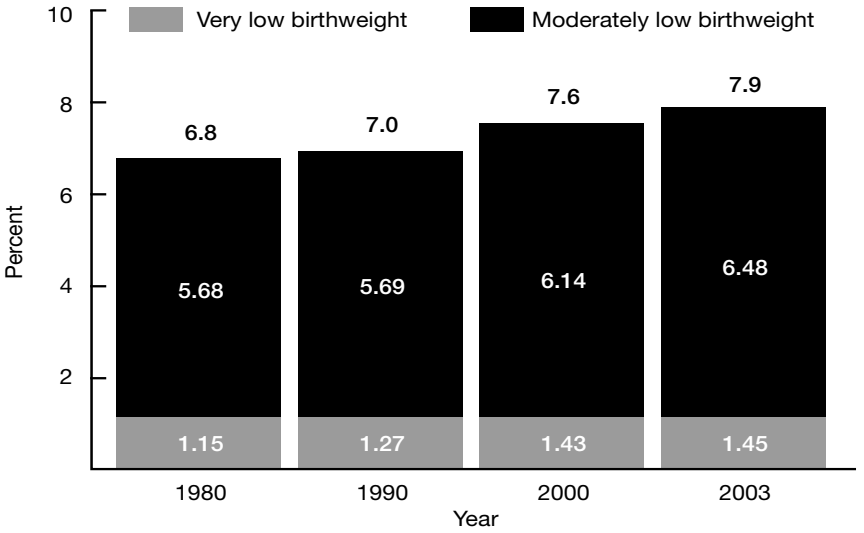
IUGR and LBW infants represent a significant health problem worldwide.[2,8-10] The rate of IUGR and LBW births is highest in South-Central Asia, followed by Middle and Western Africa, Oceania, and Latin America.[11,12] The significance of these findings should be understood within the context that 75% of these infants

are born in Asia (greater total number of live births). The rates of IUGR and LBW births are probably underestimates of the global situation because in the developing world a significant proportion of infants are born at home and not registered as live births.[13]

The incidence of preterm birth is increasing. This rise is particularly noted in developed countries (the quality of data from developing countries precludes any firm conclusions) (Figures 1 and 2).[8,9,14-17] Dramatic reductions in mortality rates have been reported in the last two decades among preterm infants, with less of a reduction in morbidity.[8,18] Among developed countries, only France and Finland reported a reduction in preterm birth rates[19] until the early 1990s. However, the rates for LBW births are on the rise again in Finland (4.4% in 1998 compared to 4.0% in 1991)[20] and France (6.3% in 1998 compared to 3.8% in 1988).[21] The incidence of preterm birth has increased in Canada (excluding data from Ontario) (6.4% in 1981 to 6.7% in 1992, 7.1% in 1997, 7.2% in 1998, 7.4% in 1999, 7.5% in 2000, and 7.9% in 2004) (Figure 3).[16,17,22,23] The increase has been chiefly attributed to a rising incidence of multiple births.[20,21] There is a reported increase in the incidence of medically indicated preterm birth, especially secondary to ischemic placental disease.[24] Preterm and LBW birth rates are higher in the United States compared to other developed countries and are believed to contribute to the higher infant mortality rate in the United States compared to other industrialized nations, despite technological advances.[18]

Figure 1: Incidence of very low birth weight and moderately-low birth weight births in the United States between 1980 and 2003

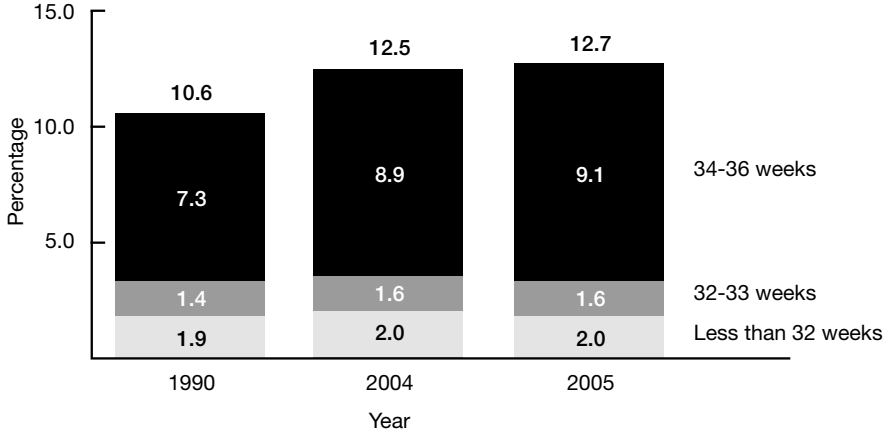
(Reproduced from the report entitled "Births: Final data for 2003", published by the National Center for Health Statistics, Centers for Disease Control and Prevention)



Note: Very low birthweight is less than 1,500 grams; moderately low birthweight is 1,500-2,499 grams; and low birthweight is less than 2,500 grams.

Figure 2: Preterm birth rates in the United States between 1990 and 2005

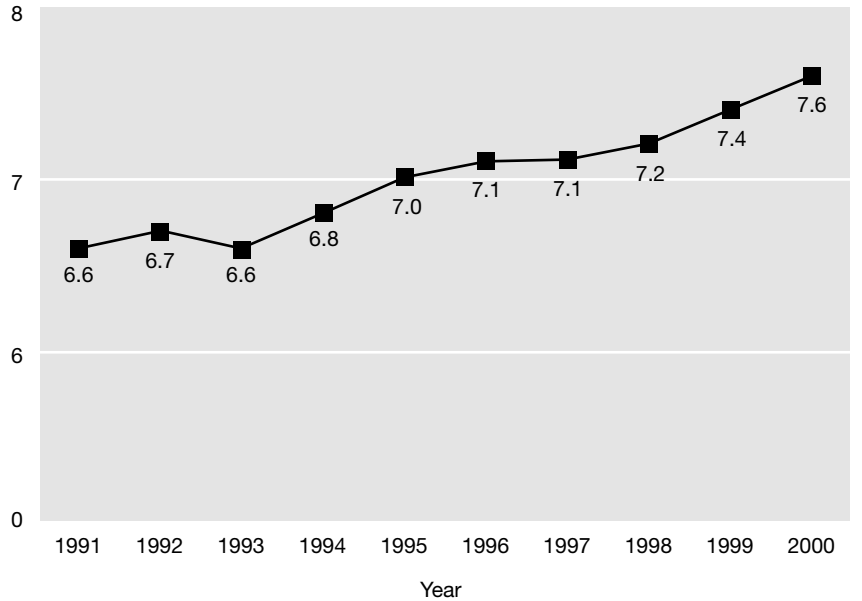
(Reproduced from the report entitled "Births: Preliminary data for 2005", published by the National Center for Health Statistics, Centers for Disease Control and Prevention)



[1] Based on preliminary data.
Source: CDC/NCHS, National Vital Statistics System

Figure 3: Preterm birth rates in Canada from 1990 to 2000

(Reproduced from the report entitled, "Canadian Perinatal Health Report 2003", published by Health Canada 2003, with permission from the Minister of Public Works and Government Services, Canada)



Source: Statistics Canada, Canadian Vital Statistics System, 1991-2000 (unlinked live birth files).
*Data for Ontario were excluded because of data quality concerns.
**Excludes live births with unknown gestational age.

Financial Overview

For each preterm LBW infant born in Canada, the neonatal intensive care and post-neonatal cost up to one year of age was conservatively estimated at CN $8443 in 1987 and CN $48,183 in 1995 per surviving LBW infant.[25] Petrou[26] reviewed studies assessing the neonatal hospital costs of infants with BW <1 kg (extremely LBW or ELBW) and infants with BW >1.5 kg. The hospitalization costs during the neonatal period were higher for ELBW infants (GB £39,483) than for infants with BW >1.5 kg (GB £9207). The costs of post-neonatal care for ELBW infants over their first 6 years of life were estimated at GB £9541 per year compared to GB £3883 per year for term infants.[27] The lifetime costs for permanent impairments of neonatal origin were estimated to be US $676,800 per preterm LBW infant. Hypothetically increasing the BW from the 800 to 1000 g range to the "normal" weight range would save over US $127,000 in initial hospital charges.[28] A population-based prevention strategy that reduces the preterm birth rate by 20% could save US $2 billion dollars per year in healthcare costs nationally in the United States.[25]

Objectives and Overview of the Book

This book is a synopsis, or overview[29], of summaries and individual studies on the determinants and prevention of preterm/LBW births. Evidence-based practice is the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients".[30] The objectives of this synopsis were to critically appraise the available evidence from systematic reviews (or, in their absence, randomized controlled trials, cohort studies, and other study types) regarding:

a) the contributors/factors/determinants related to preterm/LBW births; and

b) the effectiveness/efficacy of strategies/approaches/interventions to prevent preterm/LBW births.

Currently recommended interventions undertaken in clinical practice, as well as newly proposed interventions, were reviewed for this synopsis.

The intent was to concisely synthesize the best available evidence on this vast subject to guide public health initiatives in addressing the issue of preterm/LBW births using the evidence-based practice concept. In chapter 2 the methods used to identify, retrieve, and compile the evidence are outlined. In chapter 3 the effects of maternal demographic factors, including maternal age, parity, inter-pregnancy interval, marital status, and intendedness of pregnancy, are reviewed. In chapter 4 the effects of maternal anthropometric factors, including maternal height, pre-pregnancy weight, obesity, and weight gain during pregnancy, are reviewed. In chapter 5 the effects of genetic factors, intergenerational influences, and paternal factors are reviewed. In chapter 6 the effects of maternal medical conditions, pregnancy-associated conditions, and history of induced abortion

are reviewed. In chapter 7 the effects of multi-fetal pregnancies achieved either with or without the assistance of artificial reproductive technology are reviewed. In chapter 8 the effects of race, ethnicity, psychosocial and socioeconomic factors, and stress are reviewed. In chapter 9 the effects of lifestyle factors such as smoking, alcohol, caffeine, substance use, use of herbal medicines, and exercise during pregnancy are reviewed. In chapter 10 the effects of environmental factors such as air and water pollution, use of pesticides, seasonal variations, and use of electromagnetic beds by mothers are reviewed. In chapter 11 the effects of occupational factors, noise, violence, and maternal trauma are reviewed. In chapter 12 the effects of nutritional factors, including intake of protein, iron, folic acid, zinc, calcium, fish oil, and multiple micronutrients, are reviewed. In chapter 13 the effects of infections, including urinary tract infection, bacterial vaginosis, chlamydia, syphilis, trichomoniasis, gonorrhea, and malaria, are reviewed. In chapter 14 the effects of antenatal care and the early detection of at-risk fetuses are reviewed. In chapter 15 the effects of secondary prevention of fetuses identified as being at a very high risk of preterm or LBW births are reviewed. In chapter 16 we conclude with an evidence-based summary of the findings for both determinants and interventions to inform the reader of important factors that contribute to preterm/LBW births and strategies that are or are not effective in reducing their incidence.

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CHAPTER 2

Methods of the Synopsis

Search strategy

A comprehensive literature search was conducted with the help of an experienced librarian. The following databases were searched.

- MEDLINE (January 1966 to December 2006)
- EMBASE (January 1992 to December 2006)
- *The Cochrane Library* (Issue 1, 2007)
- PsycINFO (January 1992 to December 2006)
- Sociological Abstracts (January 1992 to December 2006)
- Relevant project monographs (January 1994 to December 2006)

The reference lists from recent textbooks, reviews, and reports of primary studies were examined for additional relevant material. The retrieval was limited to published studies written in English.

During the periodic re-running of the searches, two important articles were identified that were published after December 2006. These studies are highlighted in the text to indicate that they were identified after the predetermined cut-off period for the search.

Inclusion criteria

The synopsis was planned to summarize the evidence available from systematic and narrative reviews on the determinants and prevention of preterm/low birth weight (LBW) births. When a systematic review was not identified for a particular determinant or preventive intervention, selected primary studies were included. The authors do not claim the selection of primary studies to be comprehensive. No attempt was made to perform a systematic review of the primary studies. If more than one systematic review was identified, the latest review was summarized. If there were discrepancies between two reviews, the discrepancies were described and both reviews were summarized. In cases where a primary study was published after a review was prepared, it was also summarized.

Explicit inclusion criteria with a view to answering the clinical research question were used for selecting studies. Reviews that did not provide a clear description of the study selection criteria and search strategy were excluded. The selection criteria for this synopsis were categorized to allow for the elimination of reviews that did not provide relevant information or contained information available from already included reviews.

Studies have reported LBW births using different definitions, such as small for gestational age (SGA) or intrauterine-growth-restricted (IUGR) births. We included this information when data specifically on preterm/LBW births were not available.

Study selection

Two authors (PS, AO) independently assessed the titles, abstracts, and keywords for each citation to identify studies potentially eligible for inclusion. The full-text publication was retrieved if it was deemed likely to have information relevant to the research question. Each retrieved article was assessed for eligibility and methodological rigor. All differences of opinion were resolved by consensus.

Assessment of methodological qualilty

The quality of each systematic review related to determinants and interventions was assessed according to the guidance from the QUOROM statement.[1] This included detailed assessment of the abstract, methodology, results, discussion, and comprehensiveness of the review. The reviews for which data were abstracted regarding epidemiological association or effectiveness of interventions were assessed for selection bias, quality assessment of the included studies, and data synthesis.

Primary studies were assessed for sample selection method, confounder assessment, data collection, attrition rate, precision of reported estimates, and analyses. Occasionally studies were identified that examined the impact of a certain determinant on a subgroup; the results from such studies were reported for interest.

Format of the chapters

The chapters are organized to assess the impact of a similar group of characteristic as either a determinant or an intervention. Individual determinants are described in the following format: biological plausibility, epidemiological association, and conclusions. Epidemiological associations are described with evidence from systematic and other reviews, followed by evidence from other study designs. To maintain continuity, interventions related to a particular determinant are described with the determinant. Secondary interventions are described as follows: biological mechanism of action followed by evidence of effectiveness from systematic reviews. When a systematic review was not available, evidence from primary studies was reported.

Classification of the evidence for determinants

1. No association: no association identified in multiple studies that adjusted for most known confounders.
2. Very weak/inconclusive association: association identified in some studies

(did not adjust for confounders or results were not statistically significant after adjusting for confounders), but not in studies of adequate quality (adjusted for confounders).

3. Weak association: some studies of adequate quality revealed an association and other studies of adequate quality showed no association (with or without adjustment for confounders).
4. Moderate association: association identified in most studies (adjusted for confounders), but some studies revealed no association or indicated the need for further research based on trends.
5. Strong association: consistent association identified in multiple studies of adequate quality that adjusted for most known confounders.
6. Lack of information: lack of information regarding association.

For classifying determinants, data were combined for the categories of strong and moderate association, and weak and very weak association.

Classification of the evidence for interventions/strategies

1. Strong evidence of effectiveness: cumulative evidence of effectiveness from well-designed systematic reviews.
2. Probable evidence of effectiveness: some evidence of effectiveness from systematic reviews, randomized controlled studies, or clinical studies.
3. Not effective: most of the cumulative evidence indicates ineffectiveness.
4. Lack of/inadequate information: insufficient evidence to determine either benefit or harm.

Limitations of the Synopsis

Definition of IUGR and SGA

The definitions of preterm and LBW births are universally accepted. However, IUGR and SGA births are defined variably by different authors ($<10^{th}$ centile, $<5^{th}$ centile, $<3^{rd}$ centile, or 2 standard deviations below the mean) and by using various growth charts. This underscores the importance of having a population-based growth reference standard that is ethnically appropriate and acceptable. For this synopsis, the definition used by individual authors was taken at face value. Thus, some inconsistencies are likely in the reported data.

Search strategy

The search strategy was restricted to articles published in the English language. This may have resulted in the inadvertent omission of relevant articles published in other languages.

Selection criteria and data abstraction

Narrative reviews were included for topics where no systematic review was available. This might have introduced an element of bias when narrative reviews formed the sole evidence base. Two authors selected articles for retrieval from the literature search results, but data were extracted from the included studies by only one author.

Assessing causal and associative relationships

Variations in the duration of exposure, timing and method of exposure assessment, and the presence of and adjustment for different confounders among the studies made it difficult to analyze the evidence. Evaluation of associations for particular determinants was based on the authors' subjective assessment of the evidence according to the basic principles of causation. No attempt was made to untangle the potential effects of individual intermediate variables in the chain of causation.

Validity of the included studies

The validity of the primary studies included in the systematic reviews was not assessed. If two reviews were identified on a single topic, the included and excluded studies were crosschecked. If there were major discrepancies, both reviews were reported and the differences described. Similarly, no attempt was made to check the accuracy of primary studies. All results reported were taken at face value.

Critical appraisal of the included studies and data synthesis

The included studies were not formally appraised with a quality tool. No attempt was made to perform a systematic review on any determinant or intervention.

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CHAPTER 3

Maternal Demographical Factors

Main Summary Points

- Moderately strong evidence indicates that the risk of preterm/low birth weight births is increased in adolescents. This problem is regarded differently depending on the social structures of the community in which the teenager lives, and may require varied approaches.
- Interventions targeting nutritional improvement with enhanced prenatal care and psychosocial support for adolescents have shown benefit in reducing preterm/low birth weight births. School-based health education programs and innovative simulation experiences have shown improved knowledge of adolescents; however, the impact of this knowledge on birth outcomes has not been well studied.
- Advanced maternal age can increase (increased use of artificial reproductive techniques) or decrease (improved socioeconomic factors) the incidence of preterm/low birth weight births. Further research is needed.
- In some studies, primiparity was associated with an increased risk of preterm and intrauterine growth-restricted births. The effect of grand multiparous and great grand multiparous status on preterm birth is unclear and needs further studies.
- Short (<18 months) and long (>60 months) inter-pregnancy intervals are associated with preterm/small for gestational age/intrauterine growth-restricted/low birth weight births. From the strength of the association and other criteria, some researchers have suggested a causal role. The inter-pregnancy interval could be a significant modifiable factor if women are informed about the advantages of an optimal inter-pregnancy interval of approximately 18 to 24 months.
- Unmarried women have an increased risk of preterm/intrauterine growth-restricted births compared with married women. In regions where poverty is common and the practice of cohabiting is uncommon, cohabiting women have an increased risk of preterm birth compared with married women.
- Unintended pregnancies may be associated with preterm labour and low birth weight births; however, further studies are needed.

In chapter 3 we review maternal demographical factors and their impact on pregnancy outcomes. Factors studied include maternal age, parity, birth interval, marital status, and the impact of whether the pregnancy was intended or not.

Maternal Age

The incidence of low birth weight (LBW) births has been described as following a U-shaped curve, with high numbers of LBW births at the extremes of maternal age.[1] We divide this section into two components: adolescent mothers and women of advanced maternal age.

Adolescent mothers

Biological plausibility

- Reduced blood supply to the cervix and uterus due to immaturity, leading to reduced supply of nutrients to the developing fetus[1] and an increased incidence of infections.[2]
- Delayed initiation of prenatal care due to missed cycles assumed to be irregularity in menstrual cycles[2]; concealment of pregnancy until late stages due to social taboos or fear.
- Nutritional competition between the immature adolescent and her fetus; resistance to recommended dietary and caloric intake in order to remain slim.[1]
- Higher incidence of unplanned pregnancies than in adult women.
- Experimenting and testing of social boundaries, leading to an increased incidence of risk behaviours such as drinking alcohol, smoking, and substance use.[1]

Roth et al.[1] indicated that the interplay of these factors is crucial in the higher incidence of preterm and LBW infants born to adolescent mothers than to adult mothers.

Epidemiologic association

Evidence from systematic and other reviews

No specific systematic review assessing the link between adolescent mothers and risks of preterm/LBW births was identified. Most of the data regarding associations are derived from primary studies.

Elfenbein and Felice,[3] in an overview, reported that there was a recent reduction in the incidence of adolescent pregnancy in the United States due to a reduction in the number of adolescents having sexual intercourse, increased use of contraceptives at first intercourse, and availability of long-lasting contraceptives. Risk factors for pregnancy included poor educational performance, poverty, being a child of a single-parent family, positive family history of adolescent pregnancy, and drug or substance use. Protective factors included higher educational achievements, higher socioeconomic status, being a child of a two-parent family, and attendance at religious places or events.

Bonnel,[4] in a review of quantitative research, reported that there was a difference in the approach taken towards teenage pregnancy in the United States and that in the United Kingdom. Teenage pregnancy was viewed as problematic because of welfare expenditure in the studies originating from the United States, whereas the conceived poor health status of the mother and problems with parenthood were the reasons for exploring this aspect in studies from the United Kingdom.

Klerman[5] reviewed pregnancy outcomes in multiparous teenage mothers and identified that teenage multiparous mothers are not at an increased risk for LBW or preterm births and that the results are similar to what has been observed in adult women. Klerman noted that a large number of adolescents who have a second adolescent pregnancy have lower socioeconomic status, which may influence adverse pregnancy outcomes.

Evidence from other study designs

Data on the cohort studies reporting on adolescent pregnancy outcomes are summarized in Table 3.1.

Table 3.1: Studies reporting outcomes of adolescent pregnancy

Study	Population	Characteristics	Results
Fraser et al.[6]	Women of 13 to 24 years of age who gave birth to singleton live newborns	1970 to 1990 Utah, US	Adolescents 13 to 17 years old: preterm births (RR 1.9; 95% CI 1.7, 2.1) LBW births (RR 1.7; 95% CI 1.5, 2.0) SGA births (RR 1.3; 95% CI 1.2, 1.4)
Miller et al.[7]	Adolescents <18 years of age	1989 to 1993 Arizona, US	VLBW births (RR 1.7, 95% CI 1.2, 2.2) Delayed initiation of prenatal care by 8 weeks
Orvos et al.[8]	National data	1991 to 1996 Hungary	Preterm births 18.6% in adolescents compared with 8.2% in the national cohort Rate of IUGR births was 16.3% in adolescents compared with 8.6% in the national cohort
Slap and Schwartz[9]	Mothers <20 years of age	Pennsylvania, US	OR for LBW births 1.99 (95% CI 1.52, 2.61) for inadequate prenatal care among adolescents OR for LBW births 1.38 (95% CI 1.03, 1.84) for history of maternal illness among adolescents

CI: confidence interval; IUGR: intrauterine growth restricted; LBW: low birth weight; OR: odds ratio; RR: risk ratio; SGA: small for gestational age; VLBW: very low birth weight.

Interventions:

Several interventions have been attempted to reduce the incidence of adolescent pregnancies. These interventions include home visitation, clinic visits, social support, early identification, education, and special school programs to promote abstinence alone or abstinence plus information about contraceptives.

Evidence from systematic and other reviews

Brunton and Thomas[10] systematically reviewed 15 studies, of which 13 were of moderate or high quality. In five studies, significant increases in birth weight (BW) and a reduction in preterm births were reported, whereas in eight studies no change was noted. A combination of home visiting and clinic services was effective. Interventions included a combination of strategies such as transportation to appointments, health education, social or peer support, referrals to community services, telephone contact, and coordination of prenatal appointments. The authors had difficulty discerning which component of the intervention was more effective. Staff nurses or registrars, nurse childbirth educators, public health nurses, lay or paraprofessional home visitors, and health educators provided the support in the various studies.

Nielsen et al.[11] systematically reviewed 19 studies of nutritional interventions for pregnant adolescents. The majority were case-control studies. Six of the 12 studies that reported on BW found a significant increase in BW in the intervention groups. In 9 of 16 studies in which LBW or small-for-gestational age (SGA) births were outcomes, improvement in the intervention group was reported. The intervention models in these studies included: (1) enhanced prenatal care (delivered via systematic case management, intensive and individualized psychosocial support, nutritional education, and home visits), which showed a significant reduction in the incidence of LBW and very low birth weight (VLBW) births; (2) enhanced prenatal care supplemented with health education (six studies), which, except for one study, showed a positive impact in reducing the incidence of LBW births; (3) enhanced prenatal care with home visits (three studies), which showed a positive effect on BW and a reduced incidence of LBW births (one study had reduced rates of preterm birth); and (4) programs involving nutritional prescription (two controlled trials), which showed a reduction in the incidence of LBW, VLBW, and preterm births. The authors evaluated eight studies (six studies of nutritional classes, one of prenatal care, and one of home visits) in which there was no control group. Nutritious food consumption and knowledge about nutrition improved. Overall, there were beneficial effects of nutritional intervention programs; however, the authors had difficulty in ascertaining the individual effectiveness of different components of the program. Suggested strategies included improvement of knowledge, practical self-building exercises, mentoring, consideration of family and environmental context, reinforcement of personalized behaviour change, support group discussions, and home visits to understand social context.

Bennet and Assefi[12] systematically reviewed 16 studies of school-based teenage pregnancy prevention programs. Three studies focused on abstinence-only programs, 12 studies evaluated abstinence-plus (including contraceptive information) programs, and one study compared two approaches. The settings for the programs, population studied, and number of participants varied considerably. Sexual behaviours of adolescents were assessed in 14 studies.

Studies of abstinence-only programs reported a delay in the initiation of sexual activity (i.e., 77% versus 50% remained abstinent 6 months following the intervention in one study), but other studies reported a non-significant difference at longer-term follow up. Of the eight abstinence-plus studies, no differences in sexual activity between control and intervention groups were reported in six studies; a delay in the initiation of sexual activity in males was reported in one study, and a delay for both males and females was reported in one study. In the four studies in which numbers of partners were assessed, there was no difference between control and intervention groups. In four studies of abstinence-plus programs, a reduction in the frequency of sexual activity in the intervention group was reported, whereas in three studies no difference was found. There were no negative consequences, that is, abstinence-plus programs were not associated with earlier onset of intercourse or increased frequency of intercourse. In four of five abstinence-plus programs, there was a significant improvement in the knowledge of contraceptives among adolescents in the intervention group. In 7 of 10 programs that had abstinence-plus education interventions, there was an increased frequency of contraceptive use among those in the intervention group. The pregnancy rate was no different 17 months after the intervention in one study. Overall, results indicate that these programs altered adolescent sexual behaviours, decreased frequency of sexual intercourse, increased knowledge about contraceptives, and increased use of contraceptives. The gold standard outcome for these intervention studies is the number of adolescent pregnancies that are prevented. This outcome is difficult to assess.

De Anda[13] reviewed eight reports of "Baby Think It Over" intervention. A computerized infant simulation doll is offered to adolescents so that they can experience taking responsibility for an infant during the intervention period in this program. The doll is programmed to elicit all the usual infant responses and the adolescent is required to attend to those responses by necessary actions. Six studies reviewed adolescents' views of parenthood and child-rearing responsibilities. Two studies identified change in perception, but four studies showed no effect. Parental perceptions were evaluated in one study. Parents reported an increase in adolescents' understanding of difficulties involved in caring for infants. In two studies, teachers' perceptions indicated that the program was effective. These studies had methodological limitations.

Evidence from other study designs

Several studies have focused on primary prevention (i.e., first pregnancy), improved care of the pregnant adolescent, and prevention of recurrence. These studies are summarized in Table 3.2.

Table 3.2: Studies of various interventions for adolescent pregnancy

Study	Intervention	Study type	Results
To prevent adolescent pregnancy			
De Anda[13]	Baby Think It Over – simulation doll	Pre-post comparative study	Changes in perceptions: - time and effort involved in the care of an infant - the impact of having a baby on their lives - the impact on their future goals - the importance of pregnancy prevention to ensure their future academic goals
To improve care during pregnancy			
Quinlivan and Evans[14]	Specialized teenage antenatal clinics - multidisciplinary care, screening, and treatment of infections and social support	Cohort study	Compared with general hospital group: - threatened preterm labour (OR 0.45, 95% CI 0.29, 0.68) - preterm, prelabour rupture of the membranes (OR 0.34, 95% CI 0.18, 0.63) - preterm births (OR 0.40, 95% CI 0.25, 0.62) - increase in BW (mean BW 3183 g vs. 2980 g, p = 0.0004)
To prevent repeat adolescent pregnancy			
El Kamary et al.[15]	Healthy Start Home Visiting Program - to prevent child abuse and neglect and promote child development	RCT	No between-group difference in 2nd birth soon after previous births (AOR 1.05, 95% CI 0.69, 1.58)
Black et al.[16]	Home-based curriculum intervention program - constructs of negotiation skills, adolescent development, and parenting	RCT	Control mothers were more likely to have a 2nd infant compared with the intervention group No 2nd births during study period among mothers who had >7 visits during pregnancy

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial.

Conclusions

Epidemiological and biological evidence suggest an increased risk of preterm/LBW births in adolescents; however, the strength of the evidence is moderate and further research is needed.[1] The social, economic, and educational challenges resulting from adolescent pregnancy are associated with intergenerational disadvantages for both the mother and the child.[17] Research directions based on different social structures of the underlying community differ and suggest a different approach to this issue in various parts of the world.

Prevention of adolescent pregnancy is an important public health issue. Interventions targeting nutritional improvement with enhanced prenatal care and nutritional education, home visiting, and provision of psychosocial support for

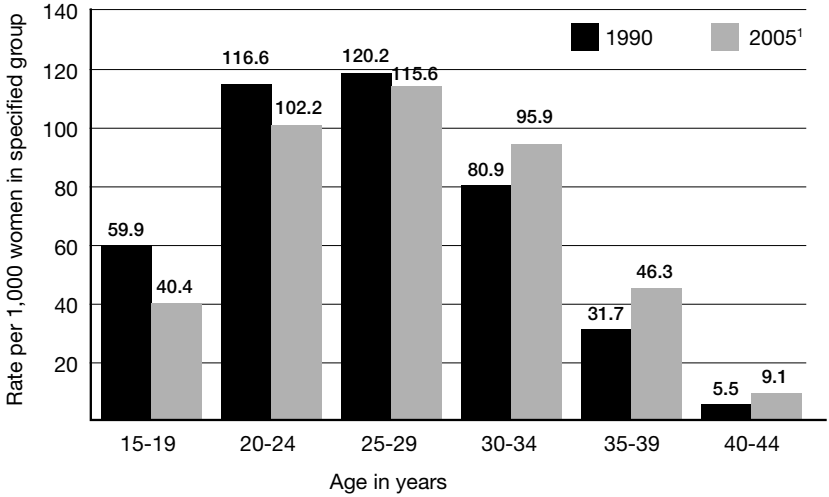
adolescents have shown benefit in reducing preterm/LBW births. School-based health education programs have shown improvement in sexual knowledge; however, the impact of this knowledge on birth outcomes is not well studied. Innovative interventions such as simulation experiences have shown an increase in the insights of adolescents for care needed by an infant; however, the impact of these interventions on reducing preterm/LBW births is unknown.

Women of Advanced Maternal Age

The number of women delaying their first pregnancy beyond 35 years of age is increasing. Changes in age- and parity-specific rates were identified as main contributors to increases in VLBW rates among white and black women and to increases in LBW rates among non-Hispanic white and Hispanic women in the United States.[18] Of the observed 10% increase in the VLBW and LBW rates among these women, >10% of the increase was attributed to a change in age-parity distribution (i.e., delayed childbearing) (see Figure 3.1).

Figure 3.1: Birth rates by maternal age in the United States between 1990 and 2005

(Reproduced from the report entitled "Births: Preliminary data for 2005," published by the National Center for Health Statistics, Centers for Disease Control and Prevention)



Biological plausibility

- Higher prevalence of age-related chronic health problems such as hypertension and diabetes in older women than in younger women. In addition, a higher incidence of pregnancy-associated complications that can influence the length of gestation and BW.[19]

- Reduced fertility potential as age advances.[20]
- Higher incidence of use of artificial reproductive technologies than in younger women, which may contribute to a higher incidence of preterm/LBW births.[19]
- Higher socioeconomic status, lower prevalence of smoking, earlier prenatal care, and healthier lifestyles associated with advanced maternal age, which may have a positive impact on BW and length of gestation.

Epidemiological association

Evidence from systematic and other reviews

Newburn-Cook and Onyskiw[19] systematically reviewed 10 studies (eight cohort studies and two case-control studies). All studies except one were rated as being of high quality. The authors reported marked between-study heterogeneity and subsequent inconsistent results. In three cohort studies, a significant association between advanced maternal age and spontaneous preterm birth was reported, whereas in three studies no association was identified. In the remaining studies, adjustment for confounders led to no significant association. The reviewers indicated that maternal age had an effect on gestational age and BW, depending on confounders such as maternal health-related issues. The authors identified the need for rigorous research to quantify independent and unfounded effects of older maternal age on the risk of birth outcomes.

Evidence from other study designs

Tough et al.,[21] in a study of 283,956 infants from Canada, reported an increase in the rate of preterm births and multiple births following delayed childbearing. An increase from 8.4% to 12.6% in the number of births to women over 35 years of age was reported. There was a 14% increase in preterm births in this population even after controlling for maternal chronic health problems.

Conclusions

The evidence linking advanced maternal age and preterm/LBW births is, at best, tentative (high risk due to increased use of artificial reproductive techniques and low risk due to improved socioeconomic factors) and needs to be studied in well-designed cohort studies that control for various age-related confounders. Studies on contributory factors and effective interventions for women of advanced maternal age are lacking.

Parity

Primiparity, grand multiparity (5 to 9 births), and great grand multiparity ($\geq$10 births) are associated with increased frequency of obstetric complications.

Biological plausibility

The biological mechanism of how parity may influence the incidence of preterm/LBW births is not clearly understood. Incidences of placenta previa, abruption, abnormal presentation, and hemorrhagic complications are increased in grand multiparas and great grand multiparas. These complications may be predisposing factors for preterm birth.[22]

Epidemiological association

Evidence from systematic and other reviews

Aliyu et al.[22] reviewed studies assessing the effect of grand multiparous and great grand multiparous status on preterm/LBW births. Conflicting reports of an association of grand multiparous state and stillbirths were identified, with some studies reporting increased incidence and others reporting no difference. Three studies reported higher incidence of LBW births among grand multiparas compared with lower parity mothers, whereas four studies reported no increase in LBW births. Several studies reported the incidence of large-for-gestational-age infants to grand multiparas, rather than the incidence of SGA infants. Similarly, four reviewed studies reported a higher incidence of preterm births, whereas six studies reported no increase in the risk of preterm births. Reviewed studies of great grand multiparity revealed that it was not associated with preterm/LBW births, but a higher incidence of large-for-gestational-age births was noted. The authors noted the paucity of well-designed population-based cohort studies and identified the limitations of the existing studies.

Evidence from other study designs

Table 3.3 represents the reported effects of parity observed in various studies in which the primary aim was to study another association.

Table 3.3: Studies assessing influence of parity on pregnancy outcomes

Study	Characteristics	Results
Kramer et al.[23]	Cohort study	Primiparous compared with multiparous women - no increased risk for preterm births (AOR 1.04, 95% CI 0.95, 1.14)
Henriksen et al.[24]	Cohort study of working women	4.3% incidence of preterm births in primiparous women and 4.4% incidence in multiparous women
Shiono et al.[25]	Cohort study of women of different ethnicity	No mean BW difference between nulliparous and multiparous births (3326 g vs. 3388 g, $p < 0.1$)
Kesmodel et al.[26]	Cohort study of effect of alcohol	Nulliparous - preterm birth rate 4.5%, primiparous rate 3.6% (RR 0.80, 95% CI 0.68, 0.93); for multiparous women, the rate was 4.2% (RR 0.94, 95% CI 0.76, 1.15)
Frisbie et al.[27]	Cohort study – ethnic differences	Risk of IUGR for primiparous women (OR 1.7, 95% CI 1.4, 1.9) compared with multiparous women Risk for preterm births not increased (OR 1.1, 95% CI 0.6, 2.0).

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; IUGR: intrauterine growth restricted; OR: odds ratio; RR: risk ratio.

Conclusions

Some studies indicate that there is a possible trend towards an increased risk of preterm and intrauterine growth-restricted (IUGR) birth for the first child compared with subsequent children, but this trend is not confirmed in other studies. The reports of grand multiparas and great grand multiparas for preterm births have yielded conflicting results. This topic needs further research in the form of well-designed population-based cohort studies.

Birth interval

Biological plausibility

Various theories have been proposed to explain the effect of inter-pregnancy interval (birth of the index child and time of conceiving the next child) and pregnancy outcome.[28]

- Short inter-pregnancy interval may result in inadequate replenishment of maternal nutrient stores and lead to reduced fetal growth.
- Short inter-pregnancy interval can lead to increased stress, resulting in preterm/LBW births.[29]
- Women with short inter-pregnancy intervals are more likely to have associated risk factors such as young age, previous history of preterm/LBW births, inadequate education, being a member of a minority race, and tobacco use.[28,30]
- A mother's ability to facilitate growth of the fetus in utero declines gradually over the years after the first pregnancy. The physiological regression hypothesis suggests that after a few years following the first pregnancy, a woman acquires the same physiological status as a true primigravida and loses the benefits gained during the previous pregnancy to sustain a fetus. This loss may lead to preterm/LBW births in mothers with long inter-pregnancy intervals.[29]
- Unidentified metabolic and anatomic factors may play a role in the interval period of infertility in women with long inter-pregnancy intervals. These factors may influence the risk for preterm/LBW births.[29]
- Maternal serum and erythrocyte folate concentrations decrease from the 5th month of pregnancy and remain low for a long time following pregnancy. Deficiency of folate at the time of conception is associated with neural tube defects, preterm births, and IUGR.[31]

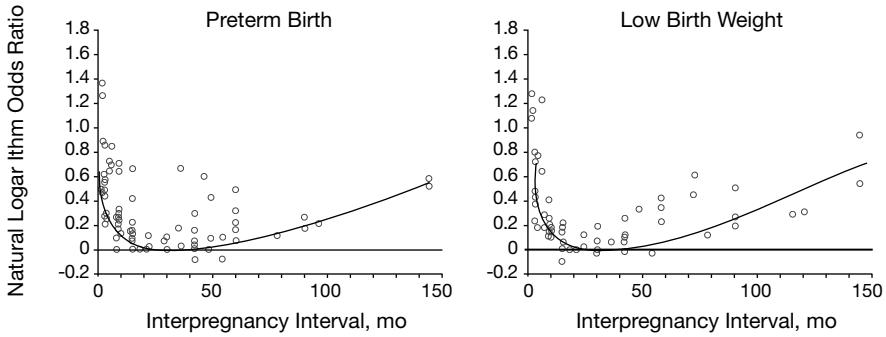
Maternal serum and erythrocyte folate concentrations decrease from the 5th month of pregnancy and remain low for a long time following pregnancy. Deficiency of folate at the time of conception is associated with neural tube defects, preterm births, and IUGR.[31]

Epidemiological association

Evidence from systematic and other reviews

Conde-Agudelo et al.[32] conducted a systematic review of 67 cohort, case-control, and cross-sectional studies of birth spacing and perinatal outcomes. There was a J-shaped relationship (see Figure 3.2) observed in relation to inter-pregnancy interval and risk of LBW, preterm, and SGA births. An inter-pregnancy interval of <6 months was associated with increased risks of preterm birth [adjusted odds ratio (AOR) 1.40, 95% confidence interval (CI) 1.24, 1.58], LBW birth (AOR 1.61, 95% CI 1.39, 1.86), and SGA birth (AOR 1.26, 95% CI 1.18, 1.33) compared with inter-pregnancy intervals of 18 to 23 months. Intervals of 6 to 17 months and longer than 59 months were also associated with a significantly greater risk for preterm births, LBW, and SGA. According to meta-regression analyses, for every 1 month <18 months of inter-pregnancy interval, the risk of preterm births increased by 1.90%, the risk of LBW births increased by 3.25%, and the risk of SGA births increased by 1.52%. Similarly, for every 1 month >59 months of inter-pregnancy interval, the risk of preterm births increased by 0.55%, the risk of LBW births increased by 0.91%, and the risk of SGA births increased by 0.76%.

Figure 3.2: Inter-pregnancy interval and preterm and low birth weight rates



Recently, Zhu[33] reviewed data from their three large US cohort studies and identified that the previously noted J-shaped relationship was consistently observed, with the lowest incidence of preterm/LBW rates occurring in an inter-pregnancy interval of 18 to 24 months. The effect was observed even when data were stratified by maternal age groups. The authors indicated that consistency, reproducibility, strength of association, biological rationale, and dose-response gradient suggest that a short inter-pregnancy interval is causative for adverse birth outcomes.

Norton[34] reviewed data on birth spacing from the perspectives of birth outcomes, including neonatal and infant mortality and maternal morbidity and its global impact. The studies suggested that all women should use effective family planning methods for 2 years following a live birth and 6 months following an abortion. Analysis indicated that almost 2 million deaths of children at <5 years old could have been prevented if women in low-income countries had birth intervals of >24 months. Thus, the author called for the inter-pregnancy interval as a revolutionary, key concept to be introduced widely in the public health education domain. High-risk populations should be especially targeted, such as women who are young, of lower parity, postpartum, newly married or engaged, and 15 to 19 years of age.

Conclusions

Epidemiological data sources indicate an impact of the inter-pregnancy interval on the risk of preterm/SGA/IUGR/LBW births. Both short (<18 months) and long (>60 months) intervals are associated with preterm/SGA/IUGR/LBW births. The strength of the association, and evidence fitting other requirements for causation, indicate a causal role of short inter-pregnancy interval in preterm/SGA/LBW births. The inter-pregnancy interval could be a significant modifiable factor for preterm/SGA/IUGR/LBW births. All mothers should be informed about the advantages of an inter-pregnancy interval of approximately 18 to 24 months. This length may reduce the risk of preterm/SGA/IUGR/LBW births.

No intervention studies assessing this strategy were identified.

Marital Status

Biological plausibility

- Compared with married mothers, unmarried mothers are younger, primiparous, unemployed, and smokers—all of these factors are associated with adverse pregnancy outcomes.
- The general health of married adults is reported to be better than that of unmarried adults.[35]
- Marriage protects an individual through the practice of healthy behaviours and through positive attitudes compared with risky behaviour undertaken by an unmarried person.[36]
- Marriage increases the likelihood of social support and reduces stress.[35]
- Raatikainen et al.[35] proposed that mothers in common-law unions or with cohabitant status experience higher stress than do married mothers because of less stable relationships.

Epidemiological association

Evidence from systematic and other reviews

Reviews of the effects of marital status on preterm/LBW/SGA births have not been published.

Evidence from other study designs

Evidence from observational studies is presented in Table 3.4.

Table 3.4: Studies of effects of marital status on pregnancy outcomes

Study	Characteristic	Results
Studies assessing impact of married, cohabitant, and unmarried status		
Raatikainen et al.[35]	Cohort study from Finland	Compared with married mothers: - LBW (AOR for unmarried mothers 1.17, 95% CI 1.03, 1.32; for cohabiting mothers 1.15, 95% CI 1.02, 1.31; and for single mothers 1.21, 95% CI 1.01, 1.46) - preterm births (AOR for unmarried mothers 1.15, 95% CI 1.03, 1.28; for cohabiting mothers 1.15, 95% CI 1.03, 1.28; and for single mothers 1.29, 95% CI 1.09, 1.54) - SGA (AOR for unmarried mothers 1.11, 95% CI 1.02, 1.22 and for cohabiting mothers 1.11, 95% CI 1.02, 1.24)
Luo et al.[37]	Cohort study from Quebec, Canada	For infants born to mothers with common-law relationships: - preterm births (AOR 1.14, 95% CI 1.11, 1.17) - LBW (AOR 1.21, 95% CI 1.18, 1.25) - SGA (AOR 1.18, 95% CI 1.16, 1.20)
MacDonald et al.[38]	Open interview study from London, UK	Preterm births: - 8% in married women - 9% in cohabiting women - 13% in women living with adults other than the father of the baby - 7% among women living alone (p = ns) LBW: - 9% in married women - 10% in cohabiting women - 5% in women living with adults other than the father of the baby - 15% among women living alone (p = ns)
Bird et al.[39]	Survey in the US	Risk of LBW births (AOR 0.9, 95% CI 0.5, 1.7 for cohabiting mothers and AOR 0.6, 95% CI 0.3, 1.2 for other types of relationships)
Study assessing social acceptability of cohabitant status		
Zeitlin et al.[40]	Case-control comparison in 17 European countries	Countries where proportion of births to married women was >80%: - preterm births (AOR 1.29, 95% CI 1.08, 1.55 for cohabiting mothers and 1.61, 95% CI 1.26, 2.07 for single mothers) Countries where proportion of births to married women was <80%: - preterm births (AOR 1.12, 95% CI 0.98, 1.27 for cohabiting mothers and 1.10, 95% CI 0.89, 1.35 for single mothers)
Studies assessing impact of changing partners		
Vatten and Skjaerven[41]	Case-control study in Norway	Among women who changed partners: - preterm births (AOR 2.0, 95% CI 1.9, 2.1) - LBW (AOR 2.5, 95% CI 2.3, 2.6) - infant mortality (AOR 1.8, 95% CI 1.6, 2.1)
Li[42]	Cohort study assessing impact of different partners	If previous preterm birth <34 weeks, changing partners resulted in a reduction in the risk of a 2nd preterm birth compared with those who did not change partners (OR 0.67, 95% CI 0.52, 0.88) If the previous birth at >36 weeks' gestation, changing partners led to increased risk of preterm births (OR 1.16, 95% CI 1.04, 1.30)

AOR: adjusted odds ratio; CI: confidence interval; LBW: low birth weight; ns: not statistically significant; OR: odds ratio; SGA: small for gestational age.

Conclusions

Results indicate an increased risk of preterm/IUGR births for unmarried women. The results also indicate increased risk among cohabiting women, particularly in a population where poverty is prevalent and the practice of cohabiting is not common. The results from these studies may be confounded by other immeasurable factors. The basis for protective effects of marriage may lie in the effects of social, psychological, emotional, and financial support provided by the partner in reducing stress. Further research is needed to understand the mechanisms of the effect of marital status on pregnancy outcomes and interventions such as counselling women of childbearing age regarding this potential risk factor.

Pregnancy – Intended or Not Intended

Approximately one third of pregnancies that result in live births and half of all pregnancies are unintended.[43] Unintended pregnancy could be mistimed (not intended at that time) or unwanted (not intended at any time).

Biological plausibility

The exact mechanism is unclear.

- Higher levels of stressful events that may affect pregnancy outcomes are reported for women with unintended pregnancies than for women with intended pregnancies.[43]
- Unwanted pregnancy can be a risk factor for depression in pregnant women.[44]
- Unintended pregnancies are associated with social and economic disadvantages and risky maternal behaviours.[45]
- Unintended pregnancies are associated with delayed initiation of prenatal care.[43]

Epidemiological association

Evidence from systematic and other reviews

No review on this topic was identified.

Evidence from other study designs

The results of studies assessing the impact of unintended pregnancy on birth outcomes are summarized in Table 3.5.

Table 3.5: Studies of impact of unintended pregnancy

Study	Characteristic	Results
Sable et al.[46]	Maternal survey	For unintended pregnancies: - AOR for VLBW compared with intended pregnancies 0.79 (95% CI 0.61, 1.02) - AOR for moderately LBW vs. normal 0.82 (95% CI 0.66, 1.02)
Orr et al.[43]	Cohort study	Among urban, clinic-attending, low-income, pregnant black women adjusted RR for preterm births was 1.82 (95% CI 1.08, 3.08) for unintended pregnancies vs. intended pregnancies
Durousseau and Chavez[47]	Maternal survey	Compared with wanted pregnancy, the risk of an IUGR infant was: - OR 1.1 (95% CI 0.7, 1.7) for mistimed pregnancy - OR 1.2 (95% CI 0.6, 2.3) for unwanted pregnancy - OR 1.5 (95% CI 0.9, 2.4) for undetermined status regarding intendedness of pregnancy
Messer et al.[48]	Cohort study	Women reporting that pregnancy was unintended had high levels of stress There was no increase in the risk of preterm birth with unintendedness of pregnancy (RR 1.0, 95% CI 0.8, 1.1)
Mohllajee et al.[49]	Survey from population data set	Women with unintended pregnancy had increased risk of preterm births (OR 1.16, 95% CI 1.01, 1.33) Women ambivalent about pregnancy intentions had increased risk of LBW (OR 1.15, 95% CI 1.02, 1.29)
Kost et al.[50]	Reanalyses of data from 2 study databases	Preterm birth rate for all pregnancies was 8.4% and 8.1% in 2 databases For unintended pregnancies, the rate was 12.9% and 8% LBW rate for all pregnancies was 5.9% and 5.8% For unintended pregnancies, the rate was 9.7% and 10.1%
Sharma et al.[51]	Survey	Unintended pregnancies had 1.5 to 2 times higher risk of preterm labour and LBW births

AOR: adjusted odds ratio; CI: confidence interval; IUGR: intrauterine growth restricted; LBW: low birth weight; OR: odds ratio; RR: risk ratio; VLBW: very low birth weight.

Conclusions

The incidence of unintended pregnancy is high. A stressful environment associated with unwanted pregnancies may have an impact on pregnancy outcomes. Some cohort studies and questionnaires reveal that unintended pregnancies are associated with preterm labour and LBW births, whereas other studies show that unintended pregnancies had no influence on pregnancy outcomes.

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CHAPTER 4:

Maternal Anthropometric Characteristics

Main Summary Points

- Short maternal stature may be associated with reduced birth weight and preterm birth.
- Mothers with low pre-pregnancy weight have smaller infants; however, population norms must be considered when interpreting the impact of this factor.
- Higher maternal pre-pregnancy body mass index predisposes the fetus to a borderline increase in the risk of preterm/low birth weight/small for gestational age births. Lower pre-pregnancy body mass index may be associated with preterm/small for gestational age births.
- Adequate maternal weight gain during pregnancy according to women's pre-pregnancy body weight is important. Higher weight gain than recommended is common. Inadequate weight gain is associated with preterm/small for gestational age births. Restricted energy/protein intake for women with excessive weight gain does not result in any benefit; however, this association has not been adequately studied.

Four anthropometric factors associated with preterm/low birth weight (LBW) births include maternal height, maternal pre-pregnancy weight, maternal body mass index (BMI), and gestational weight gain. In chapter 4, we review these factors. As they are interrelated, the information provided under the headings below sometimes includes one or more of them.

Maternal Height

Maternal height is a result of genetic factors, environmental effects, and nutrition.

Biological plausibility

The exact mechanism of how maternal height influences pregnancy outcome is not clear.

Epidemiological association

Evidence from systematic and other reviews

Honest et al.,[1] in a systematic review, included two studies that evaluated the accuracy of maternal height as a predictor of the risk of preterm births by using two different thresholds. For women whose height was <25% of normal, the positive likelihood ratio was 1.79 (95% confidence interval (CI) 1.27, 2.52), with a corresponding negative likelihood ratio of 0.75 (95% CI 0.59, 0.95) for prediction of preterm births. For height <152 cm, the positive likelihood ratio was 1.26 and the negative likelihood ratio was 0.96 for prediction of preterm births.

Evidence from other study designs

Prasad and Al-Taher,[2] in a retrospective analysis of 1000 white primigravida in the United Kingdom, identified a statistically significant positive association between maternal height and birth weight (BW) ($p < 0.001$). The mean BW (standard deviation (SD) in parentheses) of infants born to mothers whose height was <155 cm was 3180 g (447) versus 3571 g (432) for infants born to mothers whose height was >170 cm.

Blumenfeld et al.[3] retrospectively evaluated 102 triplet pregnancies. Mothers who were taller than 165 cm gave birth to significantly ($p = 0.022$) heavier neonates (mean total triplet weight 5,294 g) compared with mothers whose height was <165 cm (mean total triplet weight 4649 g). There was no significant correlation between preconceptional maternal BMI and total triplet neonatal weight and week of delivery.

Conclusions

Short maternal stature may be associated with reduced BW and preterm births.

Maternal Pre-pregnancy Weight

Pre-pregnancy weight may reflect maternal nutritional status.

Biological plausibility

Biological mechanisms regarding how pre-pregnancy weight may influence pregnancy outcome are not known. Lifelong adequacy or inadequacy of nutrition is reflected in the mother's pre-pregnancy weight.

Epidemiological association

Evidence from systematic and other reviews

No review was identified that examined pre-pregnancy weight and pregnancy outcomes.

Evidence from other study designs

The following descriptions represent the reports of longitudinal epidemiological studies. The assessment of this parameter was performed by either BMI or percentage of ideal weight for height.

Kirchengast et al.,[4] in a study of 10,240 infants from Austria, reported that a higher pre-pregnancy weight was associated with higher BW and head circumference. The incidence of LBW was significantly higher in underweight women compared with normal weight, overweight, and obese women.

Mohanty et al.,[5] in a study of 395 singleton pregnant mothers and their full-term infants from India, reported that of 395 newborns, 121 (30.6%) were LBW. For the prediction of LBW, the critical limits of maternal weight, height, mid-arm circumference, and BMI were 45 kg, 152 cm, 22.5 cm, and 20 kg/m^2, respectively.

Conclusions

Maternal weight may be associated with BW. Mothers with low pre-pregnancy weight have smaller infants; however, population norms must be considered when interpreting the impact of this factor.

Maternal Body Mass Index (BMI)

BMI reflects height, weight, and probably nutritional status.

Biological plausibility

- BMI is height and weight dependent, and thus the factors applied to these individual measures apply to BMI for explaining the effects on preterm/LBW births.
- Increased BMI or obesity is associated with increased risk of birth defects due to metabolic alterations, including hyperglycemia, elevated insulin or estrogen levels, and diabetes.[6] Congenital anomalies are known to be associated with LBW.
- Pre-pregnancy overweight is a risk factor for mild pre-eclampsia and mild transient hypertension in pregnancy and may result in preterm/LBW births.[7]

Epidemiological association

Evidence from systematic and other reviews

Honest et al.[1] systematically reviewed five studies that assessed the use of BMI as a predictor of preterm births. The accuracy of anthropometry (BMI) in predicting the risk of preterm births varied according to the BMI. For overweight (BMI 25 to 30 kg/m^2) women (in cases in which there was no heterogeneity), the positive likelihood ratio was 1.13 (95% CI 1.09, 1.17) and the corresponding negative

likelihood ratio was 0.96 (95% CI 0.95, 0.97) for predicting preterm births. The summary positive likelihood ratio was 1.10 (95% CI 0.99, 1.22) and the negative likelihood ratio was 0.97 (95% CI 0.93, 1.01) for predicting preterm births at <32 weeks.

Evidence from other study designs

Wataba et al.,[8] in a retrospective cohort study of 21,718 Japanese women with a singleton pregnancy, identified that a low BMI (<18 kg/m^2) was associated with increased risk for small for gestational age (SGA) births in nulliparous women (odds ratio (OR) 2.48, 95% CI 1.94, 3.16) compared with women with a BMI of 20 to 21.9 kg/m^2. In nulliparous women, the optimal weight gain was 0.25 to 0.40 kg/week for low (<18 kg/m^2) BMI, 0.20 to 0.30 kg/week for medium (18 to 23.9 kg/m^2) pre-pregnancy BMI, and ≥0.05 kg/week for high (≥24 kg/m^2) pre-pregnancy BMI. In parous women, the corresponding values were ≥0.20, 0.20 to 0.30, and 0.05 to 0.30 kg/week. Pre-pregnancy BMI of 18 to 23.9 kg/m^2 was least associated with pregnancy complications. Optimal weight gain is approximately inversely related to pre-pregnancy BMI.

Colletto and Segre[9] examined the correlation between maternal pre-pregnancy BMI and newborn weight, length, and BMI in singleton (n = 7979) and twin (n = 381 mothers, 562 twins) births. With higher maternal BMI, the BMI, weight, and length of the infants were higher. No significant correlation was found between maternal BMI and any of these variables in twins.

Hickey et al.,[10] in a study of ethnicity and pre-pregnancy weight, reported that low pre-pregnancy BMI was associated with an increased risk of preterm births between 33 and 36 weeks in the black population (OR 1.4, 95% CI 1.1, 1.8 for BMI 16.5 to 19.7 kg/m^2) and in the white population (OR 1.5, 95% CI 1.1, 2.0 for BMI 16.5 to 19.7 kg/m^2), but not in the Hispanic population (OR not reported).

Epidemiological associations for maternal obesity

Direct studies reporting effects of obesity on preterm/LBW births are lacking; however, obesity has been studied from other aspects related to preterm/LBW births.

Bodnar et al.[7] assessed the association of pre-pregnancy BMI with severe and mild pre-eclampsia and transient hypertension of pregnancy in 38,188 pregnant women. Compared with white women with a BMI of 20 kg/m^2, the risks of severe pre-eclampsia in white women were increased for BMI values of 25 kg/m^2 (OR 1.7, 95% CI 1.1, 2.5) and 30 kg/m^2 (OR 3.4, 95% CI 2.1, 5.6). For black women, the corresponding risks were for BMI of 25 kg/m^2 (OR 2.1, 95% CI 1.4, 3.2) and for BMI of 30 kg/m^2 (OR 3.2, 95% CI 2.1, 5.0). The effect of BMI on risk of severe pre-eclampsia was similar to its effect on mild disease.

Basso et al.[11] analyzed data from the Danish National Birth registry of 62,073 singleton and twin births from the 24th gestational week to assess the role of

obesity in twinning. The overall rate of twinning in the cohort was 2.2%, close to the national rate of 2.0% for the same period. Increasing BMI and height correlated with twinning among untreated women. Compared with a BMI of 20 to 24.9 kg/m^2, the OR associated with a BMI of <20 kg/m^2 was 0.71 (95% CI 0.54, 0.92) and that associated with a BMI of ≥30 kg/m^2 was 1.39 (95% CI 1.05, 1.84) for twinning. Widespread increase in obesity was speculated to be the explanation for part of the increase in twinning and associated complications.

Watkins et al.,[6] in a population-based case-control study, identified that obese women were more likely than average-weight women to have an infant with spina bifida (OR 3.5, 95% CI 1.2, 10.3), omphalocele (OR 3.3, 95% CI 1.0, 10.3), heart defects (OR 2.0, 95% CI 1.2, 3.4), and multiple anomalies (OR 2.0, 95% CI 1.0, 3.8). Overweight women were more likely than average-weight women to give birth to infants with heart defects (OR 2.0, 95% CI 1.2, 3.1) and multiple anomalies (OR 1.9, 95% CI 1.1, 3.4). The study did not address preterm/LBW rates, but several birth defects are associated with fetal growth restriction, spontaneous preterm birth, and iatrogenic preterm birth.

Conclusions

Higher than average maternal pre-pregnancy BMI is associated with the need for artificial reproductive treatment, pre-eclampsia, pregnancy-induced hypertension, and congenital anomalies in the fetus. These complications predispose the fetus to a borderline increase in the risk of preterm birth/LBW/SGA. Lower than average pre-pregnancy BMI may be associated with preterm/SGA births.

Gestational Weight Gain

Weight gain during pregnancy reflects an increase in uterine tissue, fat stores, plasma volume, placenta, fetus, and breast tissue. The US Institute of Medicine recommends gestational weight gain according to maternal BMI prior to the pregnancy. For a BMI of <19.8 kg/m^2, the recommended weight gain during pregnancy is 28 to 40 lb (12.7 to 18.1 kg); for a BMI of 19.8 to 26 kg/m^2, the recommended weight gain is 25 to 35 lb (11.3 to 15.9 kg); for a BMI of 26.1 to 29 kg/m^2, the recommended weight gain is 15 to 25 lb (6.8 to 11.3 kg); and for a BMI of >29 kg/m^2, the recommended weight gain is 15 lb (6.8 kg).[12]

Biological plausibility

- Poor weight gain may reflect a deficiency of substrates required for the growth of the fetus.[13]
- Zinc deficiency has been linked to poor weight gain because it can cause suppression of appetite, leading to perpetuation of existing deficient caloric intake. In addition, zinc deficiency impairs the synthesis of prostaglandins and collagen and affects uterine contractility.[13]

- Early nutritional insult can result in poor plasma volume expansion and insufficient development of maternal tissues for support of the fetus.[13]

A combination of factors is probably operating simultaneously in mediating the effects of gestational weight gain on fetal weight and duration of gestation. Appropriate but not excessive gestational weight gain is necessary to optimize infant BW and minimize maternal postpartum fat retention.[14]

Epidemiological association

Evidence from systematic and other reviews

Honest et al.[1] systematically reviewed four studies of accuracy of maternal weight gain and its impact on pregnancy outcomes. Weight gain was a borderline predictor of preterm birth, with a summary positive likelihood ratio of 1.69 (95% CI 1.48, 1.92) and a negative likelihood ratio of 0.81 (95% CI 0.77, 0.86).

Carmichael and Abrams[13] reviewed 13 epidemiological studies that reported the effect of weight gain during pregnancy on pregnancy outcomes. The authors identified several methodological issues within the studies. The rate of weight gain was described differently in the studies. Some studies compared weight gain against "a standard weight gain," whereas others followed the recommended BMI. Rate of weight gain is affected by the duration of gestation. Weight gain patterns probably provide a better description of the nutritional status than do total or average weight gain. Some studies have used self-reported pre-pregnancy weights, which may provide inaccurate information. Recall bias is likely to play a role in some studies. Confounding factors such as race, socioeconomic status, age, and tobacco use are not always accounted for in the studies. A previous history of preterm birth has been accounted for as a confounder, and in some instances a previous preterm birth could be due to similar nutritional insults present in the current pregnancy. Estimates of gestational age differ between studies. Nine studies reported on the rate of weight gain and, of these, seven reported a protective effect (reduced incidence of intrauterine growth-restricted (IUGR)/ LBW births) in the presence of adequate weight gain. All five studies reporting the pattern of weight gain showed a protective effect for slow weight gain in the initial phase and rapid weight gain in the later stage. Most of the studies reported an increased risk of preterm birth by approximately 50% to 100% in women with insufficient weight gain. The risk was similar in studies reporting poor weight gain in the later part of pregnancy in mothers with adequate weight gain in early pregnancy. The authors identified the need for further research on weight gain patterns and proper assessment of gestational age.

Luke,[15] in a review, concluded that an adequate weight gain provided a similar protective effect. The author suggested that cultural differences in metabolism of various substrates are important. Chinese mothers, despite lower pre-pregnancy weight, were found to have similar sized infants as those of white mothers. This

similarity was attributed to higher mean blood sugar levels during gestation in Chinese women compared with women of other races. These high levels may be responsible for increased BW.

Evidence from other study designs

Stotland et al.,[16] in a retrospective cohort study of 20,465 non-diabetic, term, singleton births, identified that gestational weight gain above the Institute of Medicine guidelines was more common (43.3%) than was weight gain below the guidelines (20.1%). Compared with weight gain within guidelines, gestational weight gain above guidelines was associated with a low 5-minute Apgar score (adjusted OR 1.33, 95% CI 1.01, 1.76), seizures (OR 6.50, 95% CI 1.43, 29.65), hypoglycemia (OR 1.52, 95% CI 1.06, 2.16), and large-for-gestational-age births (OR 1.98, 95% CI 1.74, 2.25). Gestational weight gain below guidelines was associated with decreased odds of neonatal intensive care unit admission (OR 0.66, 95% CI 0.46, 0.96) and increased odds of SGA (OR 1.66, 95% CI 1.44, 1.92). Gestational weight gain of <7 kg was associated with increased risk of seizure, a hospital stay of >5 days, and SGA births (2.26, 95% CI 1.76, 2.90).

Intervention

Kramer and Kakuma[17] systematically reviewed three studies involving 384 women who were overweight or who had excessive weight gain during pregnancy and who were randomly assigned to a control group or an experimental group (restricted energy/protein intake). There was a reduction in maternal weight gain (two studies, 253 women, weighted mean difference (WMD) -255 g/week, 95% CI -437, -73); however, there was no reduction in the risk of pre-eclampsia or pregnancy-induced hypertension. There was no difference in the risk of preterm births (one study, 182 women, risk ratio 0.50, 95% CI 0.09, 2.66) or mean BW (two studies, 282 patients, WMD -218 g, 95% CI -665, 229).

Conclusions

Adequate maternal weight gain during pregnancy according to a women's pre-pregnancy body weight is important. Higher weight gain than recommended is common. Inadequate weight gain is associated with preterm births and SGA births. Restricted energy/protein intake for women with excessive weight gain did not result in any benefit; however, this association has not been adequately studied.

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CHAPTER 5:

Intergenerational Influences, Paternal and Fetal Factors

Main Summary Points

- Genetic factors likely have an important role in preterm/low birth weight births, with significant contributions from genetic-environmental interactions.
- Several syndromes and genetic conditions are known to be associated with preterm/low birth weight births and advances in this field may identify further associations.
- There is an approximately two- to three-fold increase in the risk of preterm/low birth weight births for a mother with a history of preterm birth. The subsequent births are likely to occur at the same gestational age as the previous preterm birth.
- Maternal low birth weight is a risk factor for reduced fetal growth, preterm birth, or both in the offspring. There does not seem to be an association between the mother being born preterm and her offspring being born before term. Paternal birth weight is associated with the infant's birth weight, but only a few studies have assessed this impact.
- Advanced paternal age may be associated with preterm/low birth weight births.

Among preterm births, there is a preponderance of males; however, birth weight is higher for male neonates than it is for female neonates. In chapter 5 we review the influence of genetic, paternal, and fetal factors on pregnancy outcomes. The predisposing influence of intergenerational and previous history of preterm/low birth weight (LBW) births is explored.

Genetic Factors

Biological plausibility

Birth weight (BW) distribution varies in different populations. Variability is commonly due to maternal environmental and hereditary factors, with a small proportion of it being due to fetal genotype. The difference in BW between male and female neonates may be related to the genetic material that is carried on the Y chromosome. Among chromosomally abnormal infants, 22% to 38% are intrauterine growth-restricted (IUGR) infants.[1-4] The alteration in fetal growth

may be a result of the effects on cell division. Examples of chromosomal disorders associated with interine growth restriction are:[5]

Trisomy 8, 13, 18, 21
4p syndrome
5p syndrome
13q, 18p, 18q syndrome
Triploidy
XO
XXY, XXXY, XXXXY
XXXXX

Examples of genetic conditions and syndromes associated with reduced fetal growth follow:

Aarskog-Scott syndrome
Anencephaly
Bloom syndrome
Cornelia de Lange syndrome
Dubowitz syndrome
Ellis van Creveld syndrome
Meckel Gruber syndrome
Moebius syndrome
Potter syndrome
Prader Willi syndrome
Progeria
Robert syndrome
Robinow syndrome
Russell-Silver syndrome
Seckel syndrome
Smith Lemli Opitz syndrome
Williams syndrome

Epidemiological association

Evidence from systematic and other reviews

It is beyond the scope of this synopsis (and the expertise of the authors) to provide a comprehensive summary of the rapidly developing area of research in gene-disease interaction. However, in this chapter we provide a summary of important recent developments. Crider et al.[6] reviewed 18 studies published before June 1, 2004 that examined associations between polymorphism in the maternal or fetal genome and the risk of preterm births. Studies of polymorphism in the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α) showed the most consistent increase in the risk of preterm births. Environmental factors such as infection, stress, and obesity, which activate inflammatory pathways, have been associated with preterm births, suggesting that environmental and genetic risk factors might operate and interact

through related pathways. In a different meta-analysis, no statistically significant association was identified between single nucleotide polymorphisms in the TNF-α gene and preterm births.[7]

Evidence from other study designs

Ward et al.[8] studied the heritability of preterm births. Women who gave birth to a singleton infant at <36 weeks of gestation were asked about their family history. Twenty-eight families were identified in which the proband had at least five 1st or 2nd degree relatives who had given birth preterm. An extensive genealogy database (GenDB) was constructed. GenDB documents the relationships between >15.5 million ancestors and 3.5 million descendents of approximately 10,000 individuals who moved to Utah in the mid-1800s. This database was searched for the names, birth dates, and birthplaces of the four grandparents for each of the 28 probands. The coefficient for familial preterm birth grandparents was >50 standard deviations (SDs) higher (3.4×10^5, $p < 0.001$) than it was for term-born grandparents. The authors concluded that this study confirms the familial nature of preterm births. On average, pregnant women randomly selected from the population were 23rd-degree relatives, whereas the preterm birth probands were 8th-degree relatives.

Preterm births have been suspected to be the result of an interaction between a gene and the environment.[9] Several factors suggest the possibility of a genetic predisposition in preterm births: a higher risk of preterm births in mothers with a history of preterm births, racial predispositions, and the implication of certain single-gene disorders.[10] Maternal hyperhomocystinemia, for example, predisposes mothers to an increased risk of pre-eclampsia, recurrent miscarriage, placental abruption, and preterm labour. Mutations in the gene encoding methyltetrahydrofolate reductase cause elevated levels of homocystine in mothers. Variants in the folate metabolism pathway that affect the accumulation of homocysteine have been linked to adverse outcomes. Fetal thrombophilic polymorphism may be related to small for gestational age (SGA) status.[11] A nested case-control study suggested a direct or indirect role for the SHMTI(1420)T variant in spontaneous preterm and SGA births.[12] Maternal carriage of at least one copy of the interleukin-1 receptor antagonist allele 2 may be associated with an increased risk of preterm births.[13] A proposed association[14] between the maternal or fetal angiotensin gene and SGA infants has not been confirmed, however.[15] Infants with recessive dystrophic epidermolysis bullosa are of significantly lower BW than their unaffected siblings, with 30% being SGA compared with 12% of the controls (unaffected siblings, $p = 0.02$).[16] In women with preterm labour before 34 weeks gestation, maternal homozygous carriage of the -863 polymorphism may be associated with preterm births and adverse neonatal outcome.[17]

Conclusions

Genetic factors likely have an important role in preterm/LBW births. Over the next few years, many additional genetic variants associated with preterm/SGA/IUGR births will likely be discovered, opening up new avenues for potential interventions or therapy.

History of Preterm/LBW Births

Preterm and LBW births tend to recur in families.

Biological plausibility

Medical or non-medical factors responsible for preterm/SGA/IUGR/LBW births in a previous pregnancy may operate during subsequent pregnancies, leading to an increased risk.

Epidemiological association

Evidence from systematic and other reviews

No review that has evaluated the risk of preterm births or LBW births in families with a history of preterm/SGA/IUGR/LBW births was identified.

Evidence from other study designs

The studies reporting recurrence of preterm/LBW births are summarized in Table 5.1.

Table 5.1: Cohort studies reporting the recurrence risk for women with previous preterm/LBW births

Study	Characteristic	Results
Ananth et al.[18]	Population-based retrospective study	Previous spontaneous preterm birth: - spontaneous preterm births in subsequent pregnancy (AOR 3.6, 95% CI 3.2, 4.0) - medically induced preterm births (AOR 2.5, 95% CI 2.1, 3.0) Previous medically induced preterm birth: - medically induced preterm births in subsequent pregnancy (AOR 10.6, 95% CI 10.1, 12.4) - spontaneous preterm births (AOR 1.6, 95% CI 1.3, 2.1)
Bakewell et al.[19]	Population-based cohort	For 2nd LBW birth: - 1st child was preterm and SGA (AOR 10.1, 95% CI 8.8, 11.6) - 1st child was preterm and AGA (AOR 7.9, 95% CI 7.2, 8.7) - 1st child was term and SGA (AOR 6.3, 95% CI 5.4, 6.9) Smoking in both pregnancies (OR 1.85), short pregnancy interval (OR 1.33), advanced maternal age (OR 1.17), and low pre-pregnancy weight were identified as risk factors for recurrence
Kristensen et al.[20]	Nation-wide study in Denmark	Unadjusted RR 6.0 for previous preterm birth <32 weeks and 4.8 for previous preterm birth between 32 and 36 weeks Attributable risk for 2nd preterm birth of 17% if the first-born was preterm, 18% if the first-born was LBW, and 5% if first-born was SGA
Adams et al.[21]	Population-based cohort study	1st birth between 20 and 31 weeks: - white women - 8.2% had 2nd child between 20 and 31 weeks and 20.1% had their 2nd child between 32 and 36 weeks - black women - 13.4% had 2nd child between 20 and 31 weeks and 23.4% had 2nd child between 32 and 36 weeks
Bloom et al.[22]	Cohort study	Previous preterm birth at <35 weeks' gestation: - risk of recurrence (OR 5.6, 95% CI 4.5, 7.0) - 49% gave birth within 1 week of the gestational age of their 1st birth and 70% gave birth within 2 weeks
Carr-Hill and Hall[23]	Cohort study	Risk of preterm births: - with history of 1 previous full-term infant, it was 5% - with history of 1 previous preterm infant, it was 15% - with a history of a full-term and a preterm birth, it was 24% - with a history of 2 previous preterm births, it was 32%
Mercer et al.[24]	Prospective cohort	Women with a history of a spontaneous preterm birth had a 2.5-fold increased risk of a repeat spontaneous preterm birth (21.7% vs. 8.8%, $p < 0.001$)
Bratton et al.[25]	Retrospective cohort study	Risk was significantly increased for a repeat VLBW infant (RR 11.5, 95% CI 5.4, 24.4)

AGA: appropriate for gestational age; AOR: adjusted odds ratio; CI: confidence interval; LBW: low birth weight; OR: odds ratio; RR: risk ratio; SGA: small for gestational age; VLBW: very low birth weight

Conclusions

The cohort studies indicate an increased risk of preterm/LBW births in a subsequent pregnancy for women with a history of such outcomes. The interplay of genetic factors and other factors is suspected. These factors may or may not be modifiable. This information should be incorporated in the existing prevention programs and special attention should be provided to this group of mothers. With an approximate two- to three-fold increase in the incidence of preterm births in this subgroup, any intervention likely to show promise should target this population to achieve a higher benefit.

Maternal/Paternal Gestational Age and BW

Biological plausibility

The exact mechanism by which the intergenerational effects of LBW/preterm births exert an influence is not clear.

- Genetic factors, the intrauterine milieu, or both could potentially have intergenerational effects, causing the same conditions in the offspring (see the *Genetic Factors* section).
- Paternal factors are important in certain genetic conditions that may result in LBW. This association could be due to a paternal age effect on sperm.
- Paternal genes have been found to affect placental growth in animal models.[26]

Epidemiological association

Evidence from systematic and other reviews

No review addressing this topic has been published.

Evidence from other study designs

Data for maternal and paternal factors are presented in Tables 5.2 and 5.3.

Table 5.2: Influence of mother's own birth characteristics on pregnancy outcomes

Study	Characteristics	Results
Selling et al.[27]	Population-based cohort study	Mothers who were born preterm were not significantly more likely to give birth preterm compared with those born at term (AOR 1.24, 95% CI 0.95, 1.62) Mothers born preterm were not more likely to give birth to an SGA infant SGA mothers were more likely to give birth to an SGA infant (AOR 2.68, 95% CI 2.11, 3.41) or a preterm infant (AOR 1.30, 95% CI 1.05, 1.61)
Simon et al.[28]	Population-based cohort study	African American mothers who were LBW: AOR for SGA births 1.7 (95% CI 1.4, 1.9) AOR for preterm births 1.6 (95% CI 1.3, 1.9) White mothers who were LBW: AOR for SGA births 1.8 (95% CI 1.7, 2.0) AOR for preterm births 1.3 (95% CI 1.0, 1.6)
Magnus et al.[29]	Population-based sample	Mothers with LBW had a significantly increased risk of having a LBW infant (OR 3.03, 95% CI 1.79, 5.11) compared with mothers with BW >4 kg In mothers born preterm, the risk of having a preterm infant was not significantly increased (OR 1.46, 95% CI 0.96, 2.21) compared with mothers who were born at term

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; LBW: low birth weight; OR: odds ratio; SGA: small for gestational age

Table 5.3: Influence of paternal birth characteristics on pregnancy outcomes

Study	Characteristics	Results
Jaquet et al.[30]	Selected population sample	The risk of SGA was higher if the mother was SGA (AOR 4.70, 95% CI 2.27, 9.73), the father was SGA (AOR 3.48, 95% CI 0.86, 14.07), and both were SGA (AOR 16.33, 95% CI 3.16, 84.35)
Klebanoff et al.[31]	Cohort study	Father's BW <3 kg: an infant that was 176 g lighter; father's BW 3.0 to 3.9 kg: an infant that was 109 g lighter than a father who weighed >4.0 kg at birth Fathers who had a BMI of <20.08 kg/m2 had infants who were 105 g lighter compared with fathers with a BMI >23.05 kg/m2 Paternal BW, adult height, and adult weight explained 3% of variance in the BW of the offspring

AOR: adjusted odds ratio; BMI: body mass index; BW: body weight; CI: confidence interval; SGA: small for gestational age

Conclusions

Maternal LBW is a risk factor for reduced fetal growth, preterm births, or both in the offspring. There does not seem to be an association between the mother being born preterm and her offspring being born before term. These findings reinforce the importance of reducing the incidence of LBW in current pregnancies in order to have an impact on birth outcomes in the next generation. The evidence for paternal birth weight suggests an association, but only a few studies have assessed this impact. Further research is warranted.

Paternal Factors

Similar to maternal age, paternal age is suspected to have a role in preterm/LBW births.

Epidemiological association

Evidence from systematic and other reviews

No reviews were identified.

Evidence from other study designs

The effect of paternal age on preterm/LBW births is summarized in Table 5.4.

Table 5.4: Influence of paternal age on preterm/LBW births

Study	Characteristic	Results
Reichman and Teitler[32]	Population-based sample	Risk of a LBW infant when father's age was >34 years compared with fathers between 20 and 34 years of age (AOR 1.7, 95% CI 1.3, 2.2)
Astolfi et al.[33]	Cohort study	If father's age was 45 to 49 years: risk of preterm births <32 weeks (OR 1.91, 95% CI 1.08, 3.38 and OR 1.72, 95% CI 1.25 2.36) if maternal age was 20 to 24 and 25 to 29 years, respectively
Zhu et al.[34]	National database	Compared with father's age 20 to 24 years, the risk for very preterm births: for age 25 to 29 years (OR 1.3, 95% CI 0.9, 1.8) for 35 to 39 years (OR 1.4, 95% CI 1.0, 2.0) for 40 to 44 years (OR 1.7, 95% CI 1.1, 2.6) for 45 to 49 years (OR 1.6, 95% CI 0.8, 3.0) for >50 years (OR 2.1, 95% CI 0.9, 4.8)
Tough et al.[35]	Population-based sample	Risk of preterm births and LBW were not impacted by paternal age (p = 0.19 and 0.28, respectively) For singleton births, increased risk of preterm births and LBW when paternal age was >50 years (p = 0.002 and 0.03, respectively) Multiple births were significantly increased with advanced paternal age (p < 0.01)

AOR: adjusted odds ratio; CI: confidence interval; LBW: low birth weight; OR: odds ratio.

Nahum and Stanishlaw[36] found that paternal height explained 2% of the variance in BW. With each centimetre increase in paternal height, there was a 10 g increase in BW. Fathers with a height 2 SDs above or below the mean had an increase or decrease of 125 g, respectively, in the BW of their offspring.

Basso et al.[37] studied the effects of paternal factors in a fertility database in Denmark. Fathers who had an index LBW/preterm child were followed. The BW of their next child was not affected, whether they remained with the same female partner or changed partners. The father's occupational status, residence, or social status had no impact on LBW.

Savitz et al.[38] reported that fathers employed in glass, clay, textile, and mining occupations had a higher risk of preterm births. Fathers working in art and textile occupations had a higher risk of SGA births.

Conclusions

The evidence suggests a possible association between advanced paternal age and preterm births/LBW. Further research into the causative mechanism (genetic, paternal lifestyle factors, difference in the age between father and mother, alteration of gametocyte structure and function, paternal occupations, etc.) is needed.

Fetal Sex

Biological plausibility

The biological mechanisms by which the sex of the fetus influences pregnancy outcomes are not clear. On average, the weight of a male fetus is 150 g higher than that of a female fetus. The difference in fetal weight starts to appear at 28 weeks' gestation and is believed to be due to the effects of androgen, maternal fetal antigen difference, or genetic material on the Y chromosome carrying genetic material for growth.[17]

Epidemiological association

Evidence from systematic and other reviews

Ingemarsson[39] reviewed the effects of sex from conception to birth. The mortality rate was higher in male fetuses by approximately 35% in chromosomally normal spontaneous abortions (i.e., significantly higher than at birth). Data from the Swedish National Data Services for the years 1999 to 2000 (175,382 newborns, of which 672 were stillbirths) indicate that male fetuses are more likely to be born preterm (55% to 60% of all newborns between 23 and 32 weeks' gestational age). The neonatal mortality rate was higher in male infants by 50%. The infant mortality rate was 3.44 per 1000 for males compared with 2.18 per 1000 for females. The gender difference seems to persist throughout life, particularly regarding age-related degenerative changes in the brain.

Conclusions

Male fetuses are more likely to be born preterm. Male newborns are of higher weight compared with female newborns, which may have some effect at the lower end of the spectrum on the definition of LBW births.

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CHAPTER 6:

Maternal Medical Factors

Main Summary Points

- Medically indicated preterm birth is increasing. This change may be due to maternal medical conditions, pregnancy-related conditions, or fetal conditions.
- Maternal medical conditions such as acute exacerbations of asthma and moderate to severe renal insufficiency may lead to preterm/low birth weight births.
- The risk of preterm birth may be increased following an induced abortion; however, the results are not consistent among studies. Some studies suggest an even higher risk as the number of previous induced abortions increases. The practice of inducing abortion has recently changed from a surgical procedure to a medical one. The medical route may not involve trauma to the cervix and may not increase the risk of preterm birth, but further studies are needed.
- Improved fetal survival among pre-eclamptic women is associated with an increased risk of preterm/small for gestational age/intrauterine growth-restricted births. The role of different antihypertensive medications for reducing preterm/small for gestational age/intrauterine growth-restricted births is unclear. Other pregnancy-associated conditions have an important role in embryogenesis, cell differentiation, and cell growth and may have an effect on preterm/low birth weight births.

Maternal general health and altered hemodynamic status due to pregnancy can affect the fetus in several ways. In chapter 6 we review the effects of maternal medical conditions, pregnancy-associated conditions, and history of induced abortion on pregnancy outcomes.

Maternal General Medical Conditions

Nutrients and oxygen are key factors for fetal growth. Maternal conditions that alter the intrauterine environment by affecting oxygen-carrying capacity, uteroplacental blood flow, and the size of the uterus can affect the growth of the fetus and the duration of gestation.[1-6] In addition, maternal infection with organisms transmitted through the placenta can result in altered fetal growth. This topic is reviewed in detail in the subsection on infections in Pregnancy-Associated Conditions.

Chronic maternal hypertension that results from either renal parenchymal diseases or essential hypertension can reduce fetal growth by a factor of two to three.[2] Reduced growth may result from a reduction in blood flow or an increased

risk of developing pre-eclampsia.[2] Maternal diabetes can also cause long-standing changes in the microvasculature of the placenta and cause fetal growth restriction.[2] However, the majority of neonates born to mothers with diabetes mellitus are large for gestational age.

A multitude of other chronic conditions are reported to have an effect on fetal growth, including asthma, renal failure, collagen vascular disorders, inflammatory bowel diseases, cystic fibrosis, starvation, short bowel syndrome, pancreatitis, malabsorptive states, cyanotic heart disease, sickle cell anemia, and living at a high altitude.[1-6] Two important and well-reviewed maternal conditions, asthma and renal insufficiency, are described in detail in the following two sections.

Maternal Asthma

Biological plausibility

Hypoxemia associated with single or multiple severe attacks of asthma during pregnancy can affect duration of gestation, birth weight (BW), or both.

Epidemiological association

Evidence from systematic and other reviews

Murphy et al.,[7] in a review of 10 studies reporting the impact of asthma exacerbation on perinatal outcomes, identified four studies that reported significant reductions in mean BW in women who had asthma exacerbation, three studies that reported no effect on BW, and two studies that reported no effect on preterm births. Four studies provided data suitable for meta-analyses. The quality score of the studies varied from low (one study) to intermediate (one study) to high (two studies). The risk of low birth weight (LBW) was significantly increased in women who had asthma exacerbation during pregnancy compared with women without asthma (three studies, 31,364 women, risk ratio (RR) 2.54, 95% confidence interval (CI) 1.52, 4.35), but there was no statistically significant increase in the risk among women with asthma who did not have exacerbations during pregnancy (three studies, 32,357 women, RR 1.12, 95% CI 0.89, 1.40). The risk of preterm births was not significantly increased in women who had asthma exacerbation during pregnancy compared with women without asthma (four studies, 31,648 women, RR 1.46, 95% CI 0.77, 2.78) or among women with asthma who did not have exacerbations during pregnancy (four studies, 33,211 women, RR 0.93, 95% CI 0.74, 1.17). The reviewers identified two studies of interventions in women with asthma that showed that inhaled corticosteroids are as effective as other medications and have low toxicity. No changes in the adverse perinatal outcomes were reported concerning medications.

Dombrowski[8] recently reviewed cohort studies of effects of asthma on pregnancy outcomes. Some of these studies analyzed the data on the basis of disease

severity. Five studies reported no effects of asthma on preterm births, one study reported increased risk of preterm births if the mother was taking an oral steroid, and one study reported a higher incidence of preterm births if maternal disease was severe. Three studies reported no effects of asthma on small for gestational age (SGA) status, and one study reported increased risk of SGA if the mother was symptomatic every day.

Maternal Renal Insufficiency

Biological plausibility

The exact mechanism by which renal failure affects pregnancy outcomes is unknown.

Epidemiological association

Evidence from systematic and other reviews

Ramin et al.,[9] in a review of effects of various degrees of renal insufficiency on pregnancy outcomes, found two studies that reported mild effects on perinatal outcomes for women with mild renal insufficiency (serum creatinine 0.9 to 1.4 mg/dl). However, among women with moderate to severe renal insufficiency, the preterm birth rate was 86% and the intrauterine growth-restricted (IUGR) rate was 43%.

Stratta et al.,[10] in a review, identified a direct relationship between the degree of renal insufficiency and IUGR. The incidence of IUGR was 16% in nephropathic women with normal renal function and 37% in women with advanced chronic renal failure. The incidence of preterm births was 19% in nephropathic women with normal renal function, 59% in women with advanced chronic renal failure, and 35% to 60% in women who had undergone a renal transplant.

Holley and Reddy,[11] in a review of studies of women on dialysis treatment, identified a pregnancy rate of between 1% and 7% and an infant survival rate of between 30% and 50%. The mean gestational age at birth was 32 weeks and the mean BW ranged from 1164 to 1542 g. Thus, most of these women gave birth to LBW infants.

Conclusions

Maternal medical conditions have an important role in the duration of pregnancy and fetal growth. Acute exacerbations of asthma and moderate to severe renal insufficiency may lead to preterm births or a LBW infant. Optimal management of medical conditions may reduce these outcomes; however, further research is needed.

Biological plausibility

The biological plausibility link between previous abortion and subsequent preterm births has not been established in animal models. Current theories include the following:

- Overt or covert infection following previous spontaneous abortion in the mother could lead to increased risk of preterm births.[12]
- Mechanical trauma to the cervix during an abortion can lead to increased risk of cervical incompetence.[13] Surgical procedures may increase the probability of faulty implantation and subsequent placenta previa and risk of preterm births.[14]
- Recent availability and use of a pharmacological approach instead of surgical procedures for abortion may have a different effect on the incidence of preterm/LBW births.

Epidemiological association

Evidence from systematic and other reviews

Thorp et al.,[15] in a review of 24 studies, found that in 12 that reported on the history of abortion and preterm births, the risk ratios ranged from 1.3 to 2.0. A dose-response relationship was observed in seven studies, with the risk increasing as the number of abortions increased. The remaining 12 studies reported no association between these two variables. In a majority of these studies, a history of abortion was obtained by maternal self-reporting. Stigma associated with abortion before legalization or social acceptance in respective countries could have resulted in underreporting of abortion.

Evidence from other study designs

The results of studies published after the review by Thorp et al.,[15] in which the primary aim was to identify an association between previous abortion and preterm/LBW births, are reported in Table 6.1.

Table 6.1: Studies of induced abortion and its impact on pregnancy outcomes

Study	Characteristics	Result
Ancel et al.[14]	Multicentre European study	For women who had previous induced abortions: increase in preterm births (AOR 1.27, 95% CI 1.11, 1.45 for >1 abortion) AOR 1.63, 95% CI 1.31, 2.03 for women with >2 previous induced abortions risk higher for very preterm births (OR 1.47) vs. moderate preterm births (OR 1.19)
Moreau et al.[16]	Cohort study in France	For women who had previous induced abortions, an increase in preterm births: AOR 1.3, 95% CI 1.0, 1.8 for 1 previous abortion AOR 1.5, 95% CI 1.1, 2.0 for >1 previous abortion AOR 2.6, 95% CI 1.1, 5.9 for >1 previous abortion AOR 1.7 (95% CI 1.2, 2.5) for preterm births between 22 and 27 weeks AOR 1.4 (95% CI 1.0, 1.9) for preterm births between 28 and 32 weeks AOR 1.4 (95% CI 0.9, 2.1) for preterm births between 33 and 34 weeks
Raatikainen et al.[17]	Cohort study from Finland	For women who had previous abortion: no increased risk of preterm births (AOR 1.13, 95% CI 0.94, 1.35 for 1 abortion and AOR 1.35, 95% CI 0.91, 2.02 for >1 abortion) no increased risk of LBW (AOR 1.03, 95% CI 0.83, 1.37 for 1 abortion, and AOR 1.26, 95% CI 0.79, 2.00 for >2 abortions)
El-Bastawissi et al.[18]	Re-analyses of national data from US	For women with history of 1 induced abortion: increased risk of preterm births (AOR 1.5, 95% CI 1.0, 2.3) but not with >2 abortions (AOR 1.2, 95% CI 0.7, 2.0) no difference in the risk of preterm births when analyzed according to the cause of preterm birth (medically induced; spontaneous preterm labour and birth; and preterm, prelabour rupture of the membranes)

AOR: adjusted odds ratio; CI: confidence interval; LBW: low birth weight; OR: odds ratio.

Conclusions

Epidemiological evidence suggests a probable increased risk of preterm births following an induced abortion; however, the results are not consistent among studies. The increased risk of preterm births following abortion is probably due to infection, mechanical damage during the procedure, and altered placentation at previously injured sites. Some data suggest a dose-response relationship. An association was not demonstrated in all studies. Recently, the practice of inducing abortion has changed from a surgical procedure to one involving the administration of misoprostol. This new practice may not involve trauma to the cervix. Future studies assessing the impact of this change are needed.

Pregnancy-Associated Conditions

Hypertension and diabetes are the two most common pregnancy-associated conditions in which fetal growth may be affected. Uteroplacental insufficiency and placental infarcts are frequently seen in mothers with pregnancy-induced hypertension. Other conditions that may affect fetal growth include maternal infections and thrombophilia.

Hypertension

Epidemiological association

Evidence from systematic and other reviews

Misra[19] reviewed epidemiological studies undertaken from 1931 onwards that reported the effects of pregnancy-induced hypertension on fetal growth. No definite relationship was observed. Several methodological problems in the studies were identified: (1) the definition of hypertension was not consistent between studies; (2) there were differences in the way fetal growth was assessed; and (3) most studies failed to adjust for covariates, in particular, smoking. Biological plausibility was not consistently reflected in the epidemiological studies and further research is needed.

Evidence from other study designs

Villar et al.[20] recently performed secondary analyses of data from 39,615 women enrolled in the World Health Organization Antenatal Care Trial. A total of 2.2% of pregnancies were complicated by pre-eclampsia, 7.0% by gestational hypertension, and 8.1% by unexplained IUGR. Several co-existing conditions were identified that influence the risk for pre-eclampsia. The risk for preterm births was higher in women with pre-eclampsia (adjusted odds ratio (AOR) 3.8, 95% confidence interval (CI) 3.3, 4.5) and for women with gestational hypertension (AOR 1.2, 95% CI 1.1, 1.4) compared with women without blood pressure problems.

Basso et al.[21] compared population-based longitudinal data from Norway for 1991 to 2003 with data for 1967 to 1978 and found an increase in the rate of preterm births in the later period (12.6% for 1967 to 1978 versus 21.1% for 1991 to 2003) among women with pre-eclampsia. This result suggests better surveillance, early induction of labour, and likely better management of pregnancies in the 1991 to 2003 period.

Intervention for hypertension during pregnancy

Abalos et al.,[22] in a systematic review, evaluated the efficacy of antihypertensive therapy for mild to moderate hypertension during pregnancy. The risk of

developing severe hypertension was significantly reduced in mothers in the group that received any antihypertensive medication during pregnancy compared with mothers in the group that received placebo or no medication. However, there was no reduction in the risk of preterm births (14 studies, 1992 women, RR 1.02, 95% CI 0.89, 1.16) or SGA births (19 studies, 1437 women, RR 1.04, 95% CI 0.84, 1.27). When one antihypertensive medication was compared with others, beta-blockers were identified as being better than methyldopa for reducing the risk of severe hypertension in the mother, but there was no difference in the risk of preterm births (eight studies, 524 women, RR 0.80, 95% CI 0.57, 1.12) or SGA births (six studies, 498 women, RR 0.88, 95% CI 0.54, 1.46). There was no difference in the risk of preterm births (one study, 36 women, RR 0.63, 95% CI 0.20, 1.91) or SGA births (one study, 36 women, RR 1.00, 95% CI 0.10, 9.96) between calcium channel blockers and other antihypertensive therapy.

Diabetes

Gestational diabetes usually results in large-for-date infants. If the mother has previous glucose intolerance, superimposed gestational diabetes can lead to fetal growth restriction. Bartha et al.[23] compared the standard maternal gestational diabetes screening tests performed between 24 and 28 weeks of gestation (cohort between May 1994 and February 1996; 189 women with a diagnosis of gestational diabetes) with early screening tests performed at the mother's first prenatal visit (March 1996 to March 1998; 235 women with a diagnosis of gestational diabetes) in their unit. The management of gestational diabetes remained the same in both groups. There were no differences between groups in associated complications. The incidence of preterm births was significantly reduced in the early screening group (5.5% versus 11.8% in the late screening group, $p = 0.03$). There was a statistically insignificant reduction in the risk of LBW in the early screening group (3.3% versus 8.3% in the late screening group, p = not statistically significant).

Infections

Maternal infection with rubella virus, cytomegalovirus, malaria, syphilis, varicella, herpes, *Listeria*, Epstein-Barr virus, and Chagas disease can cause fetal growth restriction.[1-6] After an initial phase of viremia, the organisms cause villitis in the placenta. The exact mechanisms by which the organisms affect fetal growth are not clear. The presence of rubella virus in the cell inhibits mitotic activity (cell division), deranges the chromosomal structure, and causes cell breakdown. Rubella virus also deranges the structure of the microvasculature and leads to impaired growth. Cytomegalovirus causes cell and focal tissue breakdown. Cell destruction and inhibition of cell division affect fetal growth.[3]

Thrombophilia

Maternal thrombophilic conditions (conditions associated with increased risk of development of arterial and venous thrombi) can affect the development of the placenta and lead to IUGR.[24] The exact impact on preterm/LBW births is unknown. Further research is needed.

Conclusions

Pre-eclampsia is associated with an increased risk of preterm/SGA/IUGR births. Over the years there has been a trend towards improvements in fetal survival in women with pre-eclampsia. However, this trend has led to an increase in preterm births. The role of different antihypertensive medications for reducing preterm/SGA/IUGR births is unclear. Other conditions have an important role in embryogenesis, cell differentiation, and cell growth. Optimal control of these conditions may result in better survival and growth of the fetus; however, strategies to achieve this goal are not well understood.

Uterine Factors

Structural abnormalities in the uterus are associated with a higher incidence of preterm births. Uterine anomalies account for 3% to 16% of preterm births. Unicornuate, bicornuate, and didelphic uterus can result in preterm labour in 18% to 80% of women with such abnormalities. Uterine leiomyomas have been associated with preterm labour as a result of bleeding or preterm, prelabour rupture of the membranes.[25]

Cervical incompetence may result in preterm labour and has several causes. In utero exposure of the fetus to diethylstilbestrol can cause structural abnormalities in the uterus and cervical incompetence. Diethylstilbestrol exposure has led to numerous abortions and preterm births, as observed over a 30-year period (1940 to 1971), and the drug is no longer used. Trauma following obstetric or gynecological procedures may also lead to cervical incompetence.[25] Induced abortions and use of non-pharmacological interventions to evacuate the uterus may cause damage to the neuromuscular architecture of the cervix and cause cervical incompetence. Uterine factors as a cause of growth restriction are mainly secondary to vascular phenomena and are considered in the following section.

Placental Factors

The placenta functions as a nutrient supplier and gas exchanger and both functions are necessary for maintaining proper fetal growth. BW has been shown to be related to placental size. A reduction in the placental blood flow leads to a reduction in the transfer of nutrients from the mother to the fetus and a reduction in the production of human chorionic gonadotropin from the placenta,

which is responsible for mobilization of the maternal nutrient stores. An ongoing deprivation of nutrients leads to thickening of the vascular membranes of the placenta and further reduction in blood flow. Reduced nutrient transfer and access to maternal stores, in turn, leads to IUGR. The placental causes of IUGR are:[5,6,25]

Abnormal cord insertion
Avascular villi
Chorioangioma
Chronic placental separation
Confined placental mosaicism
Diffuse fibrinosis
Fetal vessel thrombosis
Ischemic venous necrosis
Multiple infarcts
Reduced capillarization or terminal villous branching
Syncytial knots
Twins
Vasculitis
Villitis

Pharmacological Factors

The most common manifestation of drug administration to mothers is teratogenicity. The toxic effects of drugs can be due to their appetite-suppressant effects, direct effects on cell replication (heroin, methadone, alcohol, antimetabolites), or interference with the transport of amino acids (cocaine, alcohol).[25] Many malformation syndromes are associated with IUGR. The effect of pharmacological factors on BW may represent a part of a larger spectrum. The drugs associated with IUGR are:

Amphetamine
Antimetabolites
Bromides
Cocaine
Heroin
Hydantoin
Isotretinoin
Methadone
Methylmercury
Phencyclidine
Polychlorinated biphenyls
Propranolol
Steroids
Toluene
Trimethadione
Warfarin

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CHAPTER 7:

Pregnancy with Multiple Fetuses

Most Important Points

- The incidence of multiple births is increasing in most industrialized countries.
- Artificial reproductive techniques are contributing to this increase.
- More than 50% of twins are born preterm and nearly all higher-order pregnancies result in preterm birth.
- Multi-fetal pregnancy increases the risk of birth defects and disabilities.
- Controlling the use of fertility drugs and reducing the number of implanted embryos can prevent the rise in multiple births.
- Regulations are needed for the maximum number of embryos that may be transferred under in vitro fertilization programs and for the prescribing practices of clinics and physicians regarding ovulation-inducing agents.

In chapter 7 we review the outcomes of multi-fetal pregnancies achieved either with or without the assistance of artificial reproductive technology.

Since the birth of the first baby via in vitro fertilization (IVF) in 1978,[1] the number of infants born through assisted reproductive technologies (ARTs) has steadily increased. The success rate with these techniques has increased in the last decade[2] and contributes to the increased incidence of multiple pregnancies. This incidence varies worldwide and is influenced by such factors as the mother's age, parity, and racial background. Complications and risks for women and infants in twin pregnancies are well recognized and include preterm births, stillbirths, and neonatal morbidity and mortality.[3]

Millar et al.[4] reported on Canadian trends and patterns in multiple births from 1974 to 1990. A steady increase was observed in the number of twin births (from 905 to 1037 per 100,000 confinements in 1995) and triplet and higher-order births (from 8 to 22 per 100,000 confinements between 1974 and 1990). The increase was more pronounced in women over 30 years of age. The rate of preterm births among multiple births increased from 32.8% in 1974 to 45.8% in 1990.

The rising trend has continued and the latest figures indicate that the rate of multiple births in Canada was 2.7% in 2000 (excluding Ontario).[5] The rate of preterm births is higher in multiple births than it is in singleton births. In Canada (excluding Ontario) there were 4953 twin births (2556 preterm births: preterm birth rate 52/100 live births among twins) and 218 triplet or higher-order multiple births (209 preterm births: preterm birth rate 96/100 live births among

triplets) in 1997. The rise in multiple births is secondary to an increased use of ART.[5]

Biological plausibility

In multi-fetal pregnancies, preterm labour is probably initiated by stretching of the myometrium. Labour is often preceded by prelabour rupture of the membranes or maternal or fetal complications that justify interventions to expedite birth.

Epidemiological association

Evidence from reviews and other study designs

Are multiple gestation pregnancies at an increased risk of preterm/low birth weight/intrauterine growth-restricted births?

The two types of amnionicity in twin pregnancies, monoamniotic or diamniotic, are associated with different complications and outcomes. Monoamniotic twin pregnancies are of major concern. Allen et al.[11] performed a retrospective review of outcomes of antenatally diagnosed monoamniotic twin pregnancies in Toronto, Canada. In addition, the authors performed a systematic review of the literature on perinatal outcomes in monoamniotic twin pregnancies and compared them with those of the retrospective review. In the retrospective review, of the 25 prenatally diagnosed monoamniotic twin pregnancies, seven were affected by fetal anomalies and one fetus died at 29 weeks gestation. Most of the neonatal complications were secondary to immaturity. In the systematic review of the literature, 49 case reports of 88 antenatally diagnosed cases were identified. Fourteen pregnancies were affected by major congenital anomalies and 20 fetuses died after 24 weeks gestation. Neonatal complications varied widely and depended on gestational age at birth. The risk of intrauterine fetal death was 10% to 12%.

McDonald et al.[6] reported a 43% incidence of preterm births in spontaneously conceived twins.

Ananth et al.[7] examined trends in twin preterm births that followed prelabour rupture of the membranes, which was medically indicated and followed spontaneous onset of labour, in a retrospective cohort study of 1,172,405 twin live births and stillbirths in the United States between 1989 and 2000. Twin preterm births increased from 46.6% (1989 to 1990) to 56.7% (1999 to 2000) among whites and from 56.1% to 61.0% among blacks over the same two periods. Preterm births following prelabour rupture of the membranes did not change between the two periods among whites, but it declined by 7% among blacks. Medically indicated preterm births increased between the two periods by 50% (95% confidence interval (CI) 49, 52) among whites and by 33% (95% CI 29, 36) among blacks. Preterm births following spontaneous onset of labour increased

by 24% among whites, but remained unchanged among blacks between the two periods. Perinatal mortality among twin births declined by 41% (95% CI 38, 44) among whites and by 37% (95% CI 32, 42) among blacks between the two periods.

Cassell et al.[8] conducted a retrospective study based on prospectively collected data to determine the rate, origin, maternal and perinatal outcomes, and associated hospital costs of higher-order multiple births in Nova Scotia, Canada, over a 22-year period (1980 to 2001). There were 116,785 infants born, including 3448 twins, 99 triplets, and 16 quadruplets. Of the higher-order multiple gestations, 51.4% were conceived through infertility therapy. Triplets and quadruplets had significantly higher rates of preterm births (mean gestational age at birth for triplets and quadruplets was lower at 31.9 weeks (standard deviation (SD) 4.2) compared with singletons at 39.3 weeks (SD 2.2)), low birth weight (LBW) births (mean birth weight (BW) was lower at 1644 g (SD 701) compared with singletons at 3410 g (SD 620)), major anomalies (risk ratio (RR) 2.5, 95% CI 1.4, 4.7), neonatal intensive care unit admission (RR 5.7, 95% CI 5.5, 6.0), respiratory distress syndrome (RR 18.7, 95% CI 14.9, 23.4), intrauterine growth restriction (IUGR) (RR 3.9, 95% CI 2.5, 6.1), serious morbidity (RR 7.4, 95% CI 4.2, 13.0), 5-minute Apgar scores $\leq$3 (RR 10.3, 95% CI 5.0, 21.2), and neonatal death (RR 20.1, 95% CI 11.7, 34.5) compared with singletons. For most of these outcomes, the RR was higher for twins compared with singletons.

Multiple gestation pregnancies are at an increased risk of preterm/LBW/IUGR births.

Are multiple gestation pregnancies that result from IVF at an increased risk of preterm/LBW/IUGR births compared with spontaneously conceived multiple gestation pregnancies?

Tough et al.[2] reported on the IVF component of the rise in preterm births and LBW births in Alberta, Canada. In vitro fertilization accounted for 17.8% of the rise in LBW births and 10.5% of the rise in preterm births during the period 1994 to 1996. There was an increased risk of LBW births (RR 4.89, 95% CI 4.16, 5.74) and preterm births (RR 5.36, 95% CI 4.64, 6.18) for IVF births compared with non-IVF births.

Schieve et al.[9] compared the 42,463 infants born in the United States between 1996 and 1997 by ART with the remaining 3,389,098 infants born during that period. Among singletons born after 37 weeks' gestation, there was an increased risk of LBW births (RR 2.6, 95% CI 2.4, 2.7) in the ART group. The risk of multiple gestations following the use of ART was increased, but its use was not associated with further increase in the risk of LBW births in multiple births. The total percentage of infants born with ARTs was 0.6%, which constituted 3.5% of LBW infants born to mothers >20 years old in 1997.

McDonald et al.[11] systematically reviewed perinatal outcomes of IVF twins. Eleven case-control studies that involved 2303 IVF twins and 2326

spontaneously conceived twins were included in the meta-analysis. Compared with spontaneously conceived twins who were matched for maternal age, IVF twins who were additionally matched for maternal parity had an increased risk of preterm birth between 32 and 36 weeks of gestation (OR 1.48, 95% CI 1.05, 2.10) and an increased risk of preterm birth at <37 weeks' gestation (OR 1.57, 95% CI, 1.01, 2.44). There was no significant difference in the incidences of perinatal death, LBW infants (OR 1.13, 95% CI 0.85, 1.51), SGA infants (OR 0.92, 95% CI 0.62, 1.38), or congenital anomalies (OR 1.14, 95% CI 0.85, 1.52). There was no difference in BW (weighted mean difference -51 g, 95% CI -148, 45).

Multiple gestation pregnancies that result from IVF are at an increased risk of preterm/LBW/IUGR births compared with spontaneously conceived multiple gestation pregnancies.

Are singleton pregnancies that result from IVF at an increased risk of preterm/LBW/IUGR birth compared with spontaneously conceived singletons?

McDonald et al.[6] systematically reviewed perinatal outcomes of singleton pregnancies achieved by IVF. Compared with spontaneously conceived singletons, singletons conceived by IVF have increased rates of poor obstetrical outcomes, with an increase in perinatal mortality (OR 2.40, 95% CI 1.59, 3.63), preterm births at <33 weeks' gestation (OR 2.99, 95% CI 1.54, 5.80), preterm births (OR 1.93, 95% CI 1.36, 2.74), very low birth weight (VLBW) births (OR 3.78, 95% CI 4.29, 5.75), SGA births (OR 1.59, 95% CI 1.20, 2.11), and congenital malformations (OR 1.41, 95% CI 1.06, 1.88).

Pregnancy outcomes after ART were recently reviewed in a Society of Obstetricians and Gynaecologists of Canada guideline.[12] In Canada in 2002, of the 2201 births following ART, 68% were singleton births, 29% were twin births, and 3% were triplet and higher-order births. The outcomes in singleton pregnancies after superovulation-intrauterine insemination showed an increased risk of perinatal mortality (reported RR or OR 1.5 and 1.7), preterm births (reported RR or OR 1.3, 1.7, and 2.2), and LBW births (reported RR or OR 1.4, 1.5, and 3.2). The outcomes for singleton pregnancies after IVF compared with spontaneously conceived pregnancies (controlling for maternal age and in some studies parity) showed increased risk of preterm births (12.1 % versus 6.7%, RR or OR 1.8), LBW births (10.9% versus 5.3%, $p < 0.01$), and VLBW births (3.2% versus 1.1 %, $p < 0.01$). The outcomes of twin pregnancies after IVF compared with spontaneously conceived pregnancies (controlling for maternal age $\pm$ parity) did not show an increased risk for perinatal mortality (13.0% versus 12.0%, $p > 0.05$), preterm births (43.9% versus 41.5%, $p = 0.95$), LBW births (RR or OR 0.9, $p > 0.05$), or VLBW births (RR or OR 0.9, $p > 0.05$). The guideline recommended that *"to reduce the risk of multiple pregnancies associated with ART and to optimize pregnancy rates, national guidelines should be developed on the number of embryos replaced according to characteristics such as patient's age and grade of embryos."*

Singleton pregnancies that result from IVF are at an increased risk of preterm/LBW/IUGR births and congenital anomalies compared with spontaneously conceived singletons.

Interventions

Evidence from systematic reviews

Does fetal reduction in multi-fetal pregnancies decrease the risk of preterm/LBW/IUGR births?

Dodd and Crowther[3] systematically reviewed the effects of multi-fetal pregnancy reduction for women with triplet and higher-order multiple pregnancies on fetal loss, preterm births, and perinatal and infant mortality and morbidity. The rate of multiple pregnancies with ARTs correlates directly with the number of embryos or zygotes transferred: 17.9% of IVF pregnancies after transfer of two embryos, increasing to 24.1% after transfer of four embryos; 18.7% after transfer of two oocytes, increasing to 25.8% after transfer of three oocytes. The authors did not identify any randomized controlled trials (RCTs) that assessed multi-fetal pregnancy reduction. Seven prospective studies with prospective control groups were identified, three comparing pregnancy outcomes from multi-fetal pregnancy reduction with those from twin pregnancies (conceived spontaneously or after ARTs) and four comparing pregnancy outcomes from multi-fetal pregnancy reduction with those of triplet pregnancies managed expectantly.

For multi-fetal pregnancy reduction to twins compared with expectant management of twins, a total of 209 women from three studies were included in the meta-analyses (107 underwent multi-fetal reduction to twins and 102 conceived twins spontaneously or by ARTs). No statistically significant differences were noted between women having multi-fetal pregnancy reduction to twins and women with a twin pregnancy for pregnancy loss (two studies, RR 1.32, 95% CI 0.42, 4.16), birth at <34 weeks' gestation (one study, RR 0.20, 95% CI 0.01, 3.18), stillbirth (one study, RR 0.86, 95% CI 0.05, 13.48), or neonatal death (one study, RR 0.86, 95% CI 0.05, 13.45).

For multi-fetal pregnancy reduction to twins compared with expectant management of triplets, a total of 373 women from four identified studies were included in the meta-analyses (175 underwent multi-fetal pregnancy reduction to twins, and 198 with triplet pregnancies were managed expectantly). Women allocated to the intervention group were those who chose to proceed with multi-fetal pregnancy reduction. Women allocated to the control group (expectant management) were those who declined multi-fetal pregnancy reduction or who were not offered multi-fetal pregnancy reduction by the treating physician. Women who had multi-fetal pregnancy reduction, compared with women whose triplet pregnancy was managed expectantly, were less likely to have miscarriages (four studies, RR 0.44, 95% CI 0.24, 0.81), to give birth at <36 weeks' gestation (two studies, RR 0.36, 95% CI 0.22, 0.60), and to have VLBW infants (two

studies, RR 0.26, 95% CI 0.14, 0.45). Fewer neonatal deaths occurred in the group that had multi-fetal pregnancy reduction (four studies, RR 0.2, 95% CI 0.06, 0.64). There was no difference in the incidence of stillbirths between the two groups (two studies, RR 0.63, 95% CI 0.32, 1.27). There was no difference noted for preterm births at <32 weeks' gestation (two studies, RR 0.45, 95% CI 0.16, 1.28). The authors concluded from non-randomized studies of varying quality that for women with a triplet pregnancy, multi-fetal pregnancy reduction to twins, compared with expectant management, seems to be an effective treatment option. Reduction to twins reduces rates of pregnancy loss, antenatal complications, birth at <36 weeks' gestation, caesarean birth, low BW, and neonatal death. There are currently no RCTs providing information about maternal and infant outcomes for women with a triplet or higher-order multi-fetal pregnancy undergoing multi-fetal pregnancy reduction.

Fetal reduction in multi-fetal pregnancies decreases the risk of preterm/LBW/IUGR births.

Does single versus double or double versus higher-order embryo transfer decrease the risk of preterm/LBW/IUGR births?

Dare et al.[13] conducted a systematic review to determine whether single versus two or more embryos, or double versus three or more embryos, transferred to a woman at IVF maximizes the likelihood of pregnancy while minimizing adverse outcomes. Single embryo transfer was found to significantly decrease the incidence of clinical pregnancy (two studies, 197 women, RR 0.69, 95% CI 0.51, 0.93), multiple pregnancy (two studies, 197 women, RR 0.12, 95% CI 0.03, 0.48), and LBW (two studies, 197 women, RR 0.17, 95% CI 0.04, 0.79), but not preterm births (two studies, 197 women, RR 0.15, 95% CI 0.02, 1.25). In the cohort studies, for single embryo transfer compared with transfer of two or more embryos, the incidence of singleton pregnancies and live births was unchanged, and the incidence of multiple pregnancies (eight studies, 6702 women, RR 0.03, 95% CI 0.01, 0.09) and LBW births (one study, 367 women, RR 0.22, 95% CI 0.08, 0.57) was reduced. For double-embryo transfer compared with the transfer of three or more embryos (cohort studies), the rate of pregnancy (eight studies, 5559 women, RR 0.82, 0.71, 0.94), live births at term (six studies, 49,379 women, RR 0.82, 95% CI 0.71, 0.94), preterm births (one study, 797 women, RR 0.41, 95% CI 0.21, 0.79), and LBW births (one study, 797 women, RR 0.48, 95% CI 0.29, 0.79) was reduced. Transfer of one embryo does not alter the likelihood of singleton pregnancy or birth when compared with transfer of two or more embryos. The transfer of one or two embryos decreases the risk of multiple pregnancies, preterm/LBW births. However, large, well-designed randomized trials are needed.

Single versus double, or double versus higher-order, embryo transfer decreases the risk of preterm/LBW/IUGR births.

Conclusions

The incidence of multiple births is increasing in Canada and most industrialized countries. IVF is contributing to this increase. More than 50% of twins are born preterm and the preterm birth rate increases with an increasing number of fetuses. The infants are at increased risk of birth defects and disabilities.[14] Controlling the use of fertility drugs and reducing the number of implanted embryos can prevent the rise in multiple births. The Society of Obstetricians and Gynaecologists of Canada[12] has urged the development of national regulations for the maximum number of embryos that may be transferred in ART programs in Canada, as well as for the prescribing practices of the clinics and physicians who recommend ovulation-inducing agents.

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CHAPTER 8:

Race/Ethnicity and Psychosocial Factors/ Stress/Socioeconomic Factors

Main Summary Points

- The incidence of preterm/low birth weight births varies with race in population-based reports. Researchers propose the interplay of neuroendocrine, vascular, and immune alteration to explain these differences. Studies of various domains such as direct effect, impact of acculturation, differences in biracial couples, and aboriginal populations indicate an increased risk of preterm/low birth weight births in non-Caucasian populations.
- Despite the strength of evidence in epidemiological studies, biological mechanisms and strategies or interventions to reduce the "gap" are not fully established. Further research is needed to understand the mechanisms by which race/ethnicity/racism and associated stressors affect pregnancy outcomes differently in different populations, to explore ways to reduce racism in society, and to identify relevant modifiable factors.
- Stress, both acute and chronic, is implicated in preterm/low birth weight/small for gestational age births. Some low-quality studies on acute stress (including studies of man-made disasters) indicate an increased risk of preterm/low birth weight/small for gestational age births but other studies do not. The impact of chronic stressors on increasing the risk of preterm births is indicative, but the effect on low birth weight is not convincing. Maternal depression and adverse neighborhood conditions may be associated with preterm/low birth weight births.
- Observational studies, but not randomized controlled studies, have demonstrated beneficial effects of psychological support. Proper identification of women experiencing chronic stress during the prenatal period and provision of psychosocial support to those individuals may be justified.

In chapter 8 we review the effects of race, ethnicity, psychosocial and socioeconomic factors, and stress on pregnancy outcomes.

Race/ethnicity

The influence of race/ethnicity on pregnancy outcomes has been studied from various perspectives. The major factors associated with racial differences are unplanned pregnancies, nutritional deficiencies, access to prenatal and postnatal health care, socioeconomic status, and unhealthy behaviours.[1] We discuss the impact of racial/ethnic differences, acculturation, biracial couples, and aboriginal status on pregnancy outcomes in this section.

Biological plausibility

Racial disparity and adverse birth outcomes

The biological mechanisms underlying the effects of race on pregnancy outcomes are not completely understood, but researchers have suggested the interplay of stress and race/ethnicity. Racism (defined as racial prejudice and racial discrimination) can be perceived as a component of stress.

Four suggested categories of racism[2] that have negative consequences for an individual include: (1) individual racism (personal experience with unfair and biased treatment); (2) institutional criticism (differential access to services, opportunities, wealth, and purchasing power); (3) cultural racism (cultural norms of one race are considered superior to those of others); and (4) collective racism (organization or group seeks to restrict the rights of one race). Additionally, internalization, the development of feelings of inferiority, loss of control, and frustration that may be associated with racism has been shown to have negative health outcomes.[3]

Suggested biological mechanisms are as follows:

- The most commonly held hypothesis for the effect of racism on pregnancy outcome is via stress. Corticotropin-releasing hormone (CRH) is elevated in women who give birth preterm.[4,5] Acute experiences of racism have been shown to be associated with an increase in heart rate and blood pressure, indicating the release of stress hormones. Associated factors such as psychological disturbance, poor self-esteem, alcohol use, and abuse aggravate the impact of racism.
- Vascular reactivity, which can lead to vasoconstriction and reduced uterine blood flow and fetal hypoxia, has been shown to be elevated in African Americans when compared with European Americans.[6]
- African American women exhibit increased risk of urogenital infections.[7]
- African American women have a higher vaginal pH compared with women from other origins and a low concentration of lactobacilli and thus have a high incidence of bacterial vaginosis, which is associated with preterm births.[8]
- An alteration of vitamin D metabolism in black women may result in changes in calcium homeostasis and higher incidences of hypertension, intrauterine growth restriction (IUGR), and preterm births compared with other women.[9]

Role of acculturation

Another phenomenon that has been reported and observed in the United States over the years that may affect birth outcomes is acculturation. Beck[10] defines acculturation as *"…culture change that is initiated by the conjunction of two or more autonomous cultural systems."* This change includes adoption of unhealthy behaviours such as tobacco use, alcohol intake, and illicit drug use. The frequency of these behaviours is higher in women who have moved to the United States than

it is in women who remain in their native countries. However, it is also reported that healthier people are more mobile and are able to migrate and generally have better health outcomes compared with women who are unable to relocate, a concept termed "healthy migrant theory."[11]

Epidemiological association

Impact of racism

Evidence from systematic and other reviews

No systematic review of the differences in the risk of preterm/low birth weight (LBW) births because of racism was identified. Giscombe and Lobel[12] reviewed five studies that reported direct effects of racism in adverse pregnancy outcomes. Four studies reported associations between racism and adverse pregnancy outcomes. Collins et al.[13] reported that the adjusted odds ratio (AOR) for very low birth weight (VLBW) was 3.3 (95% confidence interval (CI) 0.9, 11.3) for an African American woman. Lespinasse et al.[14] reported an AOR for VLBW of 1.9 (95% CI 1.2, 3.0) when a woman was exposed to any domain of racism and an AOR for VLBW of 2.7 (95% CI 1.3, 5.4) when a woman was exposed to more than two domains of racism. Rosenberg et al.[15] reported an AOR for preterm births of 1.3 when a woman had unfair treatment at her job and an AOR of 1.4 when a woman reported that people were acting afraid of her. Dole et al.[16,17] reported an AOR of 1.4 (95% CI 1.0, 2.0) when a woman was exposed to higher racial discrimination. One study,[18] which used interview-based reporting, indicated no association between racism and stress and birth weight (BW) or gestational age.

Hogue and Bremner,[19] in their narrative review (including four of the studies mentioned earlier), indicated that although the evidence of a direct link is not concrete, the lessons learned from these reports and the reports of other adverse health outcomes associated with racism are enough to warrant further research into the cause of adverse outcomes and the identification of appropriate interventions.

Evidence from other study designs

One study was identified that was not reviewed by Giscombe and Lobel.[12] Dubay et al.[20] compared one cohort from 1980 to 1986 to a second cohort from 1987 to 1993 and found that the percentage of late initiation of prenatal care was reduced by 6.0% to 7.8% in the recent time period. The incidence of LBW infants in white women was also reduced by 0.26% to 0.37% in the later period. However, there was no difference in the incidence of LBW infants in African American women over the two periods, suggesting a widening of the gap between the two races.

Most of our knowledge regarding the impact of race on pregnancy outcomes comes from vital statistics reports of the United States (Figure 8.1).

Figure 8.1: Rate of preterm births among singletons by race and Hispanic origin in the US

(Reproduced from a report by the National Center for Health Statistics, Volume 52, Issue 10, 2003, Centers for Disease Control and Prevention)

	2002	2001	1995	1990[1]
Total[2]		Percent		
Less than 32 weeks	1.57	1.57	1.61	1.69
32-36 weeks	8.87	8.81	8.21	8.01
Total, less than 37 weeks	10.44	10.38	9.82	9.70
Mean gestational age (standard deviation)	38.8(2.5)	38.8(2.5)	39.0(2.5)	39.2(2.6)
Non-Hispanic white				
Less than 32 weeks	1.14	1.15	1.13	1.11
32-36 weeks	7.92	7.83	6.99	6.43
Total, less than 37 weeks	9.07	8.98	8.12	7.54
Mean gestational age (standard deviation)	38.9(2.3)	38.9(2.3)	39.2(2.3)	39.4(2.4)
Non-Hispanic black				
Less than 32 weeks	3.50	3.52	3.83	4.22
32-36 weeks	12.48	12.49	12.70	13.63
Total, less than 37 weeks	15.98	16.01	16.53	17.85
Mean gestational age (standard deviation)	38.3(3.1)	38.3(3.1)	38.4(3.2)	38.5(3.4)
Hispanic[3]				
Less than 32 weeks	1.48	1.45	1.48	1.52
32-36 weeks	9.14	9.04	8.64	8.77
Total, less than 37 weeks	10.63	10.49	10.12	10.29
Mean gestational age (standard deviation)	38.9(2.5)	38.9(2.4)	39.0(2.5)	39.1(2.6)

[1]Data for 1990 by race and Hispanic origin exclude data for New Hampshire and Oklahoma, which did not require reporting of Hispanic origin of mother.

[2]Includes births to races not shown.

[3]Includes persons of Hispanic origin of any race.

NOTE: Race categories are consistent with the 1977 Office of Management and Budget guidelines; see "Technical Notes."

Impact of acculturation

Evidence from systematic and other reviews

The topic of acculturation and its impact on birth outcomes, breastfeeding, and postnatal depression for Mexican mothers was reviewed by Beck.[10] Eight studies reporting the effects of acculturation on birth outcomes were identified. Acculturation was assessed variably in these studies, with most studies using proxy variables such as the mother's birthplace, preferred language, and length of stay in the United States. Results were inconsistent not only between studies,

but also within studies. Seven studies, however, reported that a higher level of acculturation was associated with lower BW.

No review of the impact of acculturation in the African American population was identified.

Evidence from other study designs:

The results from recent studies on the impact of acculturation are summarized in Table 8.1.

Table 8.1: Studies of the impact of acculturation on pregnancy outcomes

Study	Characteristic	Results
Kramer et al.[21]	Country-wide US dataset	Ethnic-specific SGA rates for US-born blacks (AHR 1.05, 95% CI 1.04, 1.06) and foreign-born blacks (AHR 1.09, 95% CI 1.07, 1.11) were higher compared with those of whites Neonatal mortality rates for US-born blacks (AHR 2.05, 95% CI 1.99, 2.11) and foreign-born blacks (AHR 1.52, 95% CI 1.40, 1.65) were higher when compared with those of whites
Wingate and Alexander[11]	Birth/infant death cohort from US	For non-migrant local mothers, foreign-born mothers who moved from outside the region, mothers who moved within the region, and mothers who moved within the state, respectively: LBW rates were 4.5%, 5.5%, 5.6%, and 5.8% preterm birth rates were 9.2%, 10.3%, 10.1%, and 10.5% SGA rates were 8.4%, 9.0%, 9.4%, and 9.5%
Acevedo-Garcia et al.[22]	Population-wide US dataset	Reduced likelihood of LBW births among foreign-born women (AOR 0.85, 95% CI 0.83, 0.87) compared with US-born women: black women (OR 0.75, 95% CI 0.72, 0.78) Hispanic women (OR 0.81, 95% CI 0.78, 0.84) white women (OR 0.99, 95% CI 0.96, 1.03) Asian women (OR 1.24, 95% CI 1.13, 1.36)
Fuentes-Afflick et al.[23]	Population-based sample	Foreign-born Latina women had a lower risk of giving birth to moderately LBW infants (AOR 0.91, 95% CI 0.86, 0.96) Foreign-born Asian women had less favourable characteristics than US-born Asian women did, but there was no increased risk of either VLBW or moderately LBW neonates Foreign-born black women had more favourable characteristics than US-born black women did; however, there was no difference in the risk of VLBW or moderately LBW neonates
Cabral et al.[24]	Cohort study	Foreign-born African American women were less likely to give birth preterm (OR 0.46, 95% CI 0.22, 0.94) and to give birth to an infant with LBW (OR 0.59, 95% CI 0.33, 1.03) than were US-born African American women
Shiono et al.[25]	Population-based cohort	The mean BW for African American infants: 3231 g; Chinese infants: 3272 g; Dominican infants: 3484 g; Mexican infants: 3431 g, Puerto Rican infants: 3341 g; and white infants: 3503 g ($p < 0.001$)

AHR: adjusted hazard ratio; AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; LBW: low birth weight; OR: odds ratio; RR: risk ratio; SGA: small for gestational age; VLBW: very low birth weight

Impact of biracial couples on pregnancy outcomes

With an increasing immigrant population, the number of interracial relationships and children born from such relationships has increased over the years from 3.3 per 1000 in 1968 to 17.7 per 1000 in 1996.[26]

Evidence from systematic and other reviews

No systematic review on this topic was identified.

Evidence from other study designs

Getahun et al.[27] analyzed linked birth and infant death files (1995 to 2001) from the United States to identify perinatal outcomes among interracial couples. Compared with infants born to families in which both parents were white, the adjusted risk ratio (RR) for an infant born to families consisting of mother white-father black, mother black-father white, and mother black-father black for preterm births <32 weeks was 1.34 (95% CI 1.31, 1.38), 2.02 (95% CI 1.94, 2.10), and 2.70 (95% CI 2.68, 2.73), respectively; for preterm births <34 weeks, it was 1.25 (95% CI 1.23, 1.28), 1.79 (95% CI 1.74, 1.85), and 2.32 (95% CI 2.30, 2.34), respectively; and for small for gestational age (SGA) (<5th centile), it was 1.11 (95% CI 1.09, 1.13), 1.51 (95% CI 1.47, 1.55), and 1.98 (95% CI 1.97, 1.99), respectively.

Collins and David[28] examined the impact of biracial couples on adverse outcomes from census data from Illinois, United States. The risk of LBW was increased among black mother-white father parents (AOR 1.5, 95% CI 1.0, 2.1), but not among white mother-black father parents (crude OR 1.1, 95% CI 0.6, 2.2) compared with white parents. The risk of preterm births was increased among black mother-white father parents (crude OR 1.6, 95% CI 1.2, 2.2), but not for white mother-black father parents (crude OR 1.1, 95% CI 0.9, 1.5) compared with white parents. The risk of SGA births was increased among black mother-white father (crude OR 1.9, 95% CI 1.1, 3.3) and white mother-black father parents (crude OR 1.8, 95% CI 1.1, 2.8) compared with white parents.

Impact of aboriginal status and pregnancy outcomes

Disparities in health outcomes have been identified between aboriginal and non-aboriginal populations.

Evidence from systematic and other reviews

No systematic review on this topic was identified.

Evidence from other study designs

The results from studies on the impact of aboriginal status are summarized in Table 8.2.

Table 8.2: Impact of aboriginal status on pregnancy outcomes

Study	Characteristics	Results
Heaman et al.[29]	Cohort study	Incidence of preterm births was 7.7% among the aboriginal population compared with 6.4% in the non-aboriginal population Risk factors were inadequate prenatal care, poor weight gain during pregnancy, and high levels of perceived stress Lack of adequate prenatal care was secondary to lack of transportation and insensitivity of health care to cultural values of the community Young maternal age was protective in this population, probably because young mothers without a partner receive extensive support from other family members and such a pregnancy is acceptable in this community
Heaman and Chalmers[30]	Secondary analysis of cohort study	High number of aboriginal women smoked during pregnancy (61% vs. 26% of non-aboriginal women)
Luo et al[31]	Population sample	The risk of preterm births was increased in Inuit women (AOR 1.49, 95% CI 1.25, 1.78) but the risk of SGA births was reduced (AOR 0.39, 95 % CI 0.31, 0.49) compared to other ethnic women North American Indian women had significantly lower risk of SGA (AOR 0.27, 95% CI 0.24, 0.31) and LBW (AOR 0.42, 95% CI 0.36, 0.49) births compared to other ethnic women Higher levels of family responsibilities and much higher prevalence of smoking and alcohol abuse were suggested as reasons for higher preterm birth rates
Edouard et al.[32]	Population-based sample	Overall incidence of LBW was 6.5% in North American Indian women compared with 5.2% in the rest of the population LBW incidence was lower among North American Indian women <20 years of age (4.7% vs. 5.7% in the rest of population), but higher among North American Indian women 25 to 29 years of age (8.5% vs. 4.9%), 30 to 34 years of age (8.4% vs. 5.3%), and >35 years of age (8.1% vs. 6.4%)

AOR: adjusted odds ratio; CI: confidence interval; LBW: low birth weight; SGA: small for gestational age

Conclusions

The impact of race/ethnicity on birth outcomes has been studied from various perspectives (direct, acculturation, biracial couples, and aboriginal population). The majority of the studies suggest an effect of racism on adverse pregnancy outcomes. There is a 30% higher risk of birth of an LBW infant for an African American woman with an unplanned pregnancy compared with an African American woman with a wanted or planned pregnancy. Insufficient or inadequate prenatal care could be an important factor for this population of African American women. Chronic stressors from a long history of exposure to discrimination may lead to an accumulation of disadvantages.[1] Despite the strength of evidence in epidemiological studies, biological mechanisms

and strategies or interventions to reduce the "gap" are not fully established. Discrepancies in the outcomes and their biological rationale have been the focus of many studies. Researchers have proposed the interplay of neuroendocrine, vascular, and immune alteration to explain these differences. Further research is needed to understand the mechanisms by which race/ethnicity/racism and associated stressors affect pregnancy outcomes differently in different populations, to explore ways to reduce racism in each society, and to identify relevant modifiable factors.

Psychosocial Factors/Socioeconomic Factors/ Stress

Social and racial differences and their impact on pregnancy outcomes are among the most extensively studied determinants.[33] Despite years of investigation, neither the exact mechanism nor the interventions to alleviate the adverse impact are known. Disadvantaged people are exposed to long-standing psychological stress and economic constraints[34] that in turn lead to unhealthy lifestyles. Limited coping resources compound the situation. An intergenerational effect of being born in poverty has been described.[35]

Biological plausibility

The exact mechanism of how stress leads to the onset of preterm labour is not known. However, there is growing evidence of an interaction or interplay of neuroendocrine and immunological processes in the initiation of a cascade of adverse pregnancy and neonatal outcomes.[5]

Neuroendocrine mechanisms

- Chronic stressors increase the concentration of glucocorticoids and catecholamines in the mother.[36] The release of CRH from the placenta because of maternal stress increases the production of prostanoids, which are implicated in the onset of labour.
- Mothers with onset of preterm labour in the absence of any known triggering factors had higher levels of plasma CRH compared with mothers not in preterm labour or with mothers in preterm labour secondary to infection.[5]
- CRH release was observed from cultured placental tissue exposed to major biochemical substances that are released in response to stress.
- Catecholamines can reduce placental blood flow.[36]
- Researchers have suggested that a disruption of the hypothalamic-pituitary-adrenal axis may trigger the onset of preterm labour.[4,5,37]

Immunological/infection-induced changes

- Animal experiments suggest that stress hormones released because of chronic stress lead to immunosuppression[5] and alteration of both cellular and humoral immunity. The altered immune responses make the host susceptible to infection, which is a known risk factor in causing preterm labour.[38]
- Wadhwa et al.,[5] in a review, identified one human study of reduction in lymphocyte activity in mothers exposed to chronic stress.

Interaction

- Romero et al.[39] suggested a systemic response to infection in the fetus, a response that they named the fetal inflammatory response syndrome. It is triggered by fetal stress, involving activation of endocrine, immunological, and hemostatic systems, with release of inflammatory cytokines, cortisol, and enzymes into the circulation. Preterm, prelabour rupture of the membranes, and preterm labour may result from this cascade of events.

Epidemiological association

A number of epidemiological studies have reported the impact of stressors on pregnancy outcomes. However, there are methodological problems with these studies. We address this vast topic under separate headings, but the contributors to stress in pregnancy are interrelated and linked to other topics.

1. Psychosocial factors
2. Socioeconomic factors
3. Acute stress

a. Terrorism
b. Natural disasters

4. Chronic stress
5. Attempted suicide
6. Homelessness
7. Neighbourhood conditions

1. Psychosocial factors

Evidence from systematic and other reviews

Paarlberg et al.[40] reviewed the studies published up to 1995 on the impact of psychosocial factors on LBW and preterm births. Nine of the reviewed studies reported a negative impact (reduction in BW) of maternal stress and high workload, whereas six studies reported no effect. Marked differences in the methodology of the studies precluded a combined estimate. The authors' overall impression was of an association between maternal stressors and BW. Ten studies reported an increased risk of preterm birth following stress and three studies reported no effect. According to the authors, the evidence supporting the role of

stress in triggering preterm births was more conclusive than the evidence for its role in LBW births.

No additional review on the topic was identified.

Evidence from other study designs

Results from individual studies of psychosocial factors are represented in Table 8.3.

Table 8.3: Role of psychosocial factors in pregnancy outcomes

Study	Characteristic	Results
Reichman and Teitler[41]	Cohort study Comprehensive Prenatal Program from New Jersey, US	Smoking, drinking, and substance use during pregnancy had very strong adverse effects on outcomes, even after controlling for other psychosocial, social, and demographic factors. Psychosocial measures other than these three risky behaviours did not have significant effects on BW.
Ahluwalia et al.[42]	Cohort study Assessed factors such as tobacco use, alcohol use, weight gain during pregnancy, prenatal care, abuse, unwanted pregnancy, partner-associated stress, traumatic stress, financial stress, and emotional stress	AOR for giving birth to an SGA infant: 1.29 (95% CI 0.69, 2.43) for 1 risk factor 1.86 (95% CI 1.00, 3.44) for 2 risk factors 1.67 (95% CI 0.90, 3.10) for 3 risk factors 2.06 (95% CI 1.10, 3.89) for 4 risk factors 3.53 (95% CI 1.71, 7.30) for 5 risk factors 3.82 (95% CI 1.97, 7.41) for 6 risk factors
Dayan et al.[43]	Prospective cohort study Role of prenatal depression and anxiety	Risk of spontaneous preterm births: in women who scored high on depression scores (AOR 3.3, 95% CI 1.2, 9.2) with 5-point increases in State Anxiety Score (AOR 0.87, 95% CI 0.70, 1.08) or Trait Anxiety Score (AOR 0.97, 95% CI 0.73, 1.30)

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; SGA: small for gestational age

2. Socioeconomic factors

Evidence from systematic and other reviews

Kramer et al [44] reviewed published studies of the impact of socioeconomic status on pregnancy outcomes between 1985 and 2000. Increased incidences of short stature; low pre-pregnancy body mass index; reduced weight gain during pregnancy; reduced intake of nutrients; increased tobacco, alcohol, coffee, and illicit drug use; stressful work environment; increased risk of unwanted pregnancy; reduced prenatal care; increased infections; abuse; depression; and reduced levels of support were found among women from poor socioeconomic backgrounds. The authors proposed an interaction between these factors and concluded that

the important factors affecting fetal growth from a public health perspective were maternal short stature, smoking, and reduced weight gain during pregnancy in all women. Use of alcohol and illicit drugs, work-related hazards, and increased physical activity were different between the high and low socioeconomic groups. The differences between high and low socioeconomic groups need further research. Important factors identified for preterm birth were genitourinary tract infection and cigarette smoking. Work-related hazards, physical activity, and use of cocaine contribute to preterm births to a lesser extent.

Evidence from other study designs

Wilkins et al.[45] reported that in Canada the preterm birth rate was 5.7% and the IUGR birth rate was 8.0% for women in the first income quintile compared with a preterm birth rate of 7.4% and an IUGR birth rate of 12.1% for women in the fifth quintile (lowest income group).

In 1997, the singleton LBW rate in Toronto was 80% higher in the lowest income areas (6.5%) compared with the highest income areas (3.6%). If the LBW rates in the two lowest income quintiles could be reduced to 5.3%, there would be approximately 100 fewer LBW births each year.[46]

Moutquin[46] listed the following socioeconomic factors as being associated with preterm births: social class (assessed by earnings and education), working conditions (professional status, ergonomic environment, working hours), physical and traveling activities, daily life activities, lifestyle, family status, and psychosocial state as related to past and current pregnancy history together with current stress factors. The author quoted a case-control study conducted in Quebec City of 101 women in preterm labour and 202 pregnancies matched for parity and gestational age. Among the seven identified risk factors, a stress score of > 5 was associated with significantly increased risk of preterm births (OR 2.6, 95% CI 1.2, 5.5). The most stressful events were related to family illness, mortality within the close family (OR 4.8, 95% CI 2.1, 11.5), problems with own children (OR 3.3, 95% CI 1.1, 10.5), family disruption, violence, or financial distress.

3. Acute stress

Evidence from systematic and other reviews

Hoffman and Hatch[36] reviewed the studies published between 1984 and 1996 on the impact of acute life events on outcomes of pregnancy. The authors identified 12 studies that reported the effects of acute stress on fetal growth. Only three studies reported an increased risk of LBW (results report the unadjusted OR 1.5 in one study, a 55 g reduction in BW in the second study, and an explanation of 5% of the variance in the third study). The remaining nine studies, including a large prospective study, reported no effect of stress on BW. The effect of acute stress on gestational length was assessed in 11 studies. Only one case-control study reported an increased risk of preterm births (unadjusted OR of 3.2).

What constitutes an acute stressful event in a person's life could vary from one person to another. On a wide-scale population base, the effects of acute stress are studied following natural or man-made disasters.

3.a. Terrorism

The terrorist attack on the World Trade Center on September 11, 2001 was a traumatic (stressful) event that affected people around the world. Its impact on pregnancy outcomes has been reported in a few studies.

Biological Plausibility

The mechanisms for the effects on pregnancy outcomes of the World Trade Center attack include effects of stress (on local and distant populations) and effects of chemicals released (on the local population).

Stress and chemical mechanisms:

- Acute stress leading to the release of catecholamines can have effects on pregnancy outcomes.
- A toxic atmospheric plume was released that contained soot, benzene, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, polychlorinated furans and dioxins, heavy metals, pulverized glass and cement, asbestos, lead, and alkaline particulates.[48,49]
- According to Landrigan et al.,[48] particulate levels in the air were highest immediately after the attack and decreased sharply with increasing distance from the World Trade Center. The pH of the dust was alkaline (pH 9.0 to 11.0).
- Landrigan et al.[48] postulated maternal exposure to PAHs and particulates to be the cause of SGA status, whereas Lederman et al.[50] proposed an impact of pollutants, stress, or both.

Epidemiological association

Evidence from systematic and other reviews

No systematic review on the topic was identified.

Evidence from other study designs

Studies reporting the impact of the World Trade Center attack on pregnancy outcomes are outlined in Table 8.4.

Table 8.4: Pregnancy outcomes following the World Trade Center disaster

Study	Characteristics	Results
Studies reporting outcomes following World Trade Center attack[48-53]	Cohort study of 182 women inside or near the World Trade Center	A 2-fold increase in SGA births; decreases in BW, birth length, head circumference, and duration of gestation Presence of PAHs containing DNA adducts in umbilical cord blood in combination with in utero exposure to environmental tobacco smoke resulted in an average 276 g (8 %) reduction in BW (p = 0.03) and a 1.3 cm (3%) reduction in head circumference (p = 0.04)
Rich-Edwards et al.[54]	Cohort study of pregnant women living in the Boston area on September 11, 2001	Women who were pregnant on September 11, 2001, had a lower risk of preterm births than did women who gave birth before that date (OR 0.60, 95% CI 0.36, 0.98)
Smits et al.[55]	Matched case-control study conducted in the Netherlands	BWs of neonates who were in utero during the World Trade Center attacks compared with neonates who were in utero exactly 1 year later were 48 g lower (95% CI -14, -83 g)

BW: birth weight; CI: confidence interval; OR: odds ratio; PAH: polycyclic aromatic hydrocarbon; SGA: small for gestational age; DNA: deoxyribonucleic acid

3.b. Natural disasters: earthquakes and an ice storm

Evidence from other study designs

The studies assessing the impact of natural disasters on pregnancy outcomes are described in Table 8.5.

Table 8.5: Studies assessing the impact of natural disasters on pregnancy outcomes

Study	Characteristic	Results
Chang et al.[56]	171 pregnant women living close to the epicentre 6 months after the Taiwan 921 earthquake	115 pregnancies with known perinatal outcomes: the incidence of LBW was 7.8% a maternal history of abdominal injury, spousal casualty, and instability in living conditions was significantly correlated with LBW spousal casualty was the only significant factor that predicted LBW
Weissman et al.[57]	Earthquake in Haifa, Israel	Between 1971 and 1984, there were five occurrences of increased seismic activity: a significant increase in birth rate was noted during the 48 hours following an earthquake on all occasions in 2 of the 5 events, a significant increase in preterm birth rates was noted (p < 0.05)
Fukuda et al.[58]	Kobe earthquake	Decline in the male-to-female ratio at birth (0.501) compared with an expected value of 0.516 (p = 0.04, 1-tailed)
Laplante et al.[59]	Ice storm in Quebec, Canada, in January 1998	Toddlers born to mothers experiencing stress during pregnancy had lower general intellectual and language skill abilities

LBW: low birth weight

4. Chronic stress

Evidence from systematic and other reviews

In addition to their review of studies on acute life events, Hoffman and Hatch[36] reviewed studies published between 1984 and 1996 on the impact of chronic stressors on outcomes of pregnancy. The authors examined the effects of chronic stress on pregnancy outcomes in seven studies. In three of these studies, there was an increased risk of preterm/LBW/IUGR/SGA births (three-fold increase in the risk of preterm births in one study, reduction in BW of 227 g in the second, and an unadjusted OR of 2.4 for poor family functioning in the third). These studies did not include work-related stress. The authors concluded that chronic stress could be an etiological factor that affects fetal growth more than it does preterm birth. Depressive symptoms during pregnancy were associated with an increased risk of preterm births in one study. Further studies are needed to assess the impact of maternal depression on pregnancy outcomes.

Evidence from other study designs

Geva et al.[60] studied the effects of prenatal diagnosis and management of IUGR on developmental outcome and maternal coping by using a cross-sectional design. They tested the effects of the timing of the diagnosis (prenatal/perinatal) and of pregnancy management (induction of labour/conservative management at home and diagnosed at birth) on maternal stress 6 years after the mother gave birth. At that time, 49% of the variance in maternal stress could be attributed to the child's presenting behaviour and to pregnancy management of the IUGR condition. Mothers who received conservative management reported being more stressed by their child's poor emotional adjustment ($p < 0.01$) and distractibility ($p < 0.29$) and having more difficulty in accepting their child ($p < 0.01$). The authors concluded that prenatal psychological consultation to better handle stress for parents whose fetus is diagnosed with IUGR is recommended, particularly when pregnancy is managed conservatively and familial and educational resources are low.

The effect of other causes of chronic stress, such as work-related stress, is discussed in detail in chapter 11 under Occupational Conditions.

5. Attempted suicide

Evidence from systematic and other reviews

No review on this topic was identified.

Evidence from other study designs

Gandhi et al [61] retrospectively analyzed the association between attempted suicide during pregnancy and pregnancy outcomes. Between 1991 and 1999,

there were 2132 births (0.4 per 1000 pregnancies) that were complicated by attempted suicide during pregnancy. Pregnant women who attempted suicide were much more likely to be substance abusers (OR 14.2, 95% CI 12.6, 16.0). Women who attempted suicide had an increased risk of preterm labour (OR 1.3, 95% CI 1.1, 1.5), LBW births (OR 1.3, 95% CI 1.1, 1.4), and respiratory distress syndrome in their infants (1.4, 95% CI 1.1, 1.9) compared with women who did not attempt suicide. There was a non-significant increase in preterm births (OR 1.1, 95% CI 1.0, 1.3) in women who attempted suicide.

6. Homelessness

Evidence from systematic and other reviews

No review on this topic was identified.

Evidence from other study designs

Stein et al.[62] assessed the effect of homelessness on pregnancy outcomes. Homelessness is a major stressor in a woman's life. Homeless women are more likely to have unwanted pregnancy, poor antenatal care, substance abuse, stress of day-to-day survival, poor diet, and increased chance of infection. The incidence of preterm births among homeless women was 19% compared with the national average of 10%, and LBW was 17% compared with the national average of 6%. Among homeless women, African American women were at higher risk of adverse outcomes compared with white women.

7. Adverse neighbourhood conditions

In the United States, several researchers have addressed the influence of social context on preterm births among blacks, whites, and Hispanics. Research has included measures of neighbourhood disadvantage and cumulative exposure to state-level income inequality, controlling for individual-level risk factors.[63,64] These and other studies have clearly shown that neighbourhood-level factors are significantly associated with the infant's BW.[65] In some neighbourhoods, a better socioeconomic context may, for minority women, be countered by the adverse effects of racism or racial stigma.[66]

Evidence from systematic and other reviews

No review on this topic was identified.

Evidence from other study designs

Studies that assessed the impact of neighbourhood conditions on pregnancy outcomes are summarized in Table 8.6.

Table 8.6: Studies of the impact of neighbourhood conditions on pregnancy outcomes

Study	Characteristics	Results
Harding[67]	Cohort study	Growing up in a high-poverty neighbourhood doubled the odds of high school dropout and teenage pregnancy
Morenoff[68]	Multilevel spatial analysis of BW for 101,662 live births within 342 Chicago neighbourhoods	Mechanisms related to stress and adaptation (violent crime, reciprocal exchange, and participation in local voluntary associations) are the most robust neighbourhood-level predictors of BW
O'Campo et al.[69]	Cohort study	Macro-level factors had both direct associations and interactions with LBW births All individual risk factors showed interaction with macro-level variables Individual-level risk factors for LBW behaved differently depending on the characteristics of the residence neighbourhood Women living in high-risk neighbourhoods benefited less from prenatal care than did women living in lower risk neighbourhoods
Luo et al.[70]	Population-wide data	Women in the lowest income quintile were significantly more likely to give birth to a preterm infant (AOR 1.14, 95% CI 1.10, 1.17), a SGA infant (AOR 1.18, 95% CI 1.15, 1.21), or a stillborn infant (AOR 1.30, 95% CI 1.13, 1.48) compared with women in the highest quintile Mothers who had not completed high school were significantly more likely to have a preterm birth (AOR 1.48, 95% CI 1.44, 1.52), a SGA birth (AOR 1.86, 95% CI 1.82, 1.91), or a stillbirth (AOR 1.54, 95% CI 1.36, 1.74) compared with mothers who had completed community college or at least some years of university

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; LBW: low birth weight; SGA: small for gestational age

Conclusions

Considerable advances have been made in understanding the mechanism of stress in adverse pregnancy outcomes. However, the exact triggering mechanism is still unclear. Available evidence indicates a possible role for acute stress on preterm/LBW/SGA births in some studies but not in others; however, the latter studies were not of high quality. The impact of acute stress following natural or man-made disasters indicates the possibility of a direct effect. The impact of chronic stressors on increasing the risk of preterm births is suggestive, but the effect on LBW is not convincing. Emerging evidence indicates that maternal depression could play a key role. More work is needed to identify the differential effects on pregnancy outcomes of socioeconomic disparities within the society. For neighbourhood studies, multilevel modeling is an important tool that allows simultaneous study of macro- and individual-level risk factors and could have a larger role in the formulation of public health policies. Future research is needed to delineate the complexities of the stress triggers of preterm births.

Interventions for Psychosocial Factors

Various measures have been used to alleviate the impact of adverse psychosocial circumstances on birth outcomes. The commonly used methods include providing easy and reliable access to health care, improving the aspects of care, provision of financial assistance, provision of social support, increased numbers of antenatal visits, and provision of nutritional support.[71]

Evidence from systematic and other reviews

Hodnett and Fredericks[72] systematically reviewed studies reporting the efficacy of additional social support for pregnant women who are at high risk of preterm/LBW births. Eighteen randomized controlled trials (RCTs), mainly of high quality, were included in which the intervention group had additional support. The method of providing additional support varied among the studies and included home visits by professionals (midwives, social workers, or nurses) or specially trained laypersons at regular intervals, provision of psychosocial support, individual counselling at each visit, assessment of the social support network of each mother, and tangible assistance. The studies had marked heterogeneities. There was no difference in the risk of preterm births (11 studies, 10,237 women, RR 0.96, 95% CI 0.86, 1.07), SGA births (two studies, 3523 women, RR 1.05, 95% CI 0.88, 1.26), or LBW births (13 studies, 10,235 women, RR 0.98, 95% CI 0.89, 1.08) between experimental and control groups. The authors concluded that programs that offer additional support during pregnancy are unlikely to prevent the birth of a preterm/LBW infant.

Logsdon and Davis[73] conducted a systematic review of nine published studies of paraprofessional support in improving maternal and infant outcomes. The authors identified serious methodological flaws among the studies. In the studies reviewed, 67% did not have a theoretical framework, 55% did not use an experimental design, 33% had <100 subjects enrolled, and 67% used primarily gross outcome indicators from birth certificates and state databases. The authors concluded that although proponents of paraprofessional support programs for pregnant and parenting women have reported some successes, more data are needed.

Hoffman and Hatch[36] reviewed observational studies and RCTs that reported on the effect of social support on preterm/LBW births. Among the observational studies, one assessed the effectiveness of social support-by-support quality (a measure of network resources, including number of kin, close friends, living with the father of the child, etc.) and concluded that, in the group of mothers who had experienced stressors, strong support quality was associated with an increase in BW by 231 g. Two other studies demonstrated a positive impact of social support on fetal growth restriction (one study reporting an OR of 4.8 and the other explaining 11% of the variance for LBW). Two observational studies on the risk of preterm births revealed a beneficial positive effect of social support. In contrast, RCTs offering social support failed to provide a clear beneficial effect on either

preterm or LBW births. Stratified subgroup analyses in some studies showed benefit for black women, women with previous LBW births, adolescent mothers, tobacco users, and women with a high degree of stress. The apparent benefit demonstrated in observational studies was not sustained in RCTs.

Blondel and Breart[74] performed a systematic review of five studies in which the aim was to provide social support as part of antenatal care. A total of 3197 women were enrolled in the intervention group and 3159 women in the control group. There was no difference in the risk of preterm births (OR 0.9, 95% CI 0.8, 1.1) between the two groups.

Evidence from other study designs

Bastani et al.[75] conducted a randomized study (n = 110) to assess the impact on BWs and the rates of preterm and surgical births of nurse-led relaxation education for anxious pregnant Iranian women in their first trimester. Women with a high anxiety level were randomly assigned to experimental and control groups. The experimental group received routine perinatal care along with 7 weeks of applied relaxation training sessions, whereas the control group received only routine prenatal care. The BW was higher in the experimental group versus the control group (mean (SD) 3168 g (420) versus 2883 g (640), p = 0.09), and the incidence of LBW was lower in the intervention group (5.8 versus 26.9%, p = 0.03). There was no significant difference in gestational age at birth or in the incidence of preterm births.

Mamelle[76] performed a cohort study of women who were admitted with threatened preterm labour. Women in the experimental group received a psychological intervention, including a meeting with a psychologist, and the results were compared with a retrospective cohort. There was a reduction of preterm births before 35 weeks in the intervention group (5.9% compared with 25.7%). The RR for preterm births in the intervention group was 0.16 (95% CI 0.07, 0.37) after controlling for confounders. This study approached this issue differently from the other studies in that all of the enrolled women were in threatened preterm labour.

Conclusions

There were several methodological differences among the studies assessing the impact of social support. Observational studies have demonstrated beneficial effects of provision of psychological support. However, RCTs concluded that there was no evidence of benefit. A subgroup of women with adverse factors may benefit. Proper identification of women experiencing chronic stress during the prenatal period and provision of psychosocial support may be justified.

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CHAPTER 9:

Lifestyle Factors

Main Summary Points

- Tobacco use is an important modifiable risk factor for preterm/low birth weight births. Causal epidemiological evidence shows that tobacco use results in approximately a 70 to 250 g reduction in birth weight. Passive smoking results in approximately a 25 g reduction in birth weight. Tobacco users are at higher risk of preterm births. Interventions for smoking cessation are effective in reducing the incidence of tobacco use and low birth weight.
- Prenatal exposure to alcohol exposes infants to developmental issues. No recommendation on the safe amount of alcohol during pregnancy can be made. Counselling should be started in the preconceptional period, especially for binge drinkers.
- Caffeine use may have a negative impact on fetal growth but not on preterm births.
- Substance use, including cocaine, the amphetamine group, and narcotics, during pregnancy is associated with a higher risk of adverse pregnancy outcomes. Intensive education, in conjunction with a non-judgmental atmosphere, regular prenatal care, and financial incentives, may have a role in preventing adverse pregnancy outcomes.
- There is conflicting evidence for the effect of marijuana on the incidence of preterm/low birth weight births.
- Evidence is lacking regarding the effectiveness and safety of herbal medicines in pregnancy.
- Exercise improves maternal fitness, but there are insufficient data to support or reject the benefits of exercise during pregnancy related to preterm/low birth weight births.
- Pregnant women should be informed of the potential increased risk of preterm births with excessive ingestion of licorice.

In this chapter we discuss the effects of various lifestyle-related factors and their impact on preterm/low birth weight (LBW) births.

Tobacco Use

The association of tobacco use with LBW/small for gestational age (SGA)/preterm births is the most commonly studied topic in reproductive biology.

Smoking in pregnancy is recognized as the most important preventable risk factor for an adverse pregnancy outcome. In an economic analysis, Lightwood et al.[1] found that an annual reduction of 1% in the smoking rate would result in a reduction of LBW infants by 1300 in the United States, which would save $21 million in direct costs of health care for these infants.

Biological plausibility

Several mechanisms for the effect of tobacco use on pregnancy outcomes have been proposed.

Smoking exposes the mother and the fetus to a variety of chemicals. The most important of these chemicals are nicotine, the metabolite cotinine, and carbon monoxide (CO).

- Nicotine is converted to cotinine in the maternal blood and transferred across the placenta.[2,3] Nicotine is freely permeable across the placenta.
- Cotinine in animal models reduces uterine arterial blood flow and causes changes in umbilical arterial blood flow, fetal oxygen concentration, and acid-base balance.[2]
- Placental infarctions secondary to tobacco use lead to reduced uteroplacental blood flow.[2]
- CO crosses the placental barrier freely. This causes a leftward shift of the oxygen dissociation curve and reduces the availability of oxygen to the fetus.[2,4]
- Newborns of mothers who use tobacco have elevated levels of erythropoietin in the cord blood, suggestive of fetal response to hypoxia.[2]
- Cyanide from tobacco use competes with oxygen and leads to hypoxia.[2,5]
- Alteration in prostacyclin in smoking mothers may lead to placental abruption.[6]
- Disturbance in the amino acids and zinc transport may lead to an altered nutrient environment.[7]
- Mothers using tobacco have a poorer quality diet in all social classes.[8]
- Mothers using tobacco eat less and have a lower weight gain during pregnancy.[8]
- Nutritional deficiency, particularly of vitamin C, can lead to increased risk of rupture of fetal membranes and preterm labour.[2]
- Smokers are likely to eat fewer vegetables, fruits, and whole grains, and to drink less lower fat milk because of altered taste following smoking.[9]
- Alteration of the immunological responses following tobacco use can lead to infections.[2]

Epidemiological association

Evidence from systematic and other reviews

Active smoking

Cnattingius[10] reviewed time trends and maternal characteristics, as well as maternal, fetal, and infant outcomes associated with smoking during pregnancy. Cnattingius found that the prevalence of smoking among women in their reproductive years has declined in some industrialized jurisdictions. Smoking is associated with an increased risk of spontaneous abortion (risk ratio (RR) 1.0 to 1.8) and placenta previa (RR 1.5 to 3.0) and a decreased risk of pre-eclampsia (RR 0.5 to 0.7). Smoking is causally associated with an increased risk of placental abruption (RR 1.4 to 2.4) and fetal growth restriction (RR 1.5 to 2.9). The association may be causal for preterm births (RR 1.2 to 1.6) and stillbirths (RR 1.3 to 1.8).

Walsh,[11] in a review, examined the effect of maternal tobacco use on perinatal and postnatal outcomes. Walsh identified several methodological issues among the studies, in particular, controlling for confounders, self-reporting bias, and competing outcomes bias (abruption and abortion with preterm birth). Strong evidence for smoking as a cause of LBW was found, with an approximate RR of 2. The association was consistent with a strong dose-response relationship.

Lumley,[12] in a review that included the literature of over 100 published studies (total birth of half a million pregnancies) from 1957 to 1986, indicated that there is a significant reduction of birth weight (BW) among infants born to smokers compared with infants born to non-smokers.

Abel[13] pooled data from 10 studies and found that the decrease in BW among infants born to smokers varied between 70 and 242 g. A dose-response effect of smoking on BW was observed. There was a graded reduction in mean BW by number of cigarettes smoked by white women (3399 g for non-smokers, 3272 g for mothers smoking 1 to 10 cigarettes per day, 3,185 g for mothers smoking 11 to 20 cigarettes per day, and 3,128 g for mothers smoking more than one pack per day).

Passive smoking or environmental tobacco exposure

Misra and Nguyen,[14] in a review of 11 observational studies of environmental tobacco smoke exposure, found that the reduction in mean BW between the exposed and non-exposed groups in various studies was between 25 and 125 g. Studies adjusting for gestational age found a difference of 25 to 87 g in BW. The major problem with these studies was in ascertaining exposure. Three studies used biomarkers and identified a significant association between passive smoking and LBW births. Overall, there was a statistically significant reduction in the BW in the cohort (weighted mean difference (WMD) for mean BW -24 g, 95% confidence interval (CI) -39, -9), but the clinical significance of this finding was

less obvious. The difference in the incidence of LBW/SGA births was significant. The authors hypothesized that the effects of passive smoking "operate at the lower end of the BW distribution," implying that fetuses near the cut-off level of 2500 g were more affected than were heavier fetuses.

Windham et al.,[15] in a review of 29 studies of environmental tobacco smoke exposure, found that the studies of highest quality reported a decrease in BW by 15 to 60 g. The methodological problems in the studies comprised not using different methods of assessing exposure and not accounting for other biases. The pooled estimate from 22 studies revealed a difference in BW of 25 g (95% CI 34, 16). A pooled estimate from 16 studies reporting the risk of LBW births resulted in an odds ratio (OR) of 1.07 (95% CI 1.0, 1.15). Three studies that adjusted for confounders provided an OR of 1.38 (95% CI 1.01, 1.87) for LBW births.

Evidence from other study designs

Recent studies reporting on the association between tobacco use and various adverse pregnancy outcomes are summarized in Table 9.1.

Table 9.1: Studies reporting the impact of smoking on pregnancy outcomes

Study	Characteristics	Results
Studies of active smoking		
Bada et al.[16]	Cohort study	Tobacco use in pregnancy was associated with an increased risk of LBW births (OR 2.0, 95% CI 1.6, 2.6), preterm births (OR 1.2, 95% CI 1.0. 1.4), and IUGR births (OR 2.0, 95% CI 1.7, 2.4) The etiologic fraction of LBW births attributable to tobacco was 5.6% The population-attributable risk factor for preterm births was 3.7%, and for IUGR births it was 13.8% with maternal tobacco use
Delpisheh et al.[17]	Cohort study	The incidence of adolescent pregnancy was 5.6% 46.2% of adolescents smoked during pregnancy BWs in infants born to smoking adolescents were significantly lower by 170 g ($p = 0.005$) Adolescents smoking >10 cigarettes/day gave birth to infants with larger BW reduction ($p = 0.001$).
Perkins et al.[18]	Cohort study	207 g reduction in BW of infants born to smokers 100 g reduction in BW for every 1 µg/l rise in serum cotinine level
Nordentoft et al.[19]	Cohort study	Risk of IUGR births for mothers smoking: 0 to 9 cigarettes/day had an AOR of 2.40 (95% CI 1.51, 3.80) 10 to 15 cigarettes/day had an AOR of 2.68 (95% CI 1.52, 4.68) 15 or more cigarettes/day had an AOR of 2.88 (95% CI 1.36, 6.09)
Horta et al.[5]	Postpartum interviews	Increased risk of IUGR births (AOR 2.07, 95% CI 1.69, 2.53) Preterm birth risk (OR 1.54, 95% CI 1.24, 1.92) An etiologic fraction of 17.7% for LBW
Studies of passive smoking		
Hegaard et al.[20]	Prospective survey	Exposure to tobacco smoke was associated with a reduction in BW of 78.9 g (95% CI -143.7, -14.1) Irrespective of exposure inside or outside home
Dejin-Karlsson et al.[21]	Prospective cohort study	The risk of SGA births: increased in mothers exposed to passive smoking, either at home or in the workplace (OR 2.3, 95% CI 1.1, 4.6) increased more if exposed to active and passive smoking (OR 3.6, 95% CI 1.5, 8.6) no relationship to preterm births was found
Ahluwalia et al.[22]	Cohort study	Risks for LBW births (OR 2.42, 95% CI 1.51, 3.87) and preterm births (OR 1.88, 95% CI 1.22, 2.88)

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; IUGR: intrauterine growth restricted; LBW: low birth weight; OR: odds ratio; SGA: small for gestational age.

Other aspects of smoking, such as risk factors for maternal smoking,[23,24] maternal smoking and subsequent nicotine dependency in offspring,[25,26] and effects of maternal smoking on infantile growth,[27,28] have been studied.

Interventions

Reports indicate that most women stop smoking within 1 to 2 months of being pregnant. Adolescent, unmarried, less educated, and heavy smokers are less likely to quit smoking. The reported rates of relapse during the postnatal period are high.[29]

Evidence from systematic and other reviews

Lumley et al.[30] systematically reviewed 64 randomized and quasi-randomized controlled studies of interventions to decrease smoking. The interventions included individualized support and advice, peer support, group counselling, self-help materials, nicotine replacement therapy, and use of rewards and incentives. Information regarding the benefits of quitting, recommendations to quit, and strategies to assist quitting were provided. The authors noted substantial variations in the intensity of the intervention and the extent of reminders of adverse effects of smoking. There was a reduction in continued smoking in pregnancy in the intervention groups (47 trials, 13,882 women, RR 0.94, 95% CI 0.92, 0.96). Studies that tested the biochemical validity of smoking cessation showed a reduction in continued smoking in pregnancy (35 studies, 10,362 women, RR 0.94, 95% CI 0.92, 0.97) in the intervention group. There was a reduction in the risk of LBW births (13 trials, 8930 women, RR 0.82, 95% CI 0.70, 0.95, number needed to treat 50, 95% CI 33, ∝) and preterm births (<36 or <37 gestational weeks) (11 trials, 10,932 women, RR 0.84, 95% CI 0.72, 0.98) and a mean increase in BW (16 trials, 13,618 women, WMD 33 g, 95% CI 11, 55). The authors recommended that, because there is benefit of smoking cessation programs in reducing smoking, attention to smoking behaviour, support for smoking cessation, and prevention of relapse should be a part of routine antenatal care. Interventions involving additional group sessions were poorly attended, did not show benefit, and should not be recommended.

Oncken and Kranzler[31] reviewed pharmacotherapies to enhance smoking cessation during pregnancy. The authors found that five first-line agents, including nicotine gum, patch, inhalers, and nasal spray, as well as sustained-release bupropion, are safe, equally effective, and approved for non-pregnant individuals. These agents double the quit rates compared with placebo. Nicotine replacements (nicotine gum (single-dose studies, multiple-dose study) and transdermal nicotine) have been studied in pregnancy, but nicotine nasal spray, inhaler, lozenge, and sublingual tablet have not been studied in pregnancy. The information on the use of other drugs in pregnancy is limited. Pharmacotherapies may be a useful adjunct to behavioural interventions to increase quit rates in pregnancy. More studies are needed to examine the safety, tolerability, efficacy, and effectiveness of medications to treat smoking in pregnant women.

Benowitz[4] reviewed nicotine replacement therapy during pregnancy. No study has evaluated its effectiveness for pregnant women. Nicotine replacement therapy is likely to present lower risk than is active smoking because of the very low doses of nicotine delivered. Nicotine replacement therapies help an individual to avoid exposure to other chemicals in the smoke. The authors concluded that nicotine replacement therapy could be an adjunct to smoking cessation therapy, especially in highly dependent smokers.

Klesges et al.,[32] in a review, found that the rate of quitting smoking was higher for pregnant women compared with the general population. Overall, 30% to 40% of mothers quit or reduced smoking during pregnancy; however, 70% continued to smoke throughout pregnancy. Important factors for successful smoking cessation were motivation, psychosocial support, and lack of associated stress. Women living with partners who continued to smoke were less likely to quit compared with women living with partners who were motivated to stop. Approximately 21% of mothers who stopped tobacco use relapsed before giving birth. Of the mothers who quit smoking during pregnancy, 25% relapsed within 1 month of giving birth, 50% relapsed within 4 months, and 70% to 90% relapsed within 1 year.[33]

Dolan-Mullen et al.[34] performed a meta-analysis of 11 studies aimed at smoking cessation. The interventions included personalized counselling, supplementation of pamphlets, self-help guides, educational videotapes, buddy support, and regular contact with reinforcement. The combined RR for smoking cessation after intervention was 1.94 (95% CI 1.61, 2.34). Higher rates of smoking cessation were related to a lower risk of LBW births. Higher quit rates came from more intense interventions, which included strategies such as intensive counselling, use of multiple contacts, provision of supportive materials, and patient follow up.

Edwards et al.[35] reviewed studies of postpartum smoking relapse prevention strategies. The authors noted that spontaneous quit rates of smoking during pregnancy have been estimated at 18% to 42%. Approximately 60% of women who quit smoking during pregnancy resume smoking within 6 months postpartum. Brief, infrequent interventions provided in antenatal clinic settings failed to demonstrate any impact on relapse prevention. Teaching women to resist urges to smoke and to avoid situations where they were tempted to smoke did not help them to maintain cessation status during pregnancy or the postpartum period.

Conclusions

Tobacco use is an important modifiable risk factor for LBW/preterm births. The biological mechanisms of tobacco use are well studied and the interaction of various factors plays a role. Bio-epidemiological studies have confirmed the association. Causal epidemiological evidence shows that tobacco use results in approximately a 70 to 250 g reduction in BW. Passive smoking results in approximately a 25 g reduction in BW. Tobacco users are at higher risk of preterm births and other perinatal and infantile adverse outcomes. The

association satisfies most of the causal criteria (strength, consistency, reversibility, dose response, biological plausibility, and epidemiological sense). Interventions for smoking cessation are effective in reducing the incidence of tobacco use and LBW. In particular, interventions that include intensive counselling, multiple contacts, supportive materials, and follow up are beneficial in reducing the rate of LBW births. Screening and counselling of high-risk mothers should be a part of all routine antenatal care. Further research is needed to improve the attitude of professionals and to develop culturally sensitive educational materials, relapse prevention strategies, and nicotine replacement programs.

Alcohol Use

Alcohol is the second most common substance studied in relation to pregnancy. Fetal alcohol spectrum disorders include fetal alcohol syndrome, fetal alcohol effects, and alcohol related neuro-developmental disorders.[36-38]

Biological plausibility

The exact mechanism of alcohol-induced effects on the fetus is not clear. This lack of knowledge has hampered the efforts to predict or diagnose these infants earlier. The following theories have been proposed to explain some of the biological phenomena:

- The placental barrier is freely permeable to ethanol and thus the fetus is directly exposed to maternal levels of ethanol. The excretion of ethanol by the fetus is ineffective. The prolonged circulation of acetaldehyde, a breakdown product of alcohol, is fetotoxic.[39]
- Risk to the fetus appears to be related to the peak levels of blood alcohol concentrations;[37] however, the threshold level is unknown. Repeated binge drinking and its associated high levels of alcohol correlate with adverse pregnancy and neonatal outcomes in some studies.[37]
- Alcohol use is often associated with deficiencies of certain nutrients such as zinc.[39]
- High levels of ethanol exposure lead to increased production of prostaglandins.[40] Prostaglandins increase the cyclic adenosine monophosphate (AMP) activity, which leads to a decrease in cell division and resultant LBW.[41]
- A protective effect of "mild" drinking has been suggested because of an increase in estrogen concentration[39] in the blood, leading to an altered estrogen-to-progesterone ratio. Mildly elevated estrogen levels may have protective effects on overall perinatal outcomes.

Epidemiological association

Evidence from systematic and other reviews

In a review of reported studies on alcohol exposure during pregnancy, Abel and Hannigan[42] found that 26 of the 56 reported studies of prenatal exposure to alcohol demonstrated a decrease in BW. In a subset of 13 studies reporting actual values of alcohol consumption, more than two drinks per day was associated with a reduction in mean BW by approximately 200 g. Maternal blood alcohol levels were not found to have a linear relationship with preterm birth.

Evidence from other study designs

The reports of the effects of alcohol ingestion during pregnancy on preterm/LBW births are summarized in Table 9.2.

Table 9.2: Studies of the impact of alcohol use on pregnancy outcomes

Study	Characteristics	Results
Bada et al.[16]	Cohort study	For women who consumed >1 drink/week: risk of LBW births (OR 1.57, 95% CI 1.12, 2.22) risk of preterm births (OR 1.11, 95% CI 0.86, 1.43) risk of IUGR births (OR 1.35, 95% CI 1.03, 1.76) Alcohol consumption of <1 drink a month was associated with a decreased risk of preterm births (OR 0.83, 95% CI 0.72, 0.96)
Mariscal et al.[43]	Case-control study	Alcohol consumption of <6 g/day decreased the risk of LBW births (AOR 0.64, 95% CI 0.46, 0.88) Alcohol consumption of >12 g/day increased the risk of LBW births (AOR 2.67, 95% CI 1.39, 5.12)
Naimi et al[44]	Cohort study	Binge drinking in white women was associated with unintended pregnancy (AOR 1.63, 95% CI 1.47, 1.80)
Lundsberg et al.[39]	Prospective interviews	"Mild drinking" (0.10 to 0.25 ounces of absolute alcohol/day) during the 1st month of pregnancy had a protective effect on IUGR (OR 0.39, 95% CI 0.20, 0.76) Alcohol consumption during the 7th month of pregnancy ("light drinking" OR 2.88, 95% CI 1.64, 5.05; and "mild to moderate drinking" OR 2.96, 95% CI 1.32, 6.67) was associated with higher risk for preterm births Binge drinking was associated with a trend towards increased risk of IUGR births (OR 1.89, 95% CI 0.93, 3.83) and preterm births (OR 2.19, 95% CI 0.83, 5.79)
Kesmodel et al.[45]	Survey	Increased risk of preterm births with >10 drinks/week of alcohol consumption before 16 weeks' gestation (RR 2.93, 95% CI 1.52, 5.63) and at 30 weeks' gestation (RR 3.00, 95% CI 1.02, 8.8)

AOR: adjusted odds ratio; CI: confidence interval; IUGR: intrauterine growth restricted; LBW: low birth weight; OR: odds ratio; RR: risk ratio.

Intervention

Evidence from systematic and other reviews

Dogget et al.[46] systematically reviewed six studies of home visits during pregnancy and after birth for women with alcohol or drug problems. Most of the studies had methodological limitations, particularly large losses to follow up. There was no reduction in continued alcohol use (RR 1.08, 95% CI 0.83, 1.41) with home visits. Further large high-quality trials are needed, and women's views on home visiting need to be assessed.

Rayburn and Bogenschutz[47] reviewed pharmacotherapy for pregnant women with addictions. Pregnant women were excluded systematically from almost all drug trials. Most knowledge about the fetal effects from maternal substance and medication use comes from animal data and from case reports and small clinical series. With the exception of methadone and nicotine replacement, clinical experience with anti-addictive medications in pregnant women is either very limited (alcohol, stimulants) or non-existent (cannabis, hallucinogens). Future directions will be towards increasing knowledge about current drug therapy and developing new anti-addiction medications.

Evidence from other study designs

A significant number of women are at risk of alcohol-exposed pregnancy (AEP) because of binge drinking paired with ineffective use of contraception. Ingersoll et al.[48] conducted a randomized controlled trial (n = 228) of a one-session motivational interview-based intervention (a 60- to 75-minute counselling session guided by a semi-structured counselling manual) to reduce AEP risk among college women. At 1-month follow up, the proportion of women reporting no-risk drinking was higher (25% of the intervention women and 15% of the control women), use of contraception was higher, and significantly more women in the intervention group were no longer at risk for AEP compared with control women (74% versus 54%, $p < 0.005$).

Conclusions

Alcohol exposure during the prenatal period can lead to adverse consequences. The biological mechanism, although not clear, is highly indicative of an effect on cell growth in the developing fetus. The epidemiological data reveal that the effect of alcohol on BW is protective at low levels of consumption and deleterious at high levels of consumption. Observational studies have suggested an increased tendency towards preterm births, but further research is needed. The effects of prenatal exposure of alcohol on the fetus other than weight and gestation length are multifaceted and include effects on development and brain growth. No recommendation on the safe amount of alcohol during pregnancy can be made from available evidence. Because of the teratogenic effects of alcohol on the fetus, counselling should be started in the preconceptional period. Special attention

should be paid to women who binge drink. Interventional studies to assess the impact of such advice are needed.

Caffeine Use

Coffee is consumed widely throughout the world, with certain areas having a higher consumption than others. One hundred millilitres of coffee contains 57.4 mg of caffeine, 100 ml of cola contains 13.0 mg, 100 ml of tea contains 27.0 mg, 100 ml of milk chocolate contains 2.1 mg, and 100 g of chocolate contains 66.7 mg of caffeine.

Biological plausibility

The exact mechanisms of the effects of prenatal exposure to caffeine are not clear.

- Caffeine is metabolized three times more slowly in pregnant women than in non-pregnant women.[49]
- The placenta transfers caffeine freely.[49]
- Newborns have not developed the enzyme to completely metabolize caffeine.[49]
- Caffeine inhibits the enzyme phosphodiesterase and increases levels of cyclic AMP, which together interfere with cell division and may result in LBW.[50]
- Increased levels of cyclic AMP induce catecholamine-mediated vasoconstriction, affecting uteroplacental perfusion.[50]
- Caffeine blocks adenosine receptors, which leads to an imbalance between available oxygen and oxygen utilization and may cause LBW.[51]

Epidemiological association

Evidence from systematic and other reviews

In a recent review on coffee and health, which included 25 studies on caffeine and pregnancy complications, Higdon and Frei[52] concluded that it appears unlikely that caffeine intakes of <300 mg/day will adversely affect fetal growth or the incidence of preterm birth or that these levels will cause birth defects in non-smoking women. In a systematic review of seven studies, there was no evidence of teratogenic effects of caffeine in humans.[53]

Leviton and Cowan[54] did an extensive critical review of 68 studies relating caffeine consumption by women and reproductive hazards. The studies were heterogeneous and of differing quality. The authors identified no reproductive adversity consistently associated with caffeine consumption.

Evidence from other study designs

Vik et al.[55] reported results of a case-control study in which caffeine intake from

coffee, tea, soft drinks, and chocolate was estimated and dichotomized as low or high on the basis of the median value. Mothers who gave birth to SGA infants had a higher mean intake of caffeine [281 mg/day, standard deviation (SD) 150 mg] in the third trimester compared with mothers who did not give birth to SGA infants (212 mg/day, SD 150 mg, $p < 0.001$). The risk of a SGA birth was nearly doubled if the mother had a high versus a low caffeine intake in the third trimester (OR 1.8, 95% CI 1.2, 2.7). High caffeine intake versus low intake during week 17 was not associated with SGA births (OR 1.4, 95% CI 0.9, 2.1). High caffeine intake in both periods resulted in an increased risk for SGA (OR 1.6, 95% CI 1.1, 2.5).

Intervention

Evidence from systematic and other reviews

No review on the topic was identified.

Evidence from other study designs

Bech et al.[56] conducted a randomized double-blind controlled trial of pregnant women who drank at least three cups of coffee a day when recruited at <20 weeks' gestation. Women were randomly assigned to drink caffeinated instant coffee (568 women) or decaffeinated instant coffee (629 women). No significant differences were found for mean BW or mean length of gestation between women in the decaffeinated coffee group (whose mean caffeine intake was 182 mg lower than that of the other group) and women in the caffeinated coffee group. After adjustment for confounders, the mean BW of infants born to women in the decaffeinated group was 16 g (95% CI -40, 73) higher than those born to women in the caffeinated group. The adjusted difference (decaffeinated group versus caffeinated group) of length of gestation was -1.3 days (95% CI -2.9, 0.3).

Conclusions

Coffee consumption is common in the general population. The biological evidence indicates that caffeine use may have a negative impact on fetal growth. There is no evidence of an effect on the incidence of preterm birth.

Cocaine Use

Cocaine is one of the commonly used substances for recreational purposes. The prevalence of cocaine use is variable and is higher among pregnant women not seeking prenatal care.[57]

Biological plausibility

The exact mechanism of the effects of cocaine on pregnancy outcomes is not clear.

- Cocaine crosses the placenta freely and is stored in the placenta.[3,57] Plasma cholinesterase is reduced in pregnant women and fetuses, which hampers the excretion of cocaine.[3]
- Exposure of the fetus to cocaine inhibits the uptake of neurotransmitters such as dopamine and norepinephrine, which can lead to vasoconstriction and reduced nutrient uptake and may stimulate uterine contractility.[3,57]
- Cocaine causes vasoconstriction in the uterine arteries by a similar mechanism.[58]
- Cocaine inhibits the uptake of amino acids across the placenta.[3]
- Cocaine has an appetite-suppressant effect that decreases maternal nutrient intake.[57]
- Cocaine elevates maternal body temperature, with resultant possible damage to the fetus.[57]
- Animal studies have shown that cocaine reduces the activity of ornithine decarboxylase, which is a key enzyme in the regulation of fetal growth.[57]

Epidemiological association

Evidence from systematic and other reviews

Addis et al.[59] reviewed 33 studies of pregnancy outcomes following cocaine exposure. Infants exposed to cocaine and children exposed to polydrugs but not cocaine had higher risks of major malformations, LBW/preterm births, placental abruption, and prelabour rupture of the membranes, as well as lower mean BW, length, and head circumference than did children of women not exposed to any drug. Only the risk of placental abruption (RR 4.72, 95% CI 1.63, 13.70) and prelabour rupture of the membranes (RR 2.84, 95% CI 1.42, 5.68) were statistically significantly associated with cocaine use itself in analyses of cocaine exposure versus exposure to polydrugs but not cocaine.

Holzman and Paneth[60] reviewed 24 studies (in which at least 100 pregnant women were enrolled per study) that reported use of cocaine during pregnancy. Twenty-three studies showed a negative association between maternal cocaine use and BW. The influence of gestational age was controlled in 16 studies and the effect remained unchanged. The populations studied included African American women, referred populations from drug treatment centres, prospectively screened mothers from prenatal care programs, women with no prenatal care, and postnatal patients. Overall, unadjusted analyses showed a reduction of BW in the range of 265 to 610 g and adjusted analyses showed a weight reduction of between 78 and 382 g. The reported increase in the risk of preterm birth varied between the studies. The rate differed among studies that adjusted for confounders and non-adjusted reports. The difference in mean gestational age ranged from 0.3 to 2.4 weeks and the increased risk (OR or RR) ranged from

1.1 to 10.6. There was an increased risk of placental abruption (OR ranged from 1.0 to 6.6). Several methodological problems were identified in the studies: (1) different methods of ascertaining exposure; (2) confounding due to other adverse social circumstances that may have led to substance abuse; (3) multiplicity of drug usage; and (4) possible publication bias.

Hulse et al.[61] systematically reviewed studies on cocaine use in pregnancy that were controlled for simultaneous tobacco use. A large number of studies (n = 18) that did not adjust for tobacco use were excluded. A meta-analysis of five studies of any prenatal cocaine exposure showed an increased risk of LBW births (RR 2.15, 95% CI 1.75, 2.64). A meta-analysis of three studies reporting more intense prenatal exposure suggested an increased risk of LBW births (RR 4.42, 95% CI 2.24, 8.71). Data from five studies that reported on BW identified a statistically significant reduction in BW (WMD 112 g, 95% CI 62, 161) with the use of cocaine in pregnancy.

Evidence from other study designs

The study designs to ascertain prevalence of cocaine use included self-reported questionnaires and assessment of cocaine in the urine, hair, or meconium. Forman et al.[62] assessed fetal cocaine exposure by using neonatal hair and urine tests for benzoylecgonine among 600 neonates in three nurseries in Toronto, Canada, from 1990 to 1991. A total of 37 infants (6.25%) tested positive for cocaine exposure by hair test, urine test, or both. In infants born to mothers from downtown Toronto, the rate of fetal exposure to cocaine was 12.5% (25/200) compared with 3% (12/400) from two suburban nurseries. Data from the province of Alberta, Canada,[63] indicate that the reported use of illicit drugs during pregnancy was 1.5% in 1997, 1.6% in 1998, and 1.5% in 1999.

Bada et al.[16] identified that cocaine use in pregnancy was associated with an increased risk of LBW births (OR 3.6, 95% CI 2.4, 5.4), preterm births (OR 1.3, 95% CI 1.0. 1.6), and IUGR births (OR 1.4, 95% CI 1.0, 2.1). Cocaine use was ascertained from maternal history and testing of meconium from the infant.

Intervention

Elk et al.,[64] in a small randomized trial, tested the effectiveness of contingency management interventions (CMIs) in 12 women who reported having used cocaine during the current pregnancy but who had stopped using >30 days before enrolment in the study. After randomization, both groups received weekly prenatal care visits, drug counselling (twice weekly individual sessions and a weekly group session), monthly nutritional education, and human immunodeficiency virus pre- and post-test counselling. A supportive, non-judgmental atmosphere, free transportation to all required visits, and child care during appointments were provided. The intervention group received an adjunctive CMI designed to reinforce both cocaine abstinence and compliance with prenatal care. There was a high rate of retention (83% in the CMI group and

67% in the control group, p = 0.21) and abstinence from cocaine (100% in the CMI group vs. 98% in the control group, p = 0.34) in both groups. None of the patients in the CMI group (0%) experienced prelabour rupture of the membranes, preterm labour, preterm birth, or LBW birth compared with four patients (67%) in the control group.

Weisdorf et al.[65] reported on the results of a study that compared treatment retention of cocaine-abusing indigent pregnant women before and after incorporating pregnancy-specific interventions. These interventions included parenting classes, pregnancy and nutrition classes and videos on pregnancy, and substance abuse. The regular program included detoxification, assessment, and in-patient rehabilitation over a 12- to 14-day period and an intensive outpatient program for 3 hours a day, 5 days a week, for 4 weeks. Audits were performed on charts of women enrolled between 1988 and 1994 in either a traditional treatment program (n = 114) or in this specific program (n = 489). There was a higher rate of completion of outpatient treatment in the intervention group compared with the control group (34.4% versus 13.5%, p < 0.005).

Chazotte et al.[66] compared cocaine-using mothers who received prenatal care and those who did not receive prenatal care. The authors found that mothers who received prenatal care had a significantly lower incidence of LBW births (34.3% versus 52.3%, p < 0.05).

Chasnoff et al.[67] found that women who stopped cocaine use in the first trimester of pregnancy gave birth to infants with no difference in BW from that of infants of non-cocaine users.

Conclusions

Cocaine use is an important modifiable determinant for adverse pregnancy outcomes. Cocaine affects the fetus through various mechanisms, resulting in impaired growth or initiation of labour. Nutritional deficiency secondary to compromised uteroplacental blood flow is the major mechanism involved in LBW. Cocaine is associated with preterm/LBW/IUGR births, placental abruption, and prelabour rupture of the membranes. Stopping cocaine use during the first trimester is associated with a non-significant impact on BW. Intensive education in conjunction with a non-judgmental atmosphere, regular prenatal care, and financial incentives may have a role in preventing adverse pregnancy outcomes. However, further research is necessary.

Substance Use

Recreational drugs such as marijuana (cannabis), narcotics (e.g., heroin, methadone), amphetamine, and others have been studied for their effects on pregnancy outcomes. The use of these drugs has been observed more frequently among populations from large metropolitan cities in North America.[57]

Biological plausibility

The exact mechanisms of action of the effects of recreational drugs on the fetus are not well understood.

- Mothers who use marijuana on a regular basis have a higher frequency of precipitous labour,[68] indicating that marijuana has an effect on uterine contractions.
- Amphetamine use is associated with placental abruption and preterm birth.[69]
- Certain congenital anomalies (cardiac defects, cleft lip) are associated with prenatal use of amphetamine.[70]
- Naeye et al.[71] reported that the use of heroin is associated with a reduction in the number of cells in many organs, including the brain, and may be responsible for LBW births.
- Methadone may induce fetal hyperglycemia and result in larger infants.[72]
- Low levels of circulating corticosteroids are reported in heroin-addicted mothers and may be responsible for LBW births.[73]

Epidemiological association

Evidence from systematic and other reviews

Fried and Smith[74] reviewed studies of marijuana use and pregnancy outcomes. Two studies showed an association with preterm birth, but three studies reported no significant effect on gestational age. Two prospective studies of marijuana use found no difference in preterm births. One study identified reduction in BW and one study reported an increase in BW with the use of marijuana. The effect on gestation length was inconclusive.

English et al.[75] reviewed 10 studies of cannabis use and pregnancy outcome. When data from five studies with significant heterogeneity were combined, the authors found a reduction in mean BW by 48 g (95% CI 14, 83). There was no difference in the BW among women who were infrequent users (≤ once per week) compared with controls (WMD 62 g, 95% CI -8, 132); however, there was a significant reduction in BW among frequent users (at least four times per week) compared with non-users (WMD -131 g; 95% CI -52, -209). There was no increase in the risk of LBW births (pooled OR for any use 1.09; 95% CI 0.94, 1.27).

Hulse et al.[76] systematically reviewed studies that assessed the role of heroin use, methadone use, and heroin and methadone use on pregnancy outcomes. Five studies that reported BW revealed a reduction in BW among heroin users (WMD 489 g, 95% CI 489, 693) and higher risk of LBW births (four studies, pooled RR 4.61, 95% CI 2.78, 7.65). Two studies of both heroin and methadone use revealed a reduction in BW (WMD 557 g, 95% CI 403, 710) and a higher risk for LBW (three studies, pooled RR 3.28, 95% CI 2.47, 4.39).

Evidence from other study designs

The impact of substance use on pregnancy outcomes is summarized in Table 9.3.

Table 9.3: Studies of reports of substance use during pregnancy

Study	Characteristics	Results
Bada et al.[16]	Cohort study	Mother's self-reported use of marijuana was not associated with increased risk of preterm births (OR 0.9, 95% CI 0.73, 1.11), LBW births (OR 1.21, 95% CI 0.9, 1.61), or IUGR births (OR 1.08, 95% CI 0.85, 1.36)
Quinlivan and Evans[77]	Cohort study	No difference in mean gestational age (37.8 weeks vs. 38.5 weeks vs. 38.2 weeks, respectively) or mean BW (3,068 g vs. 3,131 g vs. 3,113 g, respectively) among marijuana users, multiple substance users, and non-users
Shiono et al.[78]	Cohort study	Incidence of marijuana use 11% No increased risk of preterm births (OR 1.1, 95% CI 0.8, 1.3) or LBW births (OR 1.1, 95% CI 0.9, 1.5) with marijuana use
Cornelius et al.[79]	Interview-based study	1st trimester marijuana use: reduction in GA by 9 days 2nd trimester marijuana use: SGA births (OR 3.8, 95% CI 1.2, 14)
Fergusson et al.[80]	Questionnaire study	Compared with non-users (mean BW 3430 g and preterm rate 4.5%): significant reduction in BW among weekly users (mean BW 3258 g) and less than weekly users (3356 g, $p < 0.0001$) before pregnancy significant reduction in BW among weekly users (mean BW 3243 g) and less than weekly users (3258 g, $p < 0.0001$) during 1st trimester significant reduction in BW among weekly users (mean BW 3225 g) and less than weekly users (3246 g, $p < 0.0001$) during mid-pregnancy no difference in the risk of preterm births among weekly users (6.8%) and less than weekly users (5.0%, $p = 0.15$) before pregnancy no difference in risk of preterm births among weekly users (9.0%) and less than weekly users (8.0%, $p = 0.69$) during 1st trimester no difference in the risk of preterm births among weekly users (7.0%) and less than weekly users (5.0%, $p = 0.97$) during mid-pregnancy after adjusting for confounding variables, there was a trend towards reduced BW among women who used cannabis at least once per week before and throughout pregnancy (-102 g, 95% CI -208, 4, $p = 0.03$)
Smith et al.[81]	Cohort study	For amphetamine users: increased risk of SGA births (AOR 3.5, 95% CI 1.7, 7.3) preterm births (12.5% vs. 6.5%, $p = 0.036$) lower BW ($p < 0.05$)

Study	Characteristics	Results
Ludlow et al.[82]	Cohort study	For amphetamine users: risk of LBW births (20% vs. 6.7% in the general population) preterm births (26% vs. 7.9% in the general population) For opiate-exposed mother: risk of LBW births (20.6% vs. 6.7% in the general population, $p < 0.0001$) preterm births (20.6% vs. 7.9% in the general population, $p < 0.0001$)
Thaithumyanon et al.[83]	Cohort study	No difference identified in the risk of preterm/LBW/IUGR births between the amphetamine and the heroin group Incidences of these outcomes were higher (32%, 32%, and 10%, respectively) in women who used either substance
Chomchai et al.[84]	Cohort study	Significant reduction in BW among infants born to mothers who used amphetamine ($p < 0.001$)
Kennare et al.[85]	Cohort study	Substance users were more likely to be aboriginal An increased risk among substance users for preterm births (OR 2.6, 95% CI 2.2, 3.1), SGA births (OR 1.79, 95% CI 1.5, 2.1), stillbirths (OR 2.5, 95% CI 1.52, 4.3), neonatal deaths (OR 2.9, 95% CI 1.4, 6.0), and congenital abnormalities (OR 1.5, 95% CI 1.0, 2.2)
Little et al.[86]	Cohort study	For substance-user mothers: Risk of preterm births (AOR 2.7, 95% CI 1.1, 6.5) Risk of BW <2 kg (AOR 8.3, 95% CI 3.4, 20.2) Risk of SGA births (AOR 2.8, 95% CI 0.7, 11.0)
Sherwood et al.[87]	Cohort study	Infants born to mothers who tested positive had: lower BW (2.92 kg (SD 0.81) vs. 3.35 kg (SD 0.58), $p < 0.002$) were born earlier (37.3 weeks (SD 4.6) vs. 39.2 weeks (SD 3.0), $p < 0.005$) had higher risk of preterm births (22% vs. 7%, $p < 0.02$)
Kelly et al.[88]	Cohort study	Substance use was associated with: higher risk of LBW births (OR 3.7, 95% CI 3.4, 4.0) higher risk of VLBW births (OR 2.8, 95% CI 2.3, 3.3) higher risk of preterm births (OR 2.4, 95% CI 2.3, 3.6)

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; GA: gestational age; IUGR: intrauterine growth restricted; LBW: low birth weight; OR: odds ratio; SD: standard deviation; SGA: small for gestational age; VLBW: very low birth weight.

Intervention

Evidence from systematic and other reviews

Hulse et al.[76] reviewed three studies that compared BW of infants among mothers who were taking methadone for the treatment of drug addiction with BW of infants among non-exposed mothers (controls). BW was reduced in infants born to women who used methadone (WMD 279 g, 95% CI 229, 328), but there was no statistically significant reduction in the risk of LBW births (four studies, RR 1.36, 95% CI 0.83, 2.22) compared with non-exposed mothers. This result signifies that with treatment, the risk of LBW births in heroin-addicted mothers may equal that of the control group population.

Evidence from other study designs

Sweeney et al.[89] evaluated the outcomes in an intensive enroll and integrated outpatient specialized abuse treatment service. Women could enrol in this program before or after giving birth. Data were compared between women who received the treatment in this clinic and women who enrolled in the program after the birth of the baby (n = 87 in each group). After adjusting for confounders, the investigators found that BW was 418 g lower in the group of women who enrolled after giving birth and that the risk of LBW (OR 0.28) was lower in the group of women who enrolled before pregnancy and received integrated services.

Armstrong et al.,[90] in a retrospective cohort study, evaluated the role of substance use in pregnancy outcomes in Northern California, United States. Outcomes were compared among four groups: (1) 782 women who were screened, assessed, and treated for substance abuse by their Early Start program; (2) 348 women who were assessed and diagnosed as having substance abuse but who did not have follow-up treatment; (3) 262 women who were screened (questionnaire or toxicology screens) for substance abuse but who were not assessed or treated; and (4) 5382 control women with no evidence of substance use (negative screening and questionnaire). The incidence of LBW births was 4.7% in group 1 ($p = 0.028$ when compared with group 2 and 0.015 when compared with group 3); 8.1% in group 2 ($p = 0.001$ when compared with group 4); 8.8% in group 3 ($p = 0.001$ when compared with group 4); and 3.7% in group 4 (control). The incidence of preterm birth was 6.4% in group 1 ($p = 0.037$ when compared with group 3); 8.9% in group 2 ($p = 0.015$ when compared with group 4); 10.3% in group 3 ($p = 0.002$ when compared with group 4); and 5.7% in group 4 (control).

McCarthy et al.[91] compared high-dose methadone (>100 mg methadone) versus low-dose methadone (<100 mg) and found that there was no difference in BW (2795 g (SD 693) in the high-dose group vs. 2787 g (SD 687) in the low-dose group) or gestational age (37.3 weeks (SD 3.1) vs. 37.2 weeks (SD 3.3)).

Conclusions

Substance use during pregnancy is associated with a higher risk of adverse pregnancy outcomes. The biological mechanisms of the effects of marijuana on either BW or duration of gestation are not clear. There is conflicting epidemiological evidence of the effect of marijuana on the incidence of preterm/LBW births. Amphetamine and methyl-amphetamine use is associated with a higher risk of SGA/LBW and preterm births. Narcotic use is associated with an increased risk of LBW/preterm and IUGR births. Although the evidence for efficacy of intervention does not exist, regular assessment for the substances implicated in adverse pregnancy outcomes and provision of information to pregnant women is important. De-addiction with methadone has been shown to reduce the effects of narcotics on birth outcomes. Further research is required regarding the development, testing, and implementation of effective public health intervention strategies.

Herbal Medicine Use

The effect of using herbal medicine for pregnancy-related conditions is largely unknown.

Biological plausibility

The mechanism of effect for herbal medicines on pregnancy outcomes is unclear from the perspectives of harm and effectiveness.

Epidemiological association

Evidence from other study designs

Rhizoma coptidis is an extremely bitter Chinese herb belonging to the Ranunculaceae family and is thought to have anti-inflammatory, antibiotic, vasodilator, and anti-pyretic properties.[92] Chuang et al.[93] studied the effects of *R. coptidis* on fetal growth in pregnant women at $\geq$26 weeks gestation in Taiwan. There was a non-significant increased risk of LBW births (OR 1.42, 95% CI 0.65, 3.10) and SGA births (OR 1.32, 95% CI 0.82, 2.12) if *R. coptidis* was used >56 times during the pregnancy.

Maté is a hot infusion of the herb *Ilex paraguayensis*. It is largely consumed in southeast Latin America, including during pregnancy.[94,95] Santos et al.[96] found that 68% of the mothers reported maté intake at least once a week during the entire pregnancy period. Crude analyses showed a 30% increase in the risk of SGA births among daily maté drinkers compared with non-users (RR 1.3, 95% CI 1.1, 1.6), whereas no statistical association was noted with preterm births.

Intervention

Some herbal medicines are used for treatment.

Evidence from systematic and other reviews

In a systematic review, Zhang et al.[97] reviewed one study of herbal medicine for the treatment of pre-eclampsia and found that a low dose of rhubarb (0.75 g/day) was associated with a reduced incidence of pregnancy-induced hypertension (5.7 % in the treatment group versus 20.8% in the control group, $p < 0.01$).

Meher and Duley[98] reviewed one study of the use of garlic and reported no difference in the risk of developing pre-eclampsia (RR 0.78, 95% CI 0.31, 1.93).

Conclusion

Evidence is lacking regarding the effectiveness and safety of using herbal medicines in pregnancy.

Exercise

Whether to continue exercise during pregnancy or not, and to what extent without causing harm to the fetus, is an important question.

Biological plausibility

Exercise could be beneficial, but is possibly risky. Suggested mechanisms for the benefits of exercise during pregnancy are as follows:

- Exercise improves muscle tone and helps during labour.[99]
- Exercise may improve immunological defence mechanisms and prevent urinary tract infection, which may be a triggering factor for preterm labour.[99]
- Exercise may increase fetal weight, probably by improving blood flow.[100]

The suggested mechanism for the disadvantage of exercise during pregnancy is that heavy exercise can be stressful and may invoke labour.[99]

Epidemiological association

Evidence from systematic and other reviews

Kramer[101] systematically reviewed the role of aerobic exercise in pregnancy. The studies were of small sample size and not of high quality. The results showed an improvement in maternal fitness (five trials). There was no statistically significant difference in BW (four trials, 125 women, WMD 127 g, 95% CI -22, 275) or gestational age (two trials, 64 women, WMD 0.32 weeks, 95% CI -0.2, 0.9). There was no statistically significant increase in the risk of preterm births (three trials, 111 women, RR 1.82, 95% CI 0.35, 9.57).

In a critical review, Morris and Johnson[102] noted that studies performed in women who exercised during pregnancy were limited and problematic in several respects: most studies were observational; there were few randomized trials; not all exercise was the same; the type, intensity, duration, and frequency of exercise differed between studies; and the studies were difficult to quantify and compare. The authors concluded that data on exercise during pregnancy are limited but suggested that moderate exercise during a low-risk pregnancy does not lead to adverse outcomes for the fetus or the mother and improves overall maternal fitness and well-being.

Wolfe and Weissgerber[103] conducted a literature review of physiological adaptations to pregnancy, effects on pregnancy of responses to acute exercise and aerobic conditioning, effects of acute maternal exercise and aerobic conditioning, effects of acute maternal exercise on indexes of fetal well-being, impact of physical conditioning on BW and other pregnancy outcomes, and use of exercise to prevent or treat gestational diabetes. A physical conditioning program did not have a significant effect on BW. One study reported that recreational athletes

who continued their normal exercise routines into late gestation gave birth to lighter infants at an earlier gestational age and another study noted a reduction in BW and gestation length in association with participation in vigorous exercise. A case-control study reported that participation in two or fewer prenatal exercise sessions a week, or five or more per week, resulted in lower BWs than did involvement in three to four sessions. Another study observed that women involved in high-intensity exercise (energy expenditure 2000 kcal/week) gave birth to infants with BWs nearly 300 g greater than those of non-exercising women. Infants of women involved in low-to-moderate exercise had BWs approximately 100 g greater than those of infants born to sedentary women.

Conclusions

Exercise improves maternal fitness, which may be beneficial during labour. There are insufficient data to support or reject benefits of exercise during pregnancy related to preterm/LBW births. Further research is needed.

Licorice Ingestion

Biological plausibility

Glucocorticoids are thought to play a role in the initiation of labour. Licorice contains glycyrrhizin, which is an inhibitor of cortisol metabolism and thus may initiate labour.

Epidemiological association

Strandberg et al.[104] reported that the risk of giving birth before 38 weeks was increased in women with a high intake (≥500 mg/week) of glycyrrhizin (OR 2.5, 95% CI 1.1, 5.5) compared with women with a low intake (<250 mg/week).

Another study reported that a higher versus a lower level of consumption was associated with more than a two-fold increased risk of preterm births. The association was even stronger for preterm births that occurred at <34 weeks (OR 3.07, 95% CI 1.17, 8.05).[105]

Conclusions

Further research in other populations on the possible association between licorice and preterm births is needed before reaching any firm conclusions. Until such evidence is available, pregnant women should be informed of the potential risks of excessive ingestion of licorice.

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CHAPTER 10:

Environmental Factors

Main Summary Points

- Investigators have found that exposure to environmental toxins can result in preterm/low birth weight births. The biological mechanisms are poorly understood for most environmental toxins. Epidemiological data support a trend towards an increase in preterm/low birth weight births following exposure; however, interpretations of the literature differ among authors. Additional research is needed from a local perspective for policy purposes.
- Exposure to high levels of disinfectant by-products is weakly associated with low birth weight/small for gestational age births, but not with preterm births.
- The effects of various pesticides on birth outcomes indicate the possibility of an increased risk of preterm births following exposure; however, the impact on low birth weight births is inconsistent. Different findings in various studies could be due to different methods of measuring the exposure. An increased risk of birth defects warrants avoidance of exposure for a pregnant woman or a woman planning to get pregnant.
- Seasonal variation may play a role in birth weight. No study has evaluated the role of seasonal variation in preterm birth. Heat and cold stress may play a role in preterm/low birth weight births.
- Exposure to electromagnetic fields from power lines may increase the risk of miscarriage but not congenital anomalies. The effect on preterm/low birth weight births has not been studied.

Various environmental factors have been implicated in adverse pregnancy outcomes. Environmental tobacco exposure, or passive smoking, was discussed in chapter 9: lifestyle factors. In chapter 10 we discuss the impact of air pollutants, water pollutants, pesticides, ambient air temperature and season, and electromagnetic fields on preterm/low birth weight (LBW) births.

Air Pollution

Outdoor air pollution has been studied for its impact on the respiratory system and from the perspective of adverse pregnancy outcomes.

Biological plausibility

Air pollution varies by location, with the highest levels occurring in the industrialized areas of the world. Of the many airborne pollutants, sulphur dioxide and total suspended particles are the major substances implicated in air pollution.[1] The biological mechanisms for the effects of air pollution on pregnancy outcomes are complex and currently not well understood. Proposed theories for common pollutants include the following:

- Exposure to pollutants leads to increased incidence of maternal infection and illness.[2]
- Pollution exposure leads to an increase in blood viscosity and may affect placental blood flow.[3,4]
- Air pollution affects deoxyribonucleic acid (DNA) transcription. DNA adducts (altered DNA), which may affect fetal growth, were observed in mothers exposed to high levels of air pollution.[5,6]
- Because of its anti-estrogenic effects, benzopyrene exposure may affect uterine and fetal growth.[7]
- Polycyclic aromatic hydrocarbons bind to receptors for placental growth factors and lead to reduced exchange of oxygen and nutrients across the placenta.[8]

Epidemiological association

Evidence from systematic and other reviews

Srám et al.[9] systematically reviewed nine studies that assessed the impact of air pollution on LBW. The risk of LBW births was increased with exposure to higher levels of sulphur dioxide in the air (odds ratio (OR) varied from 1.06 to 1.21) in five studies and was not increased in one study. The risk of LBW births was increased with increased total suspended particles in the air (OR 1.10 and 1.15) in two studies and was not increased in two studies. The risk of LBW births was increased with higher exposure to nitrous oxide (OR 1.07) in one study, whereas it was not increased in three studies. The risk of LBW births was increased where the level of carbon dioxide was higher (OR 1.08 and 1.43) in two studies. Review of two studies of indoor exposure to environmental toxins revealed that birth weight (BW) was lower (63 g, 95% CI 0, 126) in households that used wood fuel and open fires and that higher concentrations of polycyclic aromatic hydrocarbons in air sampling were associated with lower BWs ($p = 0.003$). The authors suggested that repeatability, consistency, and reproducibility of these effects are indicative of a causal relationship; however, further studies are needed to determine the exact period of vulnerability.

Four of the reviewed studies reported on the risk of preterm births; three studies reported increased risk of preterm births (ORs ranged from 1.21 to 1.41) with exposure to higher levels of sulphur dioxide; two studies reported higher risk of preterm births with higher levels of total suspended particles in the air (OR 1.10 and 1.18); and one study reported no increase in the risk of preterm births with exposure to higher levels of carbon monoxide, nitrous oxide, and ozone. Four of the reviewed studies reported on the risk of intrauterine growth-restricted (IUGR) births. Concentrations of >50 $\mu g/m^3$ of particulate matter that was >10 µm in size was associated with an increased risk of IUGR births (OR 2.14 and 2.64) and concentrations of >37 $\mu g/m^3$ of particulate matter that was >2.5 µm in size in the first month of pregnancy was associated with an increased risk of IUGR births (OR 2.11 and 1.96). One study reported an increased risk of IUGR births with exposure to polycyclic aromatic hydrocarbons levels of >30 $\mu g/m^3$ in the first months of pregnancy (OR 2.15, 95% CI 1.27, 3.63). One study reported no effect of sulphur dioxide, nitrous oxide, and ozone levels with IUGR births. One study reported that exposure to high levels of polycyclic organic matter was associated with an increased risk of small for gestational age (SGA) births (adjusted OR 1.22, 95% CI 1.16, 1.27) compared with a cohort exposed to low levels of this matter. The reviewers concluded that exposure to air pollution was associated with LBW births (probably in a causal way), but that the evidence for its association with preterm and IUGR births is weak and further studies are needed.

In another review published in 2004, Maisonet et al.[10] reviewed the effect of ambient air pollution on fetal growth. There were discrepancies in the results of the included studies between the review of Maisonet et al. and that of Srám et al.[9] Maisonet et al. concluded that air pollution has an effect on the risk of preterm births and IUGR births, but not on LBW births. Maisonet et al. reviewed only English-language articles and only articles that reported on carbon dioxide, sulphur oxide, nitrogen oxides, particulate matter, and ozone.

Evidence from other study designs

Studies that reported the impact of air pollution on preterm/LBW births are summarized in Table 10.1.

Table 10.1: Studies of the impact of air pollution on preterm/LBW births

Study	Characteristics	Results
Hansen et al.[11]	Cohort study	Exposure to elevated levels of particulate matter >10 µm in size and exposure to higher ozone levels in the 1st 3 months of pregnancy were associated with an increased risk of preterm births (AOR 1.15, 95% CI 1.06, 1.25 and AOR 1.26, 95% CI 1.10, 1.45, respectively)
Dugandzic et al.[12]	Population- based cohort study	Risk of LBW with 1st trimester exposure of: the highest quintile for sulphur dioxide (RR 1.36, 95% CI 1.04, 1.78) particulate matter >10 µm in size (RR 1.33, 95% CI 1.042, 1.74)
Mohorvic[13]	Cohort study	For a population living near coal mines: a significant negative correlation between length of gestation and exposure to sulphur dioxide at the end of the 1st month (p = 0.008) and at the end of the 2nd month (p = 0.016) of pregnancy a significant negative correlation between BW and exposure to sulphur dioxide at the end of the 1st month (p = 0.08) and at the end of the 2nd month (p = 0.03) of pregnancy
Jedrychowski et al.[14]	Cohort study	35% variability in BW was explained by the exposure to potentially hazardous fine particles 2.5 µm in size Predicted reduction of 140 g of BW if the exposure level increased from 10 to 50 µg/m3
Wilhelm and Ritz[15]	Cohort study of residential proximity to traffic	An increased risk of preterm births (RR 1.08, 95% CI 1.01, 1.15) and tendency towards an increased risk of LBW births (RR 1.12, 95% CI 0.98, 1.27) in the highest quintile of distance-weighted traffic density compared with the lowest quintile
Rogers and Dunlop[16]	Population-based cohort study	County-level exposure to particulate matter <10 µm in size: VLBW births (AOR 2.54, 95% CI 1.46, 4.22) preterm births (AOR 4.31, 95% CI 1.88, 9.87)

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; LBW: low birth weight; RR: risk ratio; VLBW: very low birth weight.

Other toxins implicated in preterm labour are aldrin, dieldrin, hexachlorocyclohexane, lead, and polychlorinated biphenyls. The chemicals implicated in LBW births are benzene, cadmium, lead, and polychlorinated biphenyls.

Intervention

No intervention studies were identified.

Conclusions

Exposure to environmental toxins can result in preterm/LBW births. The biological mechanisms are poorly understood for most environmental toxins. Epidemiological data support a trend towards an increase in preterm/LBW births following exposure; however, authors have differing interpretations of the literature. Additional research is needed from a local perspective for policy

purposes. The Canadian Institute of Child Health[17] suggests a Precautionary Principle, that is, "when an activity raises threats of harm to the environment or human health, precautionary measures should be taken, even if some cause and effect relationships are not fully established scientifically."

Water Contamination

Disinfection of drinking water is a common practice in most countries. However, disinfection leaves by-products in the water that can be harmful.

Biological plausibility

Major by-products of water disinfection include haloacetic acid, trihalomethanes, haloacetonitriles, and other classes of chemicals.[18] The exact biological mechanism of their effect on preterm/LBW births is not understood.

- Teratogenic alterations of brain, heart, and eye development were observed in mice when exposed to haloacetic acid.[19] These effects were probably due to altered cellular development.
- Reduction in BW has been described in rats exposed to chloroform.[20]

Epidemiological association

Evidence from systematic and other reviews

Bove et al.[18] systematically reviewed the effects of drinking-water contamination on the risk of preterm/LBW/SGA births. The studies evaluated the type of water disinfectants used and measured the levels of disinfectant by-products in end-user tap water and at the water source. Of the five studies that reported measuring end-user disinfectant by-product, two reported a significant increase in the risk of SGA births with increased total trihalomethanes (OR 1.5 to 5.9), one reported borderline increase in the risk of SGA births with increased levels of trihalomethanes, and one reported increased risk of SGA births with increased levels of chloroform but not bromodichloromethane. The risk of LBW was increased in one study with increased levels of total trihalomethanes, but not in three other studies. There was no increased risk of preterm births in any of the five studies with increased levels of total trihalomethanes or chloroform. Of the four studies that evaluated disinfectant by-products at the water source, one reported a significant increase in the risk of smaller head circumference in infants with increased total chlorine dioxide and sodium hypochlorite (OR 2.0 and 2.3, respectively). Two studies reported no significant increase in the risk of SGA births. The risk of LBW births was increased in one study with increased levels of sodium hypochlorite, but not in three other studies. There was an increased risk of preterm births (OR 1.3) in one study, but three other studies showed no statistically significant increase in the risk of preterm births. Exposure to solvents such as trichloroethylene or tetrachloroethylene was associated with

a borderline increase in SGA births in one study but had no effect in another. One study reported a significant reduction in BW (139 g less) after exposure to trichloroethylene. There was no effect of solvent exposure on the risk of LBW in four studies. Higher levels of carbon tetrachloride were associated with an increased risk of SGA births (OR 1.75, 95% CI 1.3, 2.3) and LBW births (OR 2.3, 95% CI 1.5, 3.4) in one study. None of the studies assessed women's exposure to toxins by directly estimating the intake.

Evidence from other study designs

The studies reporting the impact of water contamination on preterm/LBW births are summarized in Table 10.2.

Table 10.2: Studies of the impact of water contamination on preterm/LBW births

Study	Characteristics	Results
Hinckley et al.[21]	Cohort study	No association with increased levels of total trihalomethanes, and both chlorinated and brominated trihalomethanes, with IUGR or LBW births Exposure to the highest levels of dichloroacetic acid and trichloroacetic acids was associated with an increased risk of IUGR births (OR 1.28, 95% CI 1.08, 1.51 and OR 1.19, 95% CI 1.01, 1.41) but not LBW births (OR 1.10, 95% CI 0.80, 1.50 and OR 1.00, 95% CI 0.73, 1.32) Exposure to >8 µg/l of dichloroacetic acid in the last 3 weeks of pregnancy was associated with an increased risk of IUGR births (OR 1.27, 95% CI 1.02, 1.59) Exposure to moderate concentrations of dibromoacetic acid in the last 3 weeks of pregnancy was associated with an increased risk of LBW births (OR 1.38, 95% CI 1.02, 1.86)
Infante-Rivard[22]	Case-control study	No increased risk of IUGR births with levels of specific and total trihalomethanes (OR 0.97, 95% CI 0.57, 1.62) for levels >90th centile compared with <90th centile If the infant carried 1 or 2 variant alleles of CYP2E1 (G1259C), there was a significant increase in the risk of IUGR (OR 13.2, 95% CI 1.2, 146.7)
Hopenhayn et al.[23]	Comparison of infants born in 2 cities	The city of Antofagasta (424 infants) had drinking water arsenic levels of 40 µg/l and the city of Valparaiso (420 infants) had drinking water arsenic levels of 1 µg/l There was a trend towards reduction in BW in infants from the city of Antofagasta (MD -57 g, 95% CI -123, 9)

BW: birth weight; CI: confidence interval; IUGR: intrauterine growth restricted; LBW: low birth weight; MD: mean difference; OR: odds ratio

Intervention

No intervention studies were identified.

Conclusions

A weak association was observed between exposure to high levels of disinfectant by-products and LBW/SGA births. No association was observed between exposure and preterm births.

Pesticide Exposure

Pesticides are used worldwide to control insects, weeds, plant infections, and animal infections. Although exposure is ubiquitous, it is more common in farmers and gardeners.

Biological plausibility

- Exposure to pesticides can affect germ cell meiosis or induce mutation.[24]
- Potential lifelong storage of these chemicals in the body can lead to germ cell and stem cell damage.[24]
- Increased risk of fetal death is reported following pesticide exposure.[25]
- Organophosphate pesticides depress acetylcholine esterase. Acetylcholine is known to stimulate uterine contractions and may reduce the length of gestation.[26]

Epidemiological association

Evidence from systematic and other reviews

Hanke and Jurewicz[27] reviewed four studies that evaluated the role of either maternal or paternal exposure to pesticides and preterm birth. One study (Montreal, Canada) reported an increased risk of preterm births (OR 1.86); one study (Scotland) reported a borderline increased risk (OR 1.4); one study (Ontario, Canada) reported an increased risk with exposure to crop herbicide and atrazine (OR 4.9) and to crop herbicide and 2,4-DB (OR 3.5); and one study (Colombia) reported an increased risk to wives of husbands exposed to pesticides (OR 2.75). Eight studies were reviewed that explored the association of pesticide exposure and LBW. One study (Montreal) reported a higher observed-to-expected ratio of LBW infants in exposed mothers. One study reported a higher risk of LBW in rice farmers (OR 3.6, 95% CI 2.4, 5.4). One study (Brazil) reported a lower mean BW by 117 g in infants born to exposed mothers. One study (Norway) reported lower mean BWs by 32 g in infants born to grain farmers. One study (Poland) reported that exposure to synthetic pyrethroids during the second and third trimester was associated with reduced BW ($p = 0.002$). Another study (Poland) reported a lower mean BW by 100 g in exposed mothers; however, the results did not reach statistical significance. Two studies (Scotland and Ontario) reported no association between pesticide exposure and LBW birth. The association with LBW births was difficult to ascertain because, with the presence of various chemicals in the pesticides, identification of an individual chemical as the culprit could be difficult. Increased incidences of birth defects such as orofacial clefts, musculoskeletal defects, hemangioma, and nervous system defects were identified following exposure to pesticides during pregnancy.

Evidence from other study designs

The results of other studies of pesticide exposure and its effects on preterm/LBW births are summarized in Table 10.3.

Table 10.3: Impact of pesticide exposure on preterm/LBW births

Study	Characteristic	Results
Zhu et al.[28]	Population-based cohort study from Denmark	No increased risk of preterm births in gardeners (AOR 1.4, 95% CI 0.8, 2.4) or farmers (AOR 1.0, 95% CI 0.5, 1.8) An increased risk of preterm births <34 weeks among gardeners (AOR 2.6, 95% CI 1.1, 5.9) but not among farmers (AOR 0.8, 95% CI 0.2, 3.4) Reduced risk of SGA births in farmers (AOR 0.6, 95% CI 0.3, 1.0) and not significantly different in gardeners (AOR 1.0, 95% CI 0.6, 1.6)
Eskenazi et al.[26]	Cohort study from California, US	No adverse effect on BW was identified with any measures on in utero organophosphate exposure Malathion exposure was associated with shortened duration of gestation
Whyatt et al.[29]	Cohort study from New York, US	No relationship between maternal air insecticide level and BW Reduction in BW (-186 g, 95% CI -375, -45) in the highest vs. the lowest exposure levels as assessed by cord levels of chlopyrifos and diazinon A decrease in the exposure levels for infants born in the same area was noted after the year 2001 when the US Environmental Protection Agency undertook regulatory actions for the residential use of pesticides
Ronda and Regidor[30]	Population-wide data from Spain	An increase in mean BW among infants born to fathers who worked in agricultural sectors compared with non-agricultural sectors (MD 29 g, 95% CI 27, 30) Decreased risk of LBW among babies born to fathers who worked in agricultural sectors compared with non-agricultural sectors (AOR 0.86, 95% CI 0.84, 0.89)
Willis et al[31]	Cohort study from California, US	No increased risk of LBW with exposure to pesticides (RR 1.05, 95% CI 0.14, 7.97)

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; LBW: low birth weight; MD: mean difference; RR: risk ratio; SGA: small for gestational age.

Intervention

Williams et al.[32] reported on a pilot intervention study to reduce exposure of residents to pesticides by using Integrated Pest Management measures in the intervention group. Interventions included professional cleaning of the house, sealing of pest entry points, application of low-toxicity pesticides, and education of residents. The control group received only reading material that stressed the importance of reducing pesticide use and described techniques for controlling pests. Infestations by cockroaches were reduced in the intervention group ($p = 0.016$). No birth outcomes were reported in this trial.

Conclusions

Exposure to pesticides during pregnancy can lead to preterm births. The impact on LBW is inconsistent and further research is warranted on specific chemicals. A recent study of exposure to pyrethroids suggests an increased risk; however, this result needs to be confirmed in other studies. Different findings in various studies could be due to different methods of measuring the exposure. Increased risk of birth defects warrants avoidance of exposure for a pregnant woman or a woman planning to get pregnant.

Ambient Air Temperature/Seasonal Variation

Individuals adapt to seasonality and environmental conditions. The effects of different seasons and temperatures on various birth outcomes have been studied.

Biological plausibility

The exact role of seasonal variation or outdoor ambient temperature variation in birth outcomes is not clear. Extremely hot and extremely cold environments may affect pregnancy outcomes.

- Heat stress during early pregnancy reduces placental weight, decreases uterine blood flow, and reduces BW.[33]
- Higher energy intake during autumn may lead to reduced rates of LBW births.[34]
- During winter, there is a higher incidence of exposure to infections.
- Reduced physical activity and increased exposure to environmental smoke (within households) may affect BW during winter months. Exposure to low temperature may increase plasma fibrinogen and thus increase plasma viscosity and reduce uteroplacental blood flow and fetal growth.[35,36]

Epidemiological associations

Evidence from systematic and other reviews

No reviews of the effects of ambient air temperature or seasonal variations on pregnancy outcomes were identified.

Evidence from other study designs

Studies reporting the impact of ambient air temperature and seasonal variations on preterm/LBW births are summarized in Table 10.4.

Table 10.4: Reports on the effects of ambient air temperature and seasonal variation on pregnancy outcomes

Study	Characteristic	Results
Lawlor et al.[37]	Population-based cohort from Aberdeen, UK	BWs were lower for infants born in winter months (December to February) compared with those for infants born in autumn months (September to November) An increase of 1° C in the mean ambient outdoor temperature during the middle 10 days of the 1st trimester was associated with a 5.4 g (95% CI 2.9, 7.9) reduction in BW
Elter et al.[38]	Cohort from Turkey – re-analysis	Lowest BWs occurred in the group of women who had their last menstrual periods in summer and autumn ($p < 0.001$) Temperature in the 2nd trimester was identified as an independent determinant of BW
Wells and Cole[39]	WHO global dataset	Heat index explained 46% to 56% of the variance in the BW differences across populations of the world One unit decrease in the heat index was associated with a 2.7% increase in BW
Murray et al.[40]	Population-based cohort from Ireland	The lowest mean BWs were recorded in late spring and summer months The mean BWs in May, June, and July were 26, 30, and 32 g lower compared with mean BWs in January
Matsuda et al.[41]	Population data from Japan	2 peaks in mean BW occurred, in May and October to November, and 2 troughs occurred, in June to September and December

BW: birth weight; CI: confidence interval; WHO: World Health Organization.

Conclusions

From the experimental and epidemiological data, there are indications that seasonal variation may have a role in variations in BW. No study has evaluated the role of seasonal variation in preterm birth. Non-controllable variables such as heat and cold stress are important.

Electromagnetic Environment

Electromagnetic fields (electromagnetic beds)

Bracken et al.[42] performed a prospective study to assess the effects of electromagnetic field exposure, particularly that from electrically heated beds and water beds, on fetal growth. Exposure to electromagnetic fields from electromagnetic beds during pregnancy or before conception had no effect on LBW/IUGR births.

Electromagnetic fields (power lines)

Blaasaas et al.,[43] in a nested case-control study based on a Norwegian cohort, did not find a statistically significant increased risk for birth defects (central nervous system defects, cardiac defects, respiratory system defects, or esophageal defects) when the maternal residence was close to power lines during pregnancy.

Li et al.[44] conducted a prospective population-based cohort study of personal exposure to magnetic fields during pregnancy. The authors found an association between prenatal maximum magnetic field exposure (above 16 milliGauss) and an increased risk for miscarriage (RR 5.7, 95% CI 2.1, 15.7).

Conclusions

Exposure to electromagnetic fields from power lines may increase the risk for miscarriage but not for congenital anomalies. These preliminary findings regarding miscarriage and congenital anomalies need confirmation in future prospective studies, as do potential effects on fetal growth.

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CHAPTER 11:

Occupational Factors, Noise, Violence and Maternal Trauma

Main Summary Points

- Physically demanding work increases the risk of preterm/small for gestational age/low birth weight births. The evidence for efficacy of interventions to reduce work-related stressful situations is weak, but it seems logical for pregnant women to avoid prolonged work-related exertion.
- The effect of individual job type or activity on preterm/low birth weight births is variable. Certain blue-collar jobs are associated with a higher risk of preterm/low birth weight births compared with white-collar jobs. To avoid exposure, a pregnant woman may require a temporary job change.
- Good-quality studies evaluating the effects of high noise level on pregnancy outcomes are lacking. Strategies to decrease women's exposure to excessive noise may be beneficial in reducing adverse pregnancy outcomes.
- Violence and abuse are associated with preterm/low birth weight births. The value of having healthcare professionals screen all pregnant women for violence during the prenatal period is debatable. Interventions to reduce harms have indicated a degree of benefit for mothers; however, the role of interventions in reducing adverse birth outcomes is unknown.
- Maternal trauma during pregnancy increases the risk of maternal and fetal deaths and preterm/low birth weight births. Trauma prevention should be part of any public health agenda for the population at large. Women who are discharged from hospital without having given birth after trauma should be assessed carefully until giving birth, as they are at an increased risk of preterm/low birth weight births.

In this chapter we review the impact of occupation-related factors (occupational conditions and type of occupation), excessive noise, violence and abuse, and maternal trauma on preterm/low birth weight (LBW) births.

Occupational Conditions

Duration of work, type of work, and workplace activities all influence pregnancy outcomes. The number of women working in paid employment during pregnancy increased from 44% in 1961–1965 to 67% in 1991–1995. Women are working for longer periods during pregnancy, with 73% working even in the last month of pregnancy.[1] Many attempts have been made to delineate the effects of work on pregnancy outcomes.

Biological plausibility

The exact mechanism of how work may influence pregnancy outcome is not clear.

- Prolonged standing reduces venous return.[2] Heavy strenuous work that involves prolonged standing can lead to increased sympathetic vasomotor tone to skeletal muscles, leading to compromised uteroplacental perfusion and diminished nutrient and oxygen supply to the fetus.[3]
- Mothers who work in a standing position and who work late into gestation have an increased incidence of large uteroplacental infarcts.[4]
- Hyperthermia following excessive activity may have an effect on the fetus.[3]
- Some women continue to hide their pregnancy for fear of losing their job and even continue to perform strenuous activity in addition to their domestic responsibilities. Stress associated with prolonged strenuous work may initiate labour.[3]

Epidemiological association

Evidence from systematic and other reviews

Mozurkewich et al.[5] reviewed 29 case-control, cross-sectional, and prospective cohort studies assessing the impact of work on the risk of preterm/LBW births. Physically demanding work (defined as heavy and/or repetitive lifting or load carrying, manual labour, or significant physical exertion) was statistically significantly associated with small for gestational age (SGA) births (odds ratio (OR) 1.37, 95% confidence interval (CI) 1.30, 1.44) and preterm births (OR 1.22, 95% CI 1.16, 1.29). The association was similar among cross-sectional and prospective cohort studies. Prolonged standing (defined as >3 hours per day or as the predominant occupational exposure) was associated with an increased risk of preterm births (OR 1.26, 95% CI 1.13, 1.40). Shift work or night work was associated with an increased risk of preterm births (OR 1.24, 95% CI 1.06, 1.46). The authors estimated that one preterm birth might be prevented for every 27 to 80 women who discontinue prolonged standing, for every 23 to 171 women who discontinue shift or night work, and for every 36 to 65 women who discontinue physically demanding work.

Simpson[3] reviewed studies on physical activity and employment during pregnancy. Ten studies were identified that demonstrated the deleterious effect of work on preterm/LBW births, whereas six studies observed no effect of physical exertion on pregnancy outcomes. Simpson ascribed the discrepancies in the results to the following factors: (1) the effects of confounding factors for preterm/LBW births not being assessed in detail in all studies; (2) poor socioeconomic status being the possible reason that some women work late into gestation, the impact of which cannot be separated out; (3) simultaneous assessments of effects of occupational hazards not being considered in most studies; (4) some studies showing a positive correlation because of the toxin exposure rather than the duration of work; (5)

most investigators failing to identify the importance of stress in the causation of adverse pregnancy outcomes; and (6) memory and recall biases.

Nurminen[6] reviewed three studies that reported the effects of shift work on pregnancy outcomes. One study reported increased risk (adjusted OR (AOR) 2.0, 95% CI 1.1, 3.4) for preterm births, one study reported elevated observed-to-expected ratio of preterm births (1.6, non-significant difference), and one study reported no statistically significant difference in the preterm birth rate (3.9% versus 4.8%) with shift work. One study reported an increased risk of LBW with shift work (AOR 2.1, 95% CI 1.1, 4.1). Overall, rotating shifts and night shifts were indicative of increased risk of preterm/LBW births.

Evidence from other study designs

Recent reports on the effect of occupational conditions on some pregnancy outcomes are summarized in Table 11.1.

Table 11.1: Impact of occupational conditions on pregnancy outcomes

Study	Characteristic	Results
Croteau et al.[7]	Cohort study	A cumulative index was calculated by using the following variables: night shifts, irregular or shift work, standing for a minimum of 4 hours/day, lifting loads of >7 kg, noise, moderate-active or high job strain combined with poor social support Risk for SGA births increased as the cumulative index increased (for an index of 1, the OR was 1.1, 95% CI 1.0, 1.3; for an index of 2, the OR was 1.2, 95% CI 1.0, 1.4; for an index of 3, the OR was 1.2, 95% CI 1.0, 1.5; and for an index >4, the OR was 1.3, 95% CI 1.0, 1.6)
Pompeii et al.[8]	Cohort study	There was no increased risk of preterm births in women who lifted repeatedly or stood for at least 30 hours/week An increased risk of preterm births if women worked night shifts (RR 1.5, 95% CI 1.0, 2.0) Decrease in the risk of preterm births if women worked >46 hours/week (RR 0.6, 95% CI 0.4, 0.9) during the 1st trimester; this result may indicate the "healthy worker effect" No increase in the risk of SGA births with night shift work, longer work hours, lifting heavy load, or prolonged standing
Magann et al.[9]	Cohort study	Standing >4 hours/day was associated with increased risk of preterm births (OR 1.69, 95% CI 1.05, 3.16) No overall effect of lifting on preterm labour was noted No overall effect of lifting (p = 0.85) or standing (p = 0.11) on IUGR births was noted
Saurel-Cubizolles et al.[10]	Cohort study	Increased risk of preterm birth for women: working >42 hours/week (OR 1.33, 95% CI 1.1, 1.6) standing >6 hours/day (OR 1.26, 95% CI 1.1, 1.5) with low job satisfaction (OR 1.27, 95% CI 1.1, 1.5)

CI: confidence interval; IUGR: intrauterine growth restricted; LBW: low birth weight; OR: odds ratio; RR: risk ratio; SGA: small for gestational age.

Intervention

The exact quantification of work-related activity during pregnancy that may cause preterm/LBW birth is unknown. Therefore, it is difficult to standardize an intervention and to assess its effect in the general population.

Croteau et al.[7] reported the effects of eliminating the risk of occupational stress (reducing the cumulative index described in Table 11.1) through preventive measures that reduced the risk of SGA births to a level similar to that of unexposed women. When the indexed conditions were not eliminated, the risk of SGA births in women exposed to one, two, three, and four or five conditions increased from 1.14 to 1.77.

Manshande et al.[11] studied the effect of rest on pregnant women in central Zaire. Women were admitted to a "maternity village" for rest in the last month of pregnancy. The results were compared with those of women who continued heavy physical activity. All infants were born full term. The duration of rest had a strong influence on the birth weight (BW) of female infants. There was a net increase in BW of 334 g in female infants, but no significant difference in the BW of male infants.

Fortier et al.,[2] in a maternal interview-based study, identified a higher incidence of preterm births for women who stopped work between 24 and 31 weeks of gestation compared with women who were still working at 32 weeks. This result may reflect what has been described as a "healthy worker effect," that is, women who work late in pregnancy are women who are at lower risk of adverse pregnancy outcomes.

Conclusions

The evidence from epidemiological studies on work, type of work, shift work, and possibility of temporary change in work type indicates that physically demanding work increases the risk of preterm/SGA/LBW births. The biological mechanisms underlying the effect of work on pregnancy are unclear, but several mechanisms are probably working simultaneously. Further research is needed to ascertain these mechanisms, as well as the amount and timing of work exposure and the type of work control during pregnancy required to influence them. Difficulties lie in interpreting data from various studies because the amount of exposure varies and a variety of cut-offs have been used. Some studies reporting improved outcomes for women working until late pregnancy stress that the threshold time for each individual may vary. The evidence for efficacy of interventions to reduce work-related stressful situations is weak, but it seems logical for pregnant women to avoid prolonged work-related exertion.

Occupation Types

The effects of various occupations on LBW/preterm birth have been studied.

Biological plausibility

The effects of occupation on pregnancy outcome could be due to stresses associated with job activity or to exposure to various substances. The effects of job activity (type of work, shift work, standing at job, and lifting) have been described in an earlier section. Work-related exposure to various substances is beyond the scope of this review, as the list could be endless. The biological mechanisms that cause LBW births could be different for different substances.

Epidemiological association

Evidence from systematic and other reviews

No review on this topic was identified.

Evidence from other study designs

Several studies have described types of occupation and their effects on pregnancy outcomes. Two large population-based studies that evaluated the effects of various occupations on pregnancy outcomes are summarized in the following paragraphs.

Chia et al.[12] evaluated parental occupation for all singleton live births in Singapore. There were no differences in the risk of LBW births based on maternal occupational groups. However, compared with the risk of LBW births for fathers who worked as legislators, senior officers, and managers, the risk of LBW births was higher for fathers who were not working (AOR 2.0, 95% CI 1.6, 2.7), for fathers whose occupation was not classifiable (AOR 1.3, 95% CI 1.1, 1.7), or for fathers who worked as cleaners, labourers, or in related work types (AOR 1.3, 95% CI 1.1, 1.6).

Virji and Talbott[13] analyzed data from a national sample in the United States. The occupations were divided into two groups: (1) white-collar workers, which included professionals, technical personnel, managers, administrators, and clerical workers; and (2) blue-collar workers, which included all other occupations. The incidence of LBW was higher among blue-collar workers compared with white-collar workers (16.2% versus 13.2%, $p < 0.05$). The mean BW of singletons was (borderline) higher in white-collar workers compared with blue-collar workers (3299 g versus 3248 g, $p < 0.06$). However, mothers in blue-collar jobs were of lower socioeconomic status, younger, and more often primiparous. When the data were adjusted for confounders, there was no statistically significant effect of the type of job on LBW births.

Savitz et al.[14] analyzed the same data in a case-control study and found that preterm birth was associated with maternal lead exposure (OR 2.3, 95% CI 0.7, 7.0). The risk was doubled if paternal occupation was in the glass, clay, stone, or textile business.

In addition, other studies have described the effects of various occupations on preterm/LBW births. These studies are isolated, with mostly one or a few

studies for a specific occupation. Being an anaesthetist,[15] working as a nurse in anaesthesia,[16] and exposure to halothane as an anaesthetist during pregnancy[17] have been associated with LBW births or reduced mean BW. Exposure to lead at work[18] and high maternal blood lead levels[19] caused by either environmental[20] or occupational exposures have been associated with reduced gestation length and SGA births. Maternal employment in the food and drink manufacturing industry, in metal and electrical manufacturing, or as a cleaner or a maid was associated with LBW births.[21] Laboratory work involving radioimmunoassay or radiolabelling[22] was associated with preterm births (OR 2.2, 95% CI 0.8, 6.2). The risk of intrauterine growth-restricted (IUGR) births was significantly higher among hairdressers (AOR 1.20, 95% CI 1.06, 1.36).[23]

Conclusions

The effect of an individual job type or activity on preterm/LBW births is variable; however, most of the studies suggest a contributing role. Certain blue-collar jobs are associated with a higher risk of preterm/LBW births compared with white-collar jobs. The association in blue-collar jobs may reflect the poor socioeconomic or educational status of these parents. Avoidance of job exposure may be a key factor and a woman may require a temporary job change.

Noise

Excessive noise may influence preterm/LBW births.

Biological plausibility

The mechanism of a noise-induced effect on preterm/LBW births is not known.

Epidemiological association

Evidence from systematic and other reviews

Nurminen[6] reviewed six studies that reported on the effects of noise on preterm/IUGR births. Of the two studies reporting on preterm births, one reported an increased rate of preterm births (risk ratio (RR) 1.6, 95% CI 0.9, 2.9) and the other reported no association (AOR 0.7, 95% CI 0.1, 3.5). Four studies that reported on the risk of LBW births found that the RR or the OR ranged from 1.2 to 2.5 in the exposed group. One study found an insignificant reduction in BW (weighted mean difference (WMD) -228 g, 95% CI -471, 15). It was not possible to assess the cut-off values for a noise level resulting in preterm/LBW births. Noise exposure above 85 to 90 decibels (dB) was suggested as a probable cut-off in one study.

The Committee on Environmental Health, American Academy of Pediatrics,[24] reviewed the effect of noise on the developing fetus. High-frequency hearing loss and minor congenital malformations have been reported in human and animal

studies. Eight studies were reviewed. For the outcome of gestational length, four studies found a reduction, two studies found no effect, and two studies were inconclusive. Four studies of the effect of noise on BW were reviewed. Three showed a reduction in BW in the noise-exposed group. One retrospective study reported a higher incidence of BW <3000 g (23.8% compared with 18.1%) for women residing in an area where the noise level exceeded 60 to 65 dB.

Evidence from other study designs

Magann et al.[9] prospectively evaluated active-duty pregnant women in the Naval Medical Center in San Diego, United States, for job exertion and noise level (exposure around flying aircrafts and working with the machinery). There was a significant association of noise exposure (85 dB LAeq for >8 hours) with preterm labour ($p < 0.003$) but not with preterm births. After the investigators adjusted for confounders, the effects were statistically insignificant (OR 1.76, 95% CI 0.78, 3.39).

Conclusions

Few good-quality observational studies and no interventional randomized studies have been done to evaluate the effects of high noise level on pregnancy outcomes. However, available studies have suggested a possible role of noise in adverse pregnancy outcomes. The effect of noise may be a marker for other risk factors such as other environmental exposure, pattern of work or stress, or duration of work. Further research that controls for other variables is needed. Strategies to decrease women's exposure to excessive noise may be beneficial in reducing adverse pregnancy outcomes.

Violence or abuse

Violence or abuse during pregnancy poses threats to both mother and fetus. The incidence of intimate partner violence is reported to be between 6% and 8%.[25,26] Pregnancy is considered as the time when changes in abuse may occur, such as initiation, escalation, or stoppage. Up to 64% of women abused during pregnancy report escalation of abuse during pregnancy. Most (95%) report escalation after the birth of the baby. The incidence is higher in teenagers and adolescents, reaching 23% to 37%.[27] The reported rate of intimate partner violence was higher in an aboriginal population compared with non-aboriginals.[28]

Biological plausibility

The effects of violence or abuse on pregnancy outcome can be either direct or indirect.

- Direct influences include trauma to the abdomen, which leads to release of arachidonic acid and initiates contractions and preterm labour;[29] rupture of fetal membranes; placental abruption; or rarely, rupture of the uterus.[30]

- Indirect influences include resultant ongoing psychological stress from violence. This may lead to depression and adoption of risky or dangerous behaviours such as use of tobacco, alcohol, or illicit drugs or inadequate use of health services. All of these behaviours are associated with preterm/LBW births.[31]
- Verbal abuse about women's weight during pregnancy may lead to purposeful limitation of weight gain and may predispose to LBW births.[32]
- Unintended pregnancies resulting from abusive relationships can result in preterm/LBW births.[33]
- Adolescent fathers in denial disagree about their role in causing the pregnancy because of a lack of understanding and they may have suspicions regarding paternity.[31]

Epidemiological association

Evidence from systematic and other reviews

Boy and Salihu[34] reviewed 23 studies of intimate partner violence and pregnancy outcomes. Three interview-based cohort studies reported no significant differences in the risk of preterm/LBW births among abused and non-abused women. Seven studies reported mixed outcomes. Two of these studies reported higher risk of fetal death and two reported lower mean BWs; however, none of these studies reported an association with preterm/LBW births. Of the remaining 13 studies, 10 reported significant differences in the risk of LBW births among abused women and two reported a weak association with LBW births. Overall, the RR of LBW births was 1.5 (95% CI 1.1, 2.2) and the weight difference was -20 g. Four studies reported an increased risk of preterm births among abused women. The risk of preterm births varied from 1.6 (95% CI 1.4, 2.3) to 2.7 (95% CI 1.7, 4.4). Similar to the results reported by Murphy et al.[29] in a previous review, Boy and Salihu found marked heterogeneity in the definitions of violence, the times at which the mothers were assessed, the methods of ascertainment, the tools used to ascertain abuse, and the populations included in the studies.

Pallitto et al.,[33] in a review that addressed the relationship of intimate partner violence and unintended pregnancy, reported similar difficulties in combining the studies and suggested more exploration of pathways.

Gazmararian et al.[35] reviewed the method of assessing or ascertaining the incidence of abuse across various studies. The incidence of abuse during pregnancy varied between 0.9% and 20.1% among the studies. The studies differed in how violence was measured, in the population studied, and in the methods of assessment. The prevalence was higher in studies in which violence or abuse was assessed more than once during pregnancy or when it was ascertained later in pregnancy (7.4% to 20.1%). The incidence was lower among mothers attending private clinics and when personnel other than a healthcare provider asked the questions.

Evidence from other study designs

Studies reporting outcomes following maternal violence are summarized in Table 11.2.

Table 11.2: Impact of violence on pregnancy outcomes

Study	Characteristics	Results
El Kady et al.[36]	Cohort study	During the 1st admission after assault, there was a higher risk of preterm births (OR 2.4, 95% CI 1.8, 3.3) compared with non-assaulted women Women admitted at a subsequent visit had an increased risk of abruption (OR 1.8, 95% CI 1.3, 2.5), preterm births (OR 1.3, 95% CI 1.2, 1.5), and LBW births (OR 1.7, 95% CI 1.5, 1.9)
Yang et al.[37]	Cohort study	Risk of LBW was increased in mothers who reported abuse compared with non-abused mothers (AOR 2.43, 95% CI 1.06, 5.55)
Yost et al.[38]	Cohort study	6% reported domestic violence, 1% declined to answer Incidence of LBW births was higher in the abused group compared with the no-abuse group (7.6% vs. 5.1%, p = 0.002) Incidence of LBW births was higher among women who declined to answer (12.8% vs. 5.1%, p < 0.001) compared with the no-abuse group Risk of preterm births at <36 weeks was higher in the declined-to-answer group (16% vs. 6%, p < 0.001) compared with the no-abuse group, and the risk of preterm births at <32 weeks was higher in women who declined to participate compared with the no-abuse group (5.3% vs. 1.2%, p = 0.002)
Kaye et al.[39]	Cohort study	There was an increased risk of LBW births among abused women compared with non-abused women (RR 3.78, 95% CI 2.86, 5.00) Mean BW was lower in infants born to abused women compared with non-abused women (MD -186 g, 95% CI -76, -296)

AOR: adjusted odds ratio; BW: birth weight; CI: confidence interval; LBW: low birth weight; MD: mean difference; OR: odds ratio; RR: risk ratio.

Intervention

Evidence from systematic and other reviews

Interventions against violence or abuse could be viewed from two perspectives: screening and harm reduction.

Screening of women (pregnant or non-pregnant) by healthcare professionals to identify abuse or to identify women at risk of abuse has been reviewed extensively by three preventive task forces, one in the United States (US Department of Health and Human Services), one in the United Kingdom,[40] and one in Canada.[41] All three reviews concluded that there is a lack of evidence for or against routine screening for violence against women in a regular healthcare

setting. The reviews found that no studies have been performed that have linked routine screening to positive changes in the abusive relationship. Lack of training, gaps in the provider's knowledge, and shortage of time are some of the barriers reported by healthcare professionals. From a woman's perspective, shame and fear of retaliation are major factors in non-disclosure. Further qualitative and quantitative studies are needed.

Wathen and MacMillan[42] recently reviewed interventions for violence against women in general (not specific to pregnancy) in 22 studies. Reliable and valid screening instruments were identified. However, the authors did not identify any studies that used these screening instruments and demonstrated the benefits of this approach. Most of the women in such circumstances are offered shelter stays. No high-quality studies of the benefits of shelter stays were identified. A reduction in the rate of abuse has been reported for women who spent at least one night in shelter and received counselling and advocacy programs. Several other strategies used in various settings have not been evaluated in rigorous scientific studies.

Evidence from other study designs

Tiwari et al.[43] randomized 110 pregnant women with a history of intimate partner abuse to empowerment training versus control. Empowerment training was designed to increase abused women's independence and control and was culturally and locally adapted. Intervention was administered by a senior midwife at entry into the study in a personal one-to-one session. All women continued to stay with their partner during the study. Physical functioning improved significantly and there were improved scores of role limitation measures for physical and emotional problems. Psychological abuse and minor physical violence declined. No data on birth outcomes were reported.

Curry et al.[44] reported a randomized controlled trial of individualized nursing care management for pregnant women who reported abuse. Women in the intervention group (n = 499) received an abuse video demonstration and were offered access to a nurse case manager and individualized nursing care management throughout the pregnancy. Pregnant women in abusive relations were found to have very high levels of stress and a complicated life. Most of the abused women sought help for basic needs rather than for abuse alone. The authors suggested careful assessment of the needs of the abused women as an important priority for the healthcare professional. No birth outcomes were reported.

Conclusions

The reported prevalence of violence and abuse during pregnancy varies. Violence and abuse are important factors in causing adverse pregnancy outcomes. Direct effects of trauma and indirect influences such as stress and risk-taking behaviours following abuse are possible biological mechanisms. The epidemiological evidence suggests that violence and abuse are associated with preterm/LBW births. The value of screening all pregnant women by healthcare professionals for violence

during the prenatal period is debatable. The Society of Obstetricians and Gynaecologists of Canada[45] recommends prenatal screening and identification of women who are victims of violence or abuse. The Antenatal Psychosocial Health Assessment form can help healthcare providers in assessing the risk factors.[46] Interventions to reduce harms have indicated a degree of benefit for mothers; however, the role of interventions in reducing adverse birth outcomes is unknown.

Maternal Trauma

Biological plausibility

In addition to the mechanisms described in the section on intimate partner violence, trauma in pregnancy can result in utero-placental-fetal injury, maternal shock, pelvic fracture, severe head injury, and hypoxia.[47,48] Maternal trauma during pregnancy has become one of the leading causes of maternal mortality during pregnancy.

Epidemiological association

Evidence from systematic and other reviews

No review was identified.

Evidence from other study designs

Studies reporting outcomes following maternal trauma are summarized in Table 11.3.

Table 11.3: Impact of maternal trauma on maternal and fetal deaths and adverse pregnancy outcomes

Study	Characteristics	Results
El Kady et al.[49]	Cohort study	For women at the time of trauma hospitalization: maternal death (OR 69, 95% CI 42, 115), fetal death (OR 4.7, 95% CI 3.4, 6.4), uterine rupture (OR 43, 95% CI 19, 97), and placental abruption (OR 9.2, 95% CI 7.8, 11) For women sustaining trauma prenatally: an increased risk of placental abruption (OR 1.6, 95% CI 1.3, 1.9), preterm labour (OR 2.7, 95% CI 2.5, 2.9), and maternal death (OR 4.4, 95% CI 1.4, 14)
Schiff and Holt[50]	Population cohort study	Compared with pregnant women not involved in motor vehicle crashes, severely and non-severely injured women were at increased risk of placental abruption and caesarean birth and their infants were at increased risk of respiratory distress syndrome and fetal death Even women involved in motor vehicle crashes who were physically uninjured had an increased risk of preterm labour (RR 7.9, 95% CI 6.4, 9.8) and placental abruption (RR 6.6, 95% CI 3.9, 11.2)
Sperry et al.[51]	Cohort study	Injured mothers had a statistically significantly increased risk of preterm births (RR 1.9, 95% CI 1.1, 3.3) and LBW births (RR 1.8, 95% CI 1.04, 3.2) for the remainder of the pregnancy The risk was higher with increasing injury severity and among those injured early in the pregnancy

CI: confidence interval; LBW: low birth weight; OR: odds ratio; RR: risk ratio.

Intervention

The priority in the management of a pregnant woman who has sustained major trauma is stabilization. After stabilization, an assessment of obstetric complications should follow. Fetal heart rate monitoring should be used to assess the fetus in pregnancies of ≥22 weeks' gestation[52]. Active interventions, such as caesarean section, may be considered if fetal compromise is noted.[52] Kleihauer-Betke (KB) testing accurately predicts the risk of preterm labour following maternal trauma, but clinical assessment does not.[53] With a negative KB test, post-trauma electronic fetal monitoring duration may be safely limited, whereas with a positive KB test, the significant risk of preterm labour mandates close monitoring. In cases of injury inflicted by self, partners, or others, appropriate services need to be notified. No study has assessed the effectiveness of these interventions.

Conclusions

In addition to maternal and fetal deaths, maternal trauma during pregnancy increases the risk of preterm and LBW births. Trauma prevention should be part of any public health agenda for the population at large. Proper maternal stabilization and obstetric assessments during the initial hospital admission are essential to optimize pregnancy outcomes. Woman discharged without having given birth should be assessed carefully until giving birth as they are at an increased risk of preterm/LBW births.

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CHAPTER 12:

Nutritional Factors/Interventions

Main Summary Points

- Nutrition is a significant determinant for fetal growth. The major nutritional factors that can affect pregnancy outcomes are the intake of nutrients and the uptake and regulation of nutrients by the fetoplacental unit.
- Multiple factors may affect the nutritional status of pregnant women, including socioeconomic status, lifestyle behaviours, and stress.
- Adequate nutrition should be a primary goal for each pregnancy. Assessment of the nutritional status of all pregnant women and provision of nutritious food to mothers identified as having limited resources to meet the demands of pregnancy may help to break the intergenerational cycle of low birth weight births. Provision of a balanced, nutritious diet to pregnant women may reduce small for gestational age births.
- Interventions directly aimed at the fetus have not been studied adequately enough to make suggestions for their routine use.
- Fish oil supplements may help prevent preterm birth, but this effect needs confirmation.
- Supplements of iron, calcium, magnesium, and zinc have been shown to improve physiological parameters and tend to reduce the rate of preterm/low birth weight births.
- Folic acid supplementation during the pre-conceptional period has shown a beneficial effect in preventing of neural tube defects in fetuses, but its role in preventing preterm/low birth weight births is unclear.
- Vitamin A, vitamin C, vitamin B complex, and minerals need further studies to assess their impact on preterm/low birth weight births.

Inadequate fetal nutrition is the most commonly implicated cause of impaired fetal growth. The adequacy of fetal nutrition depends on nutrient intake of the mother, nutrient supply to the uterus and placenta, transport of nutrients across the placenta, fetal uptake of the nutrients, and fetal regulation of the nutrients. We examine maternal nutrition in this chapter from two standpoints: nutritional advice and the impact of micronutrients. Maternal nutritional status, as indicated by pre-pregnancy weight, body mass index, and weight gain during pregnancy, is discussed in chapter 4.

Biological plausibility

Animal experiments have shown that maternal undernutrition causes slowing of fetal growth following 3 to 4 days of malnutrition; however, the growth returns to normal after re-feeding.[1] In humans, the nutritional needs of a woman vary with the stage of gestation. During the Dutch famine at the end of the Second World War, women with malnutrition in early gestation gave birth to normal-sized infants, whereas mothers who starved in late gestation gave birth to low birth weight (LBW) infants.[2,3] A malnourished mother gives birth to a growth-restricted fetus that develops into a nutritionally deprived mother who gives birth to another child with a similar disadvantage. Factors associated with poor socioeconomic status aggravate the situation, and the intergenerational cycle at times becomes difficult to break.[4] Malnutrition may cause stress in the fetus, which is an important factor in preterm birth.

Nutrients to Fetus

Biological plausibility

- Administration of a nutrient to the fetus is a potential way of improving growth.
- Administration of a nutrient to the mother is attempted to eventually increase the nutrient supply to the fetus.

Epidemiological association

Evidence from systematic and other reviews

In a narrative review, Harding[1] indicated that a fetus obtains 10% of its caloric intake from swallowed amniotic fluid. Animal experiments showed that growth restriction is prevented by infusing nutrients into the fetal gut.[1] Uncontrolled experiments of infusion of glucose and amino acids into the amniotic fluid surrounding human fetuses have shown benefit.[5]

Say et al.[6] reviewed three studies (121 women), one of protein-free calf blood extract, one of carnitine, and one of glucose or galactose administration for suspected fetal growth restriction. There was no difference in the risk of small for gestational age (SGA) births between calf blood extract and placebo (one study, 21 women, risk ratio (RR) 0.54, 95% confidence interval (CI) 0.20, 1.47). Administration of carnitine was associated with shorter duration of pregnancy [one study, 30 women, mean difference (MD) -2.12 weeks, 95% CI -3.6, -0.7], but had no effect on birth weight (BW) (one study, 30 women, MD 79 g, 95% CI -270, 427). There was no significant difference in risk of SGA births in the glucose-supplemented group (one study, 30 women, RR 1.11, 95% CI 0.64, 1.92) or the galactose-supplemented group (one study, 30 women, RR 0.78, 95% CI 0.39, 1.54) compared with the bed rest group.

Conclusions

The evidence supporting measures to improve fetal growth by supplementing mothers with nutrients is weak. Further research is needed.

Measures to Improve Maternal Nutrition

Nutritional advice to the mother

Evidence from systematic and other reviews

Kramer[7] reviewed five studies of nutritional advice to the mother and found problems of biased allocation (three studies), exclusion of patients after randomization (three studies), and difference in caloric intake at baseline between groups. The various methods used in these studies included advice on improving the quality of the diet, nutrition classes, and counselling. There was a borderline increase in both energy and protein intake in women receiving advice. Of the five studies, only two reported on birth outcomes. The risk of preterm births (two studies, 449 women, RR 0.46, 95% CI 0.21, 0.98) declined, but there was no difference in the incidence of SGA births (one study, 404 women, RR 0.97, 95% CI 0.45, 2.11), mean BW [two studies, 426 women, weighted mean difference (WMD) 206 g, 95% CI -242, 654], or duration of gestation (one study, 399 women, MD -0.1 weeks, 95% CI -0.48, 0.28).

Conclusions

Dietary advice to pregnant women appears to be effective in increasing their protein and energy intake; however, its effect on the risk of preterm/SGA births is not convincing.

Maternal nutrients

Various macro- and micronutrients have been studied in relation to maternal and fetal outcomes.

Macronutrients

Energy and protein intake

Nutritional requirements increase during pregnancy to support fetal growth. Adequate intake of a nutritious diet results in adequate growth in animal models; starvation, for even short periods, results in reduced fetal growth.[1] Animal experiments suggest an adverse effect of protein supplementation on pregnancy outcome. Appropriateness of energy and protein intake during pregnancy may be crucial, as excessive weight gain is known to be associated with pregnancy-induced complications such as hypertension.

Epidemiological association and intervention

Evidence from systematic and other reviews

Kramer and Kakuma[8] evaluated the effects of energy and protein supplementation on pregnancy outcomes by reviewing four types of interventions. The results of their review (except for the intervention of a low-energy diet for overweight women, which is described in the section on maternal BMI in chapter 4) are summarized in Table 12.1.

Table 12.1: Impact of energy and protein supplementation on pregnancy outcomes[8]

Intervention	Participants	Results
Supplementation with a balanced protein/energy diet	13 studies involving 4,665 women	An increase in maternal weight gain (20 g/week) and a reduction in the risk of SGA births (RR 0.68, 95% CI 0.56, 0.84) No difference in BW between undernourished and adequately nourished women (24 g vs. 25 g) No difference in the risk of preterm births (RR 0.83, 95% CI 0.65, 1.06) Borderline increase in BW (WMD 38 g, 95% CI -0.2, 75) No difference in the duration of gestation (WMD -0.1 weeks, 95% CI -0.2, 0.03)
High-protein supplementation	Two studies involving 1,076 women	Increase in the risk of SGA births (RR 1.58, 95% CI 1.03, 2.41) A trend towards a reduction in mean BW (WMD -58 g, 95% CI -146, 30) No difference in the risk of preterm births in the high-protein group (RR 1.05, 95% CI 0.69, 1.60)
Isocaloric protein supplementation	Three studies involving 966 women	No difference in: maternal weight gain (WMD 52 g/week, 95% CI -75, 178) BW (WMD 33 g, 95% CI -158, 225) preterm births (RR 1.05, 95% CI 0.69, 1.60) An increased risk of SGA births was reported in the isocaloric protein intake group (RR 1.35, 95% CI 1.12, 1.61)

BW: birth weight; CI: confidence interval; RR: risk ratio; SGA: small for gestational age; WMD: weighted mean difference.

Conclusions

The available evidence to date does not support a recommendation for high protein intake or isocaloric protein supplements during pregnancy. Supplementing mothers with a balanced protein diet has been shown to reduce the risk of SGA births. A potential beneficial effect of adequate nutrition in malnourished mothers is likely. No potential adverse effects were noted. A balanced intake of protein and energy is a prerequisite for all pregnant women and should be recommended.

Biological plausibility

- Fish oil contains long-chain n-3 fatty acids.[9] They increase the formation of prostaglandin (PG) in the form of PGI_2 and PGI_3, leading to relaxation of the myometrium and prolongation of gestation,[9] and decrease the thromboxane-to-prostacyclin ratio and blood viscosity, leading to improved placental blood flow and subsequent fetal growth.[9]
- Long-chain n-3 fatty acids may postpone the onset of parturition by down-regulating the formation of PGs involved in triggering parturition (PGE_2 and $PGF_{2\alpha}$).[9]
- n-3 fatty acids protect against pre-eclampsia and pregnancy-induced hypertension.[9]
- On the other hand, consumption of seafood has been associated with the possibility of an environmental pollutant effect and reduced fetal growth.[10]

Epidemiological association

Evidence from systematic and other reviews

No review that assessed the impact of a deficiency of fish oil in the diet on preterm/LBW births was identified.

Evidence from other study designs

Olsen and Joensen[11] reported higher average BW and average gestational length among infants born to the residents of Faeroe Islands, Denmark, compared with the rest of the country. Fishery has been the principal way of life on Faeroe Islands and the authors postulated that fish consumption may be the reason for this difference.

Olsen and Secher,[12] in a prospective cohort study, reported that the rate of preterm births was 7.1% in a group of patients who never consumed fish compared with 1.9% in a group of women who reported consuming a hot meal of fish or an open sandwich with fish at least once a week (AOR for preterm birth 3.6, 95% CI 1.2, 11.2).

Oken et al.[13] reported that after adjustment for maternal and child factors, BW was 94 g (95% CI 23, 266) lower in the highest compared with the lowest quartile of first-trimester n-3 polyunsaturated fatty acid intake.

Olsen et al.,[14] in a secondary analysis, reported that, compared with non-fish consumers, women who consumed fish at least once per week: (1) during early pregnancy had a reduced risk of preterm births (OR 2.4, 95% CI 1.2, 4.6) and a prolonged gestation (MD 3.9 days, 95% CI 2.2, 5.6); (2) during the second trimester of pregnancy had a reduced risk of preterm births (OR 2.4, 95% CI 1.2,

4.8) and a prolonged gestation (MD 3.1 days, 95% CI 1.4, 4.8); and (3) in the first and second trimesters of pregnancy had a reduced risk of preterm births (OR 19.6, 95% CI 2.3, 165.0) and a prolonged gestation (MD 8.6 days, 95% CI 5.5, 11.7).

Intervention

Evidence from systematic and other reviews

Makrides et al.,[15] in a review of six randomized controlled trials (RCTs) of marine oil, and other PG precursor supplementation, reported that the length of gestation was longer in the marine oil supplementation group compared with the placebo or no-intervention groups (WMD 2.6 days, 95% CI 1.03, 4.07). There was no difference in the risk of preterm births of <37 weeks (RR 0.92, 95% CI 0.79, 1.07). There was a reduction in the risk of preterm births of <34 weeks (RR 0.69, 95% CI 0.49, 0.99). BW was higher in the marine oil group (WMD 47 g, 95% CI 1, 93) compared with the control group, but there was no difference in the risk of LBW births (RR 1.00, 95% CI 0.88, 1.12) or SGA births (RR 1.13, 95% CI 0.96, 1.34).

Olsen[16] reviewed seven studies that reported on the effect of marine oil supplementation on preterm births. Five studies were the same as those reviewed by Makrides et al.;[15] one study had been excluded by Makrides et al.[15] because of a high attrition rate and one study had been conducted in 1938 to 1939. Some studies used olive oil as a control intervention and in some studies a high concentration of linolenic acid, which is a precursor of PG, may have had an impact on the duration of gestation. Because of the inconclusive results of various studies, the author indicated that further trials are needed to address the prevention of recurrent preterm births with marine oil supplementation.

Decsi and Koletzko[17] reviewed six RCTs (only two studies were included in the review by Makrides et al.[15]). Three studies reported no significant differences in the gestational age, BW, birth length, or head circumference between newborns born to mothers who received n-3 fatty acids and those born to mothers who received placebo. One study reported significantly longer gestation in fetuses who had high levels of plasma docosahexaenoic acid levels compared with those who had low levels. One study reported a difference of 6 days in gestation length between groups. One study reported significantly higher BW in the supplemented group, particularly the group that received a very high dose of alpha-linolenic acid.

Conclusions

Biological and epidemiological evidence provide conflicting data on the benefits of fish oil consumption for women. Data from interventional studies suggest that routine supplementation with marine oil for prevention of preterm births or LBW is not recommended. However, a borderline advantage in reducing preterm births of <34 weeks' gestational age warrants further study.

Iron

Biological plausibility

Iron requirements increase during pregnancy. Changes in the hematological parameters suggestive of iron deficiency are evident in most women as pregnancy advances. The relationship between maternal hemoglobin level and BW and preterm births has been described as U-shaped, with high rates at the extremes of iron levels.[18]

- Maternal oxygen content influences the development of the placenta and the release of growth hormones from the placenta.[19]
- Iron deficiency leads to release of norepinephrine, which in turn stimulates corticotropin-releasing hormone (CRH) and may trigger the cascade of labour.[20]
- Chronic hypoxia that results from anemia can cause the release of stress hormones.[20]
- Iron-deficiency anemia predisposes women to increased risk of infection.[20]
- Iron deficiency causes increased oxidative stress, and reactive oxygen species that are released during oxidative stress can lead to damage of the fetoplacental unit.[20]
- High hemoglobin levels lead to increased viscosity and sluggishness of circulation and reduced uteroplacental blood flow.[21]

Epidemiological association

Evidence from systematic and other reviews

Rasmussen[18] reviewed studies of the association between birth outcomes and iron deficiency, iron-deficiency anemia, and anemia. The U-shaped association (increase in the proportion of LBW births and decrease in mean BWs at the extreme values of hemoglobin) was mostly confirmed in all of the largest observational studies. High hemoglobin values reflect either poor plasma volume expansion or an underlying pathological condition, whereas low hemoglobin values reflect inadequate maternal stores. Rates of preterm births were minimal when maternal hemoglobin ranged between 115 and 125 g/l in white women and between 105 and 115 g/l in black women. The reported RR of LBW births was between 0.76 and 2.96 for moderate anemia and between 1.0 and 6.33 for severe anemia. The attributable risk for LBW births for moderate anemia was reported to be between 42% and 55% and for severe anemia between 34% and 84%. Similarly, the RR for preterm births in women with moderate anemia was between 0.6 and 3.2, and for severe anemia it was between 0.55 and 4.01. The

attributable risk for preterm births from these studies was between 23% and 67% for moderate anemia and between 9% and 30% for severe anemia. Marked heterogeneity was noted among these studies. An uncontrolled estimate of a 200 to 400 g reduction in BW was noted in women with severe anemia (haemoglobin <80 g/dl).

Xiong et al.[22] performed a meta-analysis of 10 studies and reported that anemia during early pregnancy was associated with an increased risk of preterm births (AOR 1.32, 95% CI 1.10, 1.72) but not with an increased risk of LBW births (AOR 1.39, 95% CI 0.70, 2.74) or intrauterine growth restriction (IUGR) (AOR 1.01, 95% CI 0.73, 1.38). Anemia during late pregnancy was not associated with an increased risk of preterm births (AOR 0.92, 95% CI 0.54, 1.84), LBW births (AOR 0.80, 95% CI 0.64, 1.00), or IUGR births (AOR 1.09, 95% CI 0.70, 1.70).

Intervention

Evidence from systematic and other reviews

Pena-Rosas and Viteri[23] reviewed 40 randomized or quasi-randomized trials. Significant heterogeneity was noted among these studies. Combining data from four studies revealed a trend towards reduction in the risk of LBW births with iron supplementation (RR 0.59, 95% CI 0.23, 1.49), but this was not statistically significant. There was no difference if the supplementation was started before 20 weeks of pregnancy (RR 0.59, 95% CI 0.12, 2.96) or after 20 weeks of pregnancy (RR 0.55, 95% CI 0.22, 1.38), or if mothers were anemic or non-anemic at the start of supplementation. There was no difference in BW (WMD 22 g, 95% CI -99, 144) with routine supplementation. There was a trend towards a reduction in the incidence of preterm births (RR 0.76, 95% CI 0.47, 1.24), but this was not statistically significant. Subgroup analyses indicated no difference based on the timing of initiation of supplementation (before or after 20 weeks) or maternal hemoglobin status (anemic or non-anemic) on the risk of preterm births. There was no difference in BW (MD -68 g, 95% CI -398, 262) or risk for preterm births (RR 0.46, 95% CI 0.02, 8.96) if iron was given intermittently versus daily. There was no difference in the risk of LBW births (RR 5.00, 95% CI 0.25, 98.96), mean BW (MD -32 g, 95% CI -213, 149), or preterm births (RR 7.00, 95% CI 0.38, 128.61) between daily iron-folic acid supplementation and placebo. There was no difference in the risk of LBW births (RR 0.99, 95% CI 0.50, 1.97) or mean BW (WMD -8 g, 95% CI -74, 57) between the intermittent iron-folic acid group and the daily iron-folic acid group.

Cuervo and Mahomed[24] reviewed one study comparing the effect of oral iron and intravenous iron treatment on LBW births. None of the infants in either arm of the study were LBW. There was no significant difference in the mean BW (MD -119 g, 95% CI -312, 74).

Evidence from other study designs

Siega-Riz et al.[25] reported data on an RCT of 429 women who had hemoglobin levels of ≥110 g/dl and ferritin levels of >40 µg/l before 20 weeks of gestation. Women were randomized to receive either 30 mg of iron sulphate or placebo until 26 to 29 weeks of gestation. There was a significant improvement in BW (mean BW 3325 g versus 3217 g, p = 0.03), a statistically insignificant reduction in LBW births (4.8% versus 9.5%, p = 0.09), and a marginal reduction in preterm births (7.5% versus 13.9%, p = 0.05).

Conclusions

Iron deficiency is associated with LBW births and possibly preterm births. However, there was marked heterogeneity among the studies. The effects of hemoglobin levels on pregnancy outcome are manifested at extremely low and high values. Studies from various parts of the world suggest that iron supplementation is associated with improved maternal iron status. There is no evidence that supplementation reduces the incidence of preterm/LBW/IUGR births. The current approach of supplementation with iron during pregnancy was not found to be associated with any side effects and is recommended. Further research is needed to investigate the direct or indirect effects of iron supplementation on both mother and fetus.

Folic acid

Biological plausibility

- During pregnancy, the increased turnover of cells and rapid cell division in the fetus require an increased amount of folate.
- Willoughby and Jewell[26] reported megaloblastic anemia in 3.4% and folate deficiency in 33% of pregnant women.
- Elevated levels of homocysteine in folic acid deficiency can lead to vasculopathy and can cause fetal growth restriction.[27]
- Methyltetrahydrofolate reductase polymorphism, a common genetic abnormality of folate metabolism, has been associated with fetal growth restriction. Its association with vasculopathy is suspected in certain variant mutations to cause preterm birth.[28,29]

Epidemiological association

Evidence from systematic and other reviews

No review of studies of folic acid status and outcomes of pregnancies was identified.

Evidence from other study designs

Siega Riz et al.[30] conducted a study of women between 24 and 29 weeks gestation who completed an interview and a food frequency questionnaire and provided samples for red blood cell folate assay. There was an increased risk of preterm births in women whose dietary intake of folic acid was ≤500 µg/day (AOR 1.8, 95% CI 1.4, 2.6), whose serum folate level was ≤16.3 ng/ml (AOR 1.8, 95% CI 1.3, 2.5), and whose red blood cell folate level was ≤626.6 ng/ml (AOR 1.7, 95% CI 1.1, 2.6).

Intervention

Evidence from systematic and other reviews

Tamura and Picciano[31] reviewed 12 studies of folate supplementation and found that seven reported an increase in BW ranging from 40 g to 407 g, whereas five reported no increase in BW. The authors reported marked heterogeneity among studies for race, maternal size, initial folate status, socioeconomic status, and dietary habits, including the intake of folate and other nutrients among the participants.

Mahomed[32] reviewed 21 randomized and quasi-randomized controlled studies of variable quality. Supplementation with folate improved the biochemical parameters of folic acid status. There was no difference in the risk of preterm births (RR 1.03, 95% CI 0.71, 1.49) or LBW births (RR 0.75, 95% CI 0.50, 1.12).

Evidence from other study designs

Shaw et al.[33] reported data on approximately 6 million births from before and after food fortification with folic acid became mandatory in California. There was a significant reduction in the risk of very low birth weight births (RR 0.94, 95% CI 0.93, 0.96), LBW births (RR 0.91, 95% CI 0.88, 0.94), and preterm births (RR 0.96, 95% CI 0.94, 0.97) in the post-supplementation era.

Conclusions

Folic acid deficiency during pregnancy is associated with adverse pregnancy and fetal outcomes. A genetic polymorphism in folate metabolism plays a role in IUGR and preterm births. There is conflicting evidence for the effect of folate supplementation in reducing preterm/LBW/IUGR births, with some studies showing benefit and others showing a lack of effect. Further research is needed to identify the women who will benefit the most. Folic acid supplementation is currently recommended for all pregnant women as it is shown to reduce neural tube defects and other congenital anomalies.

Biological plausibility

The exact mechanism for the effects of calcium on pregnancy outcomes is unclear.

- Supplementation with calcium leads to reduced parathormone concentration. This results in reduced intracellular free calcium, which leads to smooth muscle relaxation. High levels of parathormone in calcium-deficient women increase intravascular calcium concentration and cause vasoconstriction. This effect may result in pregnancy-induced hypertensive disorders and preterm/IUGR births.[34]
- A role for plasma renin activity and calcium-regulating hormones is suspected in the development of pre-eclampsia.[35]
- Calcium may have an indirect effect by modifying the responsiveness of vasoactive substances.[36] Calcium supplementation may reduce vascular sensitivity to vasoconstrictors.[37]

Epidemiological association

Evidence from systematic and other reviews

Van den Elzen et al.[36] reviewed studies of calcium metabolism in normal and hypertensive pregnancies. There was no difference in serum calcium levels in women with pregnancy-induced hypertension, pre-eclampsia, or chronic hypertension. Three studies reported reduction in serum ionized calcium in pregnancies complicated by hypertension, whereas five studies reported no difference in ionized calcium concentration. Similar results have been obtained in studies measuring parathormone. These discrepancies could be due to varied definitions of pregnancy-associated hypertensive conditions used in various studies.

Intervention

Evidence from systematic and other reviews

Hofmeyr et al.[38] reviewed 12 high-quality studies of supplementation with calcium to prevent hypertensive disorders of pregnancy. A reduced risk of high blood pressure was noted with calcium supplementation (RR 0.70, 95% CI 0.57, 0.86) in all women, in women at risk of hypertension (RR 0.22, 95% CI 0.12, 0.42), and in women with low calcium intake (RR 0.36, 95% CI 0.18, 0.70). A statistically insignificant trend towards a reduction in the risk of preterm births in all women (RR 0.81, 95% CI 0.64, 1.03) was noted. Similarly, a statistically insignificant trend towards reduction in the incidence of LBW births (RR 0.84, 95% CI 0.68, 1.03) was noted. There was a statistically insignificant trend towards an increase in the risk of SGA births (RR 1.10, 95% CI 0.88, 1.37).

Conclusions

Epidemiological evidence indicates that calcium homeostasis plays a role in the development of pregnancy-associated hypertensive disorders. Supplementation with calcium may be beneficial to women who are particularly at risk of developing pregnancy-induced hypertensive disorders or who have low dietary intakes of calcium, as studies have shown that supplementation reduces the risk of pre-eclampsia in these women. The efficacy of supplementation in reducing preterm/LBW births, however, is not proven.

Magnesium

Biological plausibility

Magnesium is required for the synthesis of proteins and the regulation of electrical activity across cell membranes. Epidemiological studies have indicated that magnesium has a beneficial effect on fetal growth.[39]

Epidemiological association

Evidence from systematic and other reviews

Makrides and Crowther[40] reviewed RCTs and one cluster randomized study for trials of magnesium supplementation before 25 weeks gestation and reported a reduction in the risk of preterm births (RR 0.73, 95% CI 0.57, 0.94), LBW births (RR 0.67, 95% CI 0.46, 0.96), and SGA births (RR 0.70, 95% CI 0.53, 0.93) compared with placebo. However, an analysis that did not include the trial with cluster randomization (largest of the trials) revealed no statistically significant difference. The authors had major concerns regarding the quality of the studies.

Conclusions

The biological mechanism of action of magnesium supplementation is not clear. The available evidence from studies of variable quality suggests a benefit of magnesium supplementation in reducing preterm/LBW/SGA births. However, this result requires confirmation in further studies.

Zinc

Biological plausibility

Zinc plays a vital role in cellular functions. Deficiency of zinc has been reported to be associated with several pregnancy complications such as LBW births, pregnancy-induced hypertension, prolonged labour, and postpartum hemorrhage.[39] The biological mechanism is not clear.

- Zinc plays an important role in nucleic acid metabolism and protein synthesis and thus is likely to have an influence on fetal growth.[41]
- Zinc plays a vital role in the function of the immune system, which is important for preventing infection, a known cause of preterm births.[41]

Epidemiological association

Evidence from systematic and other reviews

Tamura and Goldenberg[42] reviewed the association between zinc nutriture and preterm/LBW birth rates. Eight studies evaluated the role of zinc in preterm births. Five studies identified a positive association (either a low level of maternal serum zinc or a low ratio of fetal-to-maternal zinc among preterm births); two studies reported no association with plasma or erythrocyte zinc and preterm births; and one study reported higher levels of zinc in cord blood leukocytes of preterm infants. Forty-one studies reported on the association between zinc status in the mother (measured in blood, serum, erythrocyte, leukocyte, placenta, and amniotic fluid) and BW. Twenty-two studies reported a positive association between maternal zinc status and BW, whereas 19 studies reported a negative association. Four studies reported on dietary zinc intake during pregnancy and BW of infants. Two studies reported a positive association between low dietary intake and lower BW and higher incidence of LBW births, whereas two studies reported no association between dietary intake of zinc and BW. Thus, conflicting results have been reported on the association between zinc and pregnancy outcomes.

Intervention

Evidence from systematic and other reviews

Shah and Sachdev[43] reviewed 15 RCTs of zinc supplementation during pregnancy to improve BW or length of gestation. Of the studies reviewed, 12 reported no effect on BW, whereas two reported significant improvement in BW. Nine studies reported no improvement in the rate of LBW births, whereas two reported a reduction in the incidence of LBW births. Seven studies reported no effect of zinc supplementation on the duration of gestation or preterm births, whereas three reported a reduction in the incidence of preterm births. Marked between-study heterogeneity for underlying population status, dose of zinc, duration of zinc administration, and formulation of zinc supplementation was noted.

Castillo-Duran and Weisstaub[44] reviewed 14 studies (12 studies were included in the review by Shah and Sachdev[43]). Five studies reported improvement in BW and two reported reduction in the incidence of LBW births. Nine studies reported no effect on BW. Four studies reported reduction in the incidence of preterm births, whereas eight reported no effect on the length of gestation. When the authors compared subgroups, depending on the socioeconomic status of

the communities and the level of underlying zinc deficiency, they noted that the positive effect of zinc supplementation was restricted to transitional communities where conditions are improving, although large segments of the community had a diet low in zinc.

Conclusions

The epidemiological evidence indicates that zinc deficiency may have a role in preterm/LBW births; however, results are not convincing. Further research is needed to confirm these results and to understand the exact underlying biological mechanism. From the findings of the reported studies, routine supplementation of zinc to reduce LBW or preterm birth rates cannot be recommended.

Salt intake

Biological plausibility

Salt intake has been a subject of debate as salt can lead to water retention, edema, or both. This effect could be of particular concern for pregnant women at risk of developing pregnancy-induced hypertension.

Epidemiological association

Duley and Henderson-Smart[45] reviewed two studies advising a change in salt intake (20 or 50 mmol/day compared with unchanged salt intake in the diet). There was no difference in the risk of SGA births (RR 1.5, 95% CI 0.73, 3.07), LBW births (361 women, RR 0.84, 95% CI 0.42, 1.67), or preterm births (RR 1.08, 95% CI 0.46, 2.56).

Conclusions

There is no evidence supporting the restriction of salt during pregnancy for reduction in preterm/SGA/LBW births.

Vitamin A

Vitamin A is essential for normal growth and development. Observational studies provide conflicting results regarding an association between low vitamin A levels and BW.

Intervention

Evidence from systematic and other reviews:

Van den Broek et al.[46] reviewed five studies of vitamin A supplementation during pregnancy and noted that vitamin A supplementation led to a reduction in the

risk of maternal mortality up to 12 weeks postpartum (RR 0.60, 95% CI 0.37, 0.97). However, none of the studies reported on pregnancy outcomes.

Ramkrishnan[39] reviewed four experimental studies of supplementation with vitamin A and found conflicting results. The author concluded that there is a need for a well-designed RCT to examine whether improving vitamin A status can alter BW. The teratogenic effects of high doses of vitamin A should be kept in mind.

Conclusions

Further research is needed.

Vitamin B_1 (Thiamine)

Ramakrishnan[39] reviewed the literature related to thiamine deficiency in pregnancy. Thiamine deficiency was associated with IUGR birth in rats, but no human studies have confirmed this finding. Further research in women deficient in thiamine is needed.

Vitamin B_6 (Pyridoxine)

Vitamin B_6 is an important co-enzyme for protein metabolism.

Epidemiological association

Evidence from other study designs

Chang[47] evaluated the effects of graded supplemental pyridoxine intake (0, 1, 2, and 3 mg) and reported that there was an improvement in BW when plasma pyridoxine concentration exceeded 40 nM, which was achieved with supplementation with 2 mg of pyridoxine per day.

Ronnenberg et al.,[48] in a case-control study, reported that the odds of preterm birth were 50% lower when maternal plasma vitamin B_6 was $\geq$30 nmol/L compared with maternal B_6 of <30 nmol/L (OR 0.5, 95% CI 0.2, 1.2); however, the results did not reach statistical significance.

Intervention

Evidence from systematic and other reviews

Thaver et al.[49] reviewed five trials of variable quality. Three trials had large attrition rates. There was a reduction in BW in the pyridoxine group compared with the control group; however, the results were reported in only one small study (MD -230 g, 95% CI -450, -40). The study lacked power.

Conclusions

Current available evidence does not support routine supplementation with vitamin B_6 to prevent preterm/LBW births. Further research in women deficient in vitamin B_6 is needed.

Vitamin B_{12} (Cyanocobalamin)

Vitamin B_{12} is involved in metabolic functions and deoxyribonucleic acid (DNA) synthesis.

Epidemiological association

Ramkrishnan[39] reviewed two observational studies of vitamin B_{12} status and risk of preterm labour. Both studies revealed an association between low vitamin B_{12} levels and preterm labour.

Ronnenberg et al.,[48] in a case-control study, evaluated the levels of vitamin B_{12} in mothers before conception. The odds of preterm birth were 60% lower in mothers with vitamin B_{12} levels $\geq$258 pmol/l compared with mothers with vitamin B_{12} levels <258 pmol/L (OR 0.4, 95% CI 0.2, 0.9).

Intervention

No interventional studies have been performed to date.

Conclusions

Low maternal vitamin B_{12} levels may be associated with preterm labour and preterm births. Further research is needed to evaluate the role and efficacy of supplementation.

Vitamin C

Biological plausibility

- Vitamin C is linked to preterm, prelabour rupture of the membranes because of its function in collagen integrity.
- Vitamin C has an antioxidant effect that may help reduce pre-eclampsia and IUGR births.

Epidemiological association

Mathews et al.[50] reported that vitamin C intake early in pregnancy was associated with BW after adjustment for maternal height and smoking. There was an increase in BW of 51 g (95% CI 5, 97) with each 1 mg increase in vitamin C intake.

Intervention

Evidence from systematic and other reviews

Rumbold and Crowther,[51] in a review, reported that there was no difference in BW (MD -139 g, 95% CI -518, 240) or IUGR births (RR 0.72, 95% CI 0.49, 1.04) between vitamin C supplementation and control groups. There was an increased risk of preterm births among women in the vitamin C group (RR 1.38, 95% CI 1.04, 1.82). Marked heterogeneity among studies was noted.

Conclusions

The data are too limited for conclusions about the benefit and safety of vitamin C during pregnancy. Vitamin C supplementation may increase the risk of preterm births.

Vitamin D

Biological plausibility

The requirement for vitamin D is increased during pregnancy. Whether or not supplementation is associated with any effect on pregnancy is unclear.

Epidemiological association

Mahomed and Gulmezoglu[52] reviewed two RCTs of vitamin D supplementation in pregnancy. The trials had small sample sizes. There was no difference in the risk of LBW births (one study, 126 women, RR 0.55, 95% CI 0.24, 1.25) and SGA births (one study, 126 women, RR 0.54, 95% CI 0.26, 1.10). From the small sample size, the authors concluded that the evidence was insufficient to draw any conclusions.

Conclusions

The evidence to support supplementation with vitamin D during pregnancy is insufficient. Further research is needed.

Vitamin E

Biological plausibility

Vitamin E has an antioxidant effect and may help prevent pre-eclampsia and IUGR births.

Epidemiological association

Ramkrishnan[39] reviewed observational studies and found that vitamin E levels were either lower or normal in different studies of pregnant women.

Intervention

Evidence from systematic and other reviews

Rumbold and Crowther[53] reviewed the effects of vitamin E supplementation for women who either had pre-eclampsia or who were at risk of developing it. There was no difference in the risk of preterm births (RR 1.29, 95% CI 0.78, 2.15), IUGR (RR 0.72, 95% CI 0.49, 1.04), or BW (MD -139 g, 95% CI -518, 240).

Conclusions

There is no conclusive evidence of efficacy or safety of vitamin E supplementation during pregnancy.

Copper and selenium

Epidemiological association

Ramkrishnan[39] reviewed observational studies assessing the levels of copper and selenium for their association with LBW births. Conflicting results were obtained.

Intervention

Han and Zhou[54] studied the effect of selenium supplementation in an RCT of women at risk for pregnancy-induced hypertension. There was a reduction in the incidence of pre-eclampsia but no difference in BW between the two groups.

Conclusions

Further research is warranted.

Multiple Micronutrients

The information on isolated components and their effects on pregnancy outcomes are defined under the headings for the individual components. General information about the role of micronutrients is briefly discussed here. Combining micronutrients in a single package is suggested as a cost-effective way of achieving multiple benefits.

Biological plausibility

The biological mechanism for the effect of supplementation of micronutrients on pregnancy outcomes is not understood.

- Generalized improvement in immune function with the supplementation of micronutrients can lead to reduction in infection and preterm labour.[55]
- The effects of micronutrients on energy metabolism and anabolic processes may lead to reduced incidences of IUGR births.[55]
- The detrimental effects of some stressors could be exaggerated if maternal nutritional status is suboptimal.[55]
- On the other hand, the effectiveness of the interaction between multiple micronutrients has been questioned. The absorption of one nutrient can be enhanced or decreased by other nutrients (e.g., interaction between iron and vitamin C and between iron and zinc).[56] In addition, an overdose of a component could have deleterious effects on the baby and the mother (e.g., vitamin A overdose).

Epidemiological association

Evidence from systematic and other reviews

Black[57] reviewed studies identifying deficiencies of various micronutrients (iron, folic acid, zinc, iodine, magnesium, vitamin A, selenium, copper, etc.) among pregnant women. The effects of a deficiency in various micronutrients depend on their role in cellular function. However, Black questioned the additional benefits of multiple micronutrients beyond iron-folate supplementation for efficacy, acceptance, and tolerability.

Intervention

Evidence from systematic and other reviews

Haider and Bhutta[56] reviewed the effects of multiple micronutrient supplementation (three or more) on pregnancy outcomes. There was no statistically significant reduction in the risk of preterm births between the micronutrient group and the no-supplement, placebo, or <2 nutrient groups (RR 0.92, 95% CI 0.82, 1.04). Subgroup analyses of trials of high-quality studies or studies with a <20% attrition rate did not have any effect on the results. There was a marginal reduction in the risk of SGA births (RR 0.92, 95% CI 0.86, 0.99) in the micronutrient group compared with the no-supplement/placebo or <2 nutrient groups. There was a significant reduction in the risk of LBW births (RR 0.83, 95% CI 0.76, 0.91) in the micronutrient group compared with the no-supplement/placebo or <2 nutrient groups; this difference remained significant even after excluding studies with a >20% attrition rate. Comparison of multiple micronutrients with the iron and folate groups revealed no significant difference

in the risk of preterm births (RR 0.88, 95% CI 0.76, 1.03), SGA births (RR 1.04, 95% CI 0.93, 1.17), or LBW births (RR 0.94, 95% CI 0.83, 1.06) between groups. The authors concluded that routine programs of iron-folate supplementation should be continued, as there are no advantages of multi-component micronutrients compared with what has been achieved with these programs.

Conclusions

A reduction in the risk of LBW and SGA births was noted in a small number of studies of multi-component micronutrient supplementation. However, in comparison with current iron-folate supplementation, no additional advantage was observed with multi-component micronutrient supplementation. Current data are insufficient to recommend changing existing strategies.

Conclusions for Nutritional Factors/interventions

Nutrition is a significant determinant for fetal growth. Luke[4] suggested that even an increase in BW of 40 g could have a significant impact on the population for neonatal mortality and morbidity. An understanding of the biological mechanisms of the interaction of certain micronutrients and pregnancy outcomes is evolving. The major nutritional factors that can affect pregnancy outcomes are the intake of nutrients and the uptake and regulation of nutrients by the fetoplacental unit.

The factors that may affect the nutritional status of pregnant women are multiple, including socioeconomic status, lifestyle behaviours, and stress. Adequate nutrition should be a primary goal for each pregnancy. Assessment of the nutritional status of all pregnant women and provision of nutritious food to mothers identified as having limited resources to meet the demands of pregnancy may help to break the intergenerational cycle of LBW births.

Interventions directly aimed at the fetus have not been studied adequately enough to make suggestions for their routine use. The one intervention that suggests a beneficial effect in reducing SGA births is provision of a balanced nutritious diet. Supplementation with fish oil may have an effect in preventing preterm births; however, this result needs confirmation. Certain supplements such as iron, calcium, magnesium, and zinc have been shown to improve physiological parameters and tend to reduce the rate of preterm or LBW births. Vitamin A, vitamin C, vitamin B complex, and minerals need further studies. Further clinical research of adequate power is needed to demonstrate any significant clinical impact.

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CHAPTER 13:

Infections

Main Summary Points

- One third of preterm births are secondary to infections.
- Bacterial vaginosis causes preterm/low birth weight births. Treatment of bacterial vaginosis before 20 weeks' gestation may reduce the risk of preterm births.
- Trichomoniasis, gonorrhea, and syphilis are associated with an increased risk of preterm/low birth weight births. Screening for these infections during pregnancy is common. Treatment for trichomoniasis with metronidazole probably increases the risk of preterm births.
- Malaria is probably causally associated with low birth weight births and possibly intrauterine growth-restricted births. Intermittent prophylactic treatment of all pregnant women, especially primigravida and second gravida mothers, and use of insecticide-treated nets by all pregnant women are effective in reducing the risk of low birth weight births.
- Human immunodeficiency virus infection is associated with preterm/low birth weight/intrauterine growth-restricted births. Universal screening for human immunodeficiency virus provides the opportunity for adequate treatment in pregnancy and during the birth of the infant.
- Helicobacter pylori infection in pregnant women may affect fetal growth.
- Urinary tract infections are associated with preterm births. Treatment of mothers with symptomatic or asymptomatic urinary tract infections is indicated.
- Periodontal disease may be associated with preterm or low birth weight births. A well-conducted intervention study showed an improvement in periodontal disease, but it did not alter rates of preterm/low birth weight/intrauterine growth-restricted births.
- Antibiotic administration after prelabour rupture of the membranes (PROM) is beneficial for both women and neonates, but a combination of amoxicillin and clavulanate should be avoided as it is associated with an increase in the risk of necrotizing enterocolitis.

One third of preterm births are secondary to infections. Bacterial, viral, mycoplasmal, and parasitic infections are implicated in preterm/low birth weight (LBW) births. In this chapter we outline the most common infections of major public health importance in pregnancy.

Biological plausibility

- The maternal genital tract is colonized predominantly with acidophilic lactobacilli and a scant amount of other organisms such as staphylococci, streptococci, and *Gardnerella vaginalis*.[1] Estrogen affects the distribution of these organisms throughout the life of a woman.[2] Infection of the vagina can act as a starting point in the cascade of ascending infection, release of various chemicals, rupture of fetal membranes, infection of the chorioamniotic sac, and subsequent preterm labour.[3] Experimental administration of bacteria or bacterial toxins in the blood of animal models results in abortion or labour.
- Proteases released by microorganisms hydrolyze the cervical mucous barrier, promote the entry of microorganisms,[4,5] and weaken the collagen content of fetal membranes.[6]
- Sialidase released by infectious agents breaks down sialic acid in the cervical mucus and damages the protective barrier.[4,5]
- Most organisms that infect the maternal genital tract are anaerobic and produce fatty acid salts, which are inhibitory to fibroblasts and weaken the fetal membranes.[1,4,5]
- Phospholipase A2 induced by infection initiates the synthesis of prostaglandins, which can cause uterine contractions.[7,8] Cytokines and inflammatory mediators are then released, aggravating the insult.[9]
- Sperms act as a vector for the transport of bacteria from the vagina to the uterus.[2]
- Pregnancy causes oxidative stress, and infection in pregnancy may aggravate the stress.[10]

It is unclear why there is a time lag between onset of infection and onset of labour.

Epidemiological association

Romero et al.[11] reviewed the role of infection in preterm labour from an epidemiological standpoint. The association of infection and preterm labour lacks a high degree of specificity because preterm labour can occur without microbiological or pathological evidence of infection. The evidence suggests a temporal relationship because subclinical infection of the amniotic cavity in the second trimester leads to abortion or preterm births. The association was found in most of the studies reviewed, suggesting consistency. The strength of the association among studies suggested a moderate correlation (risk ratio (RR) of 1.4 to 2.0). Studies have indicated a dose-response gradient, that is, the concentrations of bacterial endotoxins have been found to be higher in patients in preterm labour compared with patients not in labour. The authors concluded that the evidence supported a causative role of infection in preterm births.

The following sections describe individual infections and their association with preterm births, as well as the effectiveness of interventions against those infections.

Bacterial Vaginosis

Epidemiological association

Bacterial vaginosis (BV) is caused by changes in the prevailing flora in the lower genital tract.[2,5] *Gardnerella vaginalis*, *Bacteroides*, *Peptostreptococcus*, *Ureaplasma*, or *Mycoplasma* species replace the normal flora.[1,2,4,5] The incidence of BV among pregnant women in general is reported to be 10% to 41% and >50% among high-risk populations.[1] The method of ascertaining a diagnosis of BV is important in detecting its prevalence. Krohn et al.[12] reported the prevalence of BV to be 21% using clinical criteria, 12% by Gram stain examination of cervical smears, 28% by gas-liquid chromatography from cervical secretions, and 41% by culture of cervical fluid. The incidence was higher in women with more sexual partners, in those who had initiated sexual activity at an earlier age, and in those who had other sexually transmitted diseases.

Evidence from systematic and other reviews

Flynn et al.[13] reviewed case-control and cohort studies reporting on the outcome of mothers with BV. The risk of preterm births was increased in women with BV (odds ratio (OR) 2.05, 95% confidence interval (CI) 1.67, 2.50). Subgroup analysis of only cohort studies (n = 11) revealed similar findings (OR 1.75, 95% CI 1.34, 2.29). Significant heterogeneity was identified between studies. The risk of LBW births was increased in women with BV (OR 1.73, 95% CI 1.11, 2.69). Subgroup analysis of three cohort studies revealed similar findings (OR 1.43, 95% CI 1.10, 1.87) for LBW births.

McGregor and French[1] reviewed case-control and cross-sectional studies of BV. The range of RR for preterm births in various studies was 1.8 to 2.7. The presence of BV earlier in gestation was associated with an increased risk of preterm/LBW births even when BV was documented to be absent later in pregnancy.

Yost and Cox[5] reviewed the impact of BV on preterm births. The RR for preterm births ranged from 1.4 to 1.9 in mothers with BV after 26 weeks' gestation and from 5.0 to 7.5 in mothers with BV before 16 weeks' gestation.

Evidence from other study designs

In a recent international study,[14] vaginal smears were Gram stained and scored with Nugent's method at a reference laboratory. Overall, 12.3% of women had BV according to Nugent's criteria. Zimbabwe had the highest prevalence (24.4%). The prevalence of BV and the distribution of bacterial morphotypes in vaginal smears among asymptomatic pregnant women vary significantly in populations from different countries.

Thorsen et al.,[15] in a prospective population-based cohort study, determined BV by Amsel's clinical criteria (three of the following four: pH > 4.5, homogeneous discharge, clue cells, and positive amine test) at a 17-week visit in pregnancy. BV was diagnosed in 13.7% of pregnant women. The authors found, after controlling for confounding factors, that significant risk factors for BV were daily coitus (RR 2.09, 95% CI 1.43, 3.04), being single (RR 1.76, 95% CI 1.21, 2.56), smoking >10 cigarettes per day at conception (RR 1.59, 95% CI 1.29, 1.93), previous genital infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae* (RR 1.39, 95% CI 1.07, 1.79), and consuming two or more drinks per week (RR 1.33, 95% CI 1.02, 1.74). In a second report, Thorsen et al.[16] found that BV was not associated with an increased risk of spontaneous preterm births (OR 0.8, 95% CI 0.5, 1.5) or small for gestational age (SGA) births (adjusted OR (AOR) 1.6, 95% CI 0.7, 3.1), but was associated with LBW births (AOR 4.3, 95% CI 1.5, 12) for nulliparous women. No such associations were identified for multiparous women. In a third report from the same cohort, the authors suggested that *Ureaplasma urealyticum* is independently associated with fetal growth and LBW births.[17]

Intervention

Evidence from systematic and other reviews

McDonald et al.[18] systematically reviewed the effects of antibiotic treatment of BV in pregnancy. Antibiotic therapy was effective at eradicating BV during pregnancy (OR 0.17, 95% CI 0.15, 0.20). Treatment did not reduce the risk of preterm births (OR 0.91, 95% CI 0.78, 1.06) or the risk of preterm, prelabour rupture of the membranes (OR 0.88, 95% CI 0.61, 1.28). Treatment before 20 weeks' gestation reduced the risk of preterm births (OR 0.63, 95% CI 0.48, 0.84). In women with a previous preterm birth, treatment did not affect the risk of subsequent preterm births (OR 0.83, 95% CI 0.59, 1.17). There was no reduction in the risk of LBW births (RR 0.95, 95% CI 0.79, 1.15) when the results of any antibiotic treatment were compared with those of placebo. Antibiotic treatment could eradicate BV in pregnancy, but there is little evidence that screening and treating all pregnant women with asymptomatic BV will prevent preterm births and its consequences. Treatment before 20 weeks' gestation may reduce the risk of preterm births.

Varma and Gupta,[19] in different meta-analyses on the topic, found that screening and treating BV in low-risk pregnancies produced a statistically significant reduction in spontaneous preterm births (RR 0.73, 95% CI 0.55, 0.98). This beneficial effect was not observed in high-risk or combined-risk groups. These results may suggest that preterm births occur as a result of different mechanisms and causes in low-risk and high-risk populations.

Okun et al.[20] reviewed 14 studies of antibiotics for the treatment of BV or *Trichomonas vaginalis* in pregnancy and reported no evidence to support the use of antibiotic treatment for either one in pregnancy to reduce the risk of preterm births in low- or high-risk women.

Conclusions

Biological and epidemiological evidence confirms the role of BV in causing preterm/LBW births. Intervention studies suggest a possible role for antibiotic treatment in the prevention of preterm/LBW births. Treatment before 20 weeks gestation may reduce the risk of preterm births. Further research is needed to establish the effectiveness of routine screening and early treatment for low- and high-risk populations.

Trichomoniasis

Epidemiological association

Evidence from other study designs

Cotch et al.[21] reported that the prevalence of trichomoniasis at mid-pregnancy in six urban clinic centres was 12.6%. The rate was higher in smokers, unmarried women, and less educated women. In a second report from the same cohort, Cotch et al.[22] reported that vaginal infection with *T. vaginalis* at mid-gestation was significantly associated with LBW births (OR 1.3, 95% CI 1.1, 1.5), preterm births (OR 1.3, 95% CI 1.1, 1.4), and preterm birth of a LBW infant (OR 1.4, 95% CI 1.1, 1.6). The attributable risk of *T. vaginalis* infection associated with LBW births in blacks was 11.0% compared with 1.6% in Hispanics and 1.5% in whites.

Intervention

Evidence from systematic and other reviews

Gulmezoglu[23] reviewed two randomized controlled trials (RCTs) of metronidazole versus no treatment for trichomoniasis in pregnancy. There was a statistically significant increase in the risk of preterm births (RR 1.78, 95% CI 1.19, 2.66) and a trend towards an increased risk in the incidence of LBW births (RR 1.38, 95% CI 0.92, 2.06) in the metronidazole group compared with the control group. The duration of gestation did not increase (mean difference (MD) -0.30, (95% CI -0.69, 0.09). Parasitological cure was achieved, but the effects of treatment on preterm/LBW births may indicate risks associated with metronidazole use.

Evidence from other study designs

Kigozi et al.[24] conducted a secondary analysis of an RCT of therapy with azithromycin, cefixime, and metronidazole in women with *T. vaginalis*. Infants born to women treated for *T. vaginalis* had an increased risk of LBW births (RR 2.49, 95% CI, 1.12, 5.50) and preterm births (RR 1.28, 95% CI 0.81, 2.02). The authors concluded that treatment of *T. vaginalis* may be deleterious and they inferred, from the National Institute for Child Health and Human Development trial,[25] that this result may be due to the use of metronidazole.

Conclusions

T. vaginalis infection is associated with an increased risk of preterm/LBW births. However, treatment with metronidazole probably increases the risk for these adverse outcomes and should be avoided.

Chlamydia

Epidemiological association

Chlamydia is a sexually transmitted disease. Its relation to adverse pregnancy outcomes has not been well studied.

Intervention

Evidence from systematic and other reviews

Brocklehurst and Rooney[26] reviewed 11 good-quality RCTs that compared the treatment of chlamydia infection with different antibiotics versus placebo. Amoxicillin was found to be the treatment of choice for chlamydia. There was no difference in the risk of preterm births between the antibiotic group and the placebo group in one study (RR 0.9, 95% CI 0.56, 1.46). There was no difference in the risk of preterm births between the azithromycin and the erythromycin group in one study (RR 0.75, 95% CI 0.28, 2.04).

Conclusions:

More research is needed to establish the relationship between chlamydia and preterm/LBW births. Antibiotic therapy provides a cure for chlamydia, but the effect of this therapy on the incidence of preterm/LBW births has not been established.

Syphilis

Epidemiological association

Syphilis is a sexually transmitted disease. Following a decline in the incidence of syphilis in the previous two decades, an increase from 1990 to 2000 was reported in the United States. In 1995, the World Health Organization (WHO) estimated that the worldwide annual incidence of sexually acquired syphilis was 0.4% (12 million cases) and that the prevalence was 1% (28 million cases). Approximately 900,000 gestations occur annually among infected women. An estimated 360,000 of these pregnancies end in fetal or perinatal deaths, and 50% of the remaining neonates (270,000) suffer significant physical, developmental, and sensory impairments. Approximately 27,000 infants are born preterm or with LBW[27,28] worldwide as a result of syphilis. In the United Kingdom, the rate of new syphilis

diagnoses among women increased from 0.2 per 100,000 population (55 cases) in 1999 to 0.7 per 100,000 population (181 cases) in 2003. The highest rate (2.5 per 100,000) was observed in the age group of 20 to 24 years.[29]

Fiumara et al.[30] observed in 1952 that four infants were born preterm or with LBW among seven untreated mothers with syphilis.

Screening and treating mothers who test positive for syphilis is routine practice.

Intervention

Evidence from systematic and other reviews

Walker[31] reviewed 26 studies; however, no eligible study was identified. With the effectiveness of penicillin in the treatment of syphilis having been established, performing a randomized controlled study cannot be justified.

Schmid[32] and Finelli et al.[28] argued that understanding the causes of congenital syphilis in each medical setting is important because interventions can be made at each step. These interventions include preventing infection in women, giving women access to antenatal care early, ensuring that antenatal care programs provide syphilis testing, notifying women of test results promptly, providing appropriate treatment after notification, and ensuring that women remain uninfected during pregnancy.

Conclusions

Syphilis is an important risk factor for preterm births. Syphilis is a preventable and treatable condition. Routine screening is in place in most parts of the world.

Gonorrhea

Epidemiological association

Evidence from other study designs

Elliott et al.[33] reported from a case-control study in Nairobi that infection with *N. gonorrhoeae* was associated with preterm births (OR 2.9, 95% CI 1.2, 7.2). This association was independent of age, rupture of membranes, and hypertension. Other sexually transmitted diseases (STDs) were not associated with preterm births. The attributable risk for gonococcal infection for preterm births was 14%.

Donders et al.,[34] in a cohort study in Pretoria, South Africa, reported that infection with *N. gonorrhoeae* (n = 9) and untreated syphilis (n = 7) were both associated with preterm/LBW births. Multivariate regression analysis revealed that infection with *N. gonorrhoeae* and infection with syphilis were significantly associated with LBW. The attributable risk of untreated gonorrhea for preterm births was 72%, and routine cultures were cost-benefit effective.

Intervention

No reviews or studies assessing the impact of treatment of gonorrhea on preterm/LBW births were identified.

Conclusions

N. gonorrhoeae infections in pregnancy are associated with an increased risk of preterm/LBW births. These infections should be routinely looked for and treated during pregnancy.

Malaria

Infection by malarial parasites is probably the most common infection among pregnant women worldwide. In the malaria-prone regions of Africa alone, >30 million women become pregnant every year.[35] In areas of the world where the transmission rates of *Plasmodium falciparum*, one of the species that cause malaria, are low, the acquired immunity of women is low and they are susceptible to episodes of severe malaria. This susceptibility may result in stillbirths, abortion, or maternal mortality. In areas of the world where transmission rates of this species are high, the levels of acquired immunity are high and women are susceptible to placental parasitemia, infection, and anemia.[36,37]

Biological plausibility

- Maternal parasitemia and maternal anemia are responsible for effects on the fetus and the mother.[37]
- High parasitemia and chronic parasitemia in the placenta can affect glucose and oxygen consumption.[35]
- Chronically infected placentas have thickened cytotrophoblastic membranes that may affect nutrient transfer.[38]
- Compared with primigravida and second gravida mothers, multigravida mothers may acquire immunity and may not have significant changes in the placental unit that influences birth weight (BW).[39]
- Because of their selective ability to adhere to chondroitin sulphate A on the syncytiotrophoblasts, certain parasite strains are more prevalent in pregnant women.[40]

Epidemiological association

Evidence from systematic and other reviews

Guyatt and Snow[35] reviewed studies of the impact of malaria during pregnancy on LBW births in Africa. The studies included were from areas where the transmission rate was stable during the study period. Four studies on primigravida

and 11 studies of all pregnancies were included in the review of an association between placental malaria and LBW births. The prevalence of placental malaria was 5% to 52%. The prevalence ratio for LBW births among women with placental malaria (calculated as the proportion of infected women with LBW births divided by the proportion of uninfected women with LBW births) was 1.85 (95% CI 1.80, 1.92) for primigravida mothers and 2.06 (1.76, 2.27) for all pregnancies. The population attributed fraction (percentage of LBW births that were due to malaria infection) was 22 % (95% CI 21, 26%) for primigravida and 19% (95% CI 14, 25%) for all pregnancies. To assess the effects of malarial infection (with or without placental infection), the authors reviewed studies reporting on parasite rate and LBW birth prevalence. The parasite rate was calculated by the prevalence of *P. falciparum* infection in a given childhood population. Forty-four studies of LBW birth data (25 studies of primigravida mothers) were included in which the prevalence rate either was reported or could be linked from other sources during the study period. The LBW birth prevalence only increased when the prevalence rate of malaria exceeded 25%. The median prevalence of LBW births was 11.8% for all pregnancies and 11.0% for primigravida for a prevalence rate of <25%, 15.5% for all pregnancies and 19.8% for primigravida for a prevalence rate of 25% to 49%, 16.4% for all pregnancies and 19.1% for primigravida for a prevalence rate of 50% to 74%, and 17.9% for all pregnancies and 31.4% for primigravida for a prevalence rate of >74%. Caution should be exercised in interpreting these data because higher prevalence rates are associated with other underlying issues, such as poverty, that may affect the prevalence of LBW births; however, the effects have been consistently observed in multiple studies.

Steketee et al.[36] reviewed the role of malaria on birth outcomes. The population-attributable risk of malaria for LBW births was 8% to 14%; for preterm/LBW births it was 8% to 36%; and for LBW/intrauterine growth-restricted births (IUGR) it was 13% to 70%.

Interventions

Evidence from systematic and other reviews

WHO recommends a three-pronged approach to malaria control in pregnancy, including insecticide-treated bed nets, intermittent prophylactic treatment, and case management.[41]

Gamble et al.[39] reviewed three cluster randomized trials and two RCTs of insecticide-treated nets for prevention of malaria in pregnancy. For primigravida or second gravida mothers, insecticide-treated nets resulted in an increase in mean BW (four studies, 55 g, 95% CI 21, 88), a reduction in LBW births (two studies, RR 0.77, 95% CI 0.61, 0.98), and no difference in preterm births (one study, RR 0.66, 95% CI 0.34, 129).

Garner and Gulmezoglu[42] systematically reviewed 16 studies on the regular use of antimalarial drugs for pregnant women. Antimalarial drugs reduced parasitemia when given to all pregnant women (two studies, 328 participants, RR 0.53, 95% CI 0.33 to 0.86) and to those with placental malaria (three studies, 1236 participants, RR 0.34, 95% CI 0.26 to 0.45). For primigravida and second gravida mothers, antimalarial drugs reduced parasitemia (six studies, 2906 participants, RR 0.27, 95% CI 0.17, 0.44) and LBW births (six studies, 2350 participants, RR 0.57, 95% CI 0.46, 0.72). Mean BW increased (eight studies, 2648 participants, weighted mean difference 127 g, 95% CI 89 to 165).

Conclusions

Malaria is associated with LBW births and possibly IUGR births. The biological plausibility, consistency, effects of intervention, and dose-response relationship of the association indicates an almost causal relationship in endemic areas. Intermittent prophylactic treatment of all pregnant women, especially primigravida and second gravida mothers, and use of insecticide-treated nets by all pregnant women are effective in reducing the incidence of malaria and the risk of LBW births.

Human Immunodeficiency Virus

Epidemiological association

Human immunodeficiency virus (HIV) may be transmitted from mother to infant. At the end of 1998, over 33 million people were infected with HIV and over 1 million had been infected from their mothers.[43] In 2001, an estimated 800,000 children were newly infected with HIV, almost all through mother-to-child transmission, and 90% of these children were born in Africa.[44]

Evidence from systematic and other reviews

Brocklehurst and French[45] reviewed 31 prospective cohort studies that compared pregnancy outcomes of HIV-infected women and women without infection. There was an increased risk of preterm births (OR 1.83, 95% CI 1.63, 2.06), LBW births (OR 2.09, 95% CI 1.86, 2.35), and IUGR births (OR 1.7, 95% CI 1.43, 2.02) in infected women. Observer bias could be an important factor because observers were blinded to infection status in only six studies. Adjustment for other confounders such as other sexually transmitted diseases, associated illicit drug use, and maternal medical conditions was not performed in most studies.

Intervention

Evidence from systematic and other reviews

Brocklehurst and Volmink[43] systematically reviewed four studies of antiviral medication for HIV infection and reported that there was no difference in the

incidence of preterm births (RR 0.84, 95% CI 0.49, 1.43) or LBW births (RR 0.93, 95% CI 0.69, 1.24) when zidovudine and placebo/no treatment were compared. A short course of zidovudine versus placebo/no treatment did not have a significant effect on the incidence of LBW births (RR 1.06, 95% CI 0.72, 1.57) or preterm births (RR.0.48, 95% CI 0.20, 1.16). Hyperimmune immunoglobulin plus zidovudine versus non-specific intravenous immunoglobulin plus zidovudine did not show a significant difference in the risk of preterm births (RR 1.14, 95% CI 0.77, 1.69) or LBW births (RR 1.14, 95% CI 0.73, 1.76). The sample size for each of the studies was small.

Volmink et al.[46] reviewed 18 studies of antiretroviral agents used to reduce the risk of mother-to-child transmission of HIV infection. Comparing antiretroviral agents with placebo, one trial reported a significant reduction in preterm births (RR 0.14, 95% CI 0.03, 0.58), whereas the other did not (RR 1.23, 95% CI 0.60, 2.49). There was no significant reduction in LBW births in any of the three included trials: RR 0.92 (95% CI 0.57, 1.47); RR 0.75 (95% CI 0.48, 1.19); and RR 0.61 (95% CI 0.30, 1.27). Longer versus shorter regimens of the same antiretroviral agents were not associated with a significant effect on LBW births: RR 2.01 (95% CI 0.94, 4.31); RR 1.86 (95% CI 0.84, 4.12); and RR 1.75 (95% CI 0.53, 5.81). For regimens that used different antiretroviral agents and duration of treatment, there was no statistically significant effect on the incidence of preterm births (RR 1.97, 95% CI 0.37, 10.42) or of LBW births in four studies: RR 0.67 (95% CI 0.35, 1.29); RR 1.97 (95% CI 0.18, 21.24); RR1.14 (95% CI 0.85, 1.53); and RR 1.41 (95% CI 0.45, 4.42).

Evidence from other study designs

Bellón Cano et al.,[47] in a multicentre observational study, reported that of 124 HIV-infected pregnant women receiving protease inhibitor-based antiretroviral therapy, no newborn was infected with HIV-1. The preterm birth rate was 14.3 % and the rate of LBW births was 21.4%.

In Sweden, a national pregnancy screening program for HIV has been running since 1987 with a high acceptance rate, and the implementation of measures to prevent mother-to-child transmission since 1994 have resulted in a significant decrease in the number of infected children.[48] Since 1998, only one infected child has been born in Sweden (in 1999).[48]

In the United Kingdom during the last 10 to 15 years, the introduction of prelabour caesarean section, formula feeding, and antiretroviral therapy has reduced transmission to <1% for pregnant women who are aware of their HIV status.[49]

Coyle et al.[50] reported on an RCT of an educational intervention for HIV, other STDs, and pregnancy prevention in alternative school. At the 6-month follow up, students in the intervention group were less likely to have intercourse without a condom in the previous 3 months ($p = 0.02$), and they were more likely to use condoms during their last intercourse ($p = 0.006$). These effects diminished by the 12- and 18-month follow ups.

Conclusions

HIV infection is associated with preterm/LBW/IUGR births. The evidence is derived from prospective cohort studies with inadequate control for confounding factors. Universal screening for HIV provides the opportunity for adequate treatment in pregnancy and during the birth of the infant. In developed countries with high rates of antenatal screening and treatment in pregnancy, the rate of mother-to-child transmission has been dramatically decreased. In such settings, prenatal screening should continue even if the attack rate is low. Short courses of antiretroviral drugs are effective for reducing mother-to-child transmission of HIV and are not associated with any safety concerns in the short term. Further research is needed to assess the impact of antiviral therapy on preterm/LBW/IUGR births and the short- and long-term effects on mother and child. Educational interventions targeted at early school age may be effective in the short term. Strategies to create long-lasting effects are needed.

Helicobacter pylori

Epidemiological association

Evidence from other study designs

Eslick et al[51] studied pregnant women having routine examinations in the third trimester to assess the role of *Helicobacter pylori* in pregnancy outcomes. Of the 448 women, 89 (20%) were seropositive for *H. pylori*. IUGR births (BW $<10^{th}$ percentile for gestational age) were more common in *H. pylori*-seropositive women than in *H. pylori*-seronegative women (13.5% versus 6%, OR 2.42, 95% CI 1.14, 5.08). A multiple regression model revealed that smoking (OR 3.55, 95% CI 1.62, 7.79), maternal height (with every 10 cm increase in height, the chances of having a fetus with IGUR were decreased; OR 0.48, 95% CI 0.28, 0.80), and *H. pylori* seropositivity (OR 2.59; 95% CI 1.12, 5.95) were all independent risk factors for IUGR births. If *H.pylori* is casually associated with IUGR, then the attributable risk would be 24%.

No intervention studies were identified.

Conclusions

H. pylori infection in pregnant women may affect fetal growth. The result from one study needs to be confirmed in other populations.

Influenza

Influenza virus infection during pregnancy is implicated as one of the causes of preterm births, abortions, and stillbirths.[52] Secretion of bioactive interleukin-6 (IL-6) and tumour necrosis factor (TNF)-α produced by fetal membranes has

been postulated to induce preterm births. Concentrations of IL-6 and TNF-α were significantly increased in a culture of chorion cells infected by influenza virus.[52] The greater morbidity and mortality is thought to be associated with cardiorespiratory failure when pneumonia occurs.[53]

Epidemiological association

Evidence from other study designs

Influenza in pregnant women has historically been associated with a higher rate of morbidity and mortality compared with the non-pregnant population. Harris[54] reported that there were 1350 cases of influenza in 1918 in the United States during the Spanish flu. Pneumonia complicated influenza in about half of the identified pregnant women. The gross mortality rate of all cases was 27%. Pregnancy was interrupted in 26% of the uncomplicated cases and was accompanied by pneumonia in 52% of the cases. Abortion or preterm labour occurred in 62% of cases that were fatal.

During the Asian influenza A epidemic in New York in 1957, the mortality rate was higher in patients with rheumatic cardiac conditions and in pregnant women, and a combination of the two created an even higher risk.[55] Forty-seven women between the ages of 15 and 49 years died. Almost half of the women of childbearing age who died were pregnant. Of the 22 pregnant women with influenza who died, two gave birth to live-born infants at 33 to 36 weeks and four at 37 to 40 weeks; one gave birth to a stillborn infant at 20 to 24 weeks, one at 33 to 36 weeks, and two at 37 to 40 weeks; and 12 did not give birth. Overall, more pregnant women died in 1957 (178) than in each of the preceding 4 years (average 145).

In the same epidemic, 11 maternal deaths occurred in Minnesota.[53] Three of the deaths occurred in the second trimester of pregnancy, seven in the third, and one at 5 weeks' postpartum. All of the mothers died from respiratory insufficiency associated with overwhelming pulmonary edema and pneumonia. The authors did not provide information about the gestational age at death and the outcomes for the fetuses.

Prevention

Vaccination is the most widely used preventive measure. Van der Wouden et al.[56] performed an overview (synopsis) of systematic reviews (nine reviews; five addressed vaccination and four addressed medications) and reported that although vaccination is effective in healthy adults and children, the effect is modest in adults.

Because pregnant women are at increased risk of serious influenza-related morbidities, universal vaccination of pregnant women is recommended.[57] Roberts et al.[58] developed a decision analysis model to investigate the cost-effectiveness of providing inactivated trivalent influenza vaccine to all pregnant women compared

with providing supportive care only on a case-by-case basis to the unvaccinated pregnant population. Vaccination of 100% of pregnant women would save approximately $50 per woman compared with providing supportive care only.

Conclusions

Influenza infection is associated with high perinatal and maternal morbidities and mortality. Influenza vaccination is cost-effective. Currently, universal vaccination is recommended during any trimester of pregnancy in the influenza season.[59]

Avian Flu

As of March 1, 2007, 277 people had contracted avian flu, of whom 167 died (60%).[60] The effect of avian flu during pregnancy is not known, but it is expected that mortality in pregnancy would be high, similar to that observed during the Spanish influenza pandemic. Only one case has been reported of a pregnant woman with avian flu, who died from it at 4 months' gestation after having been actively involved in slaughtering and de-feathering sick poultry before they were cooked for family consumption.[61]

Prevention

Because no effective vaccine is currently available, a large number of pregnant women are expected to become infected with avian flu. A high maternal and fetal/infant morbidity and mortality rate is expected. Some infants will be born preterm. In the case of an epidemic, a huge burden on the infrastructure of society as a whole and the healthcare system is expected. In addition, difficult ethical decisions will have to be made regarding priorities for individual patient's access to intensive care and the distribution of potentially effective medications for prophylaxis. Contingency plans need to be urgently developed.

Other Infections

Several other infectious agents could potentially lead to more severe morbidity and resulting mortality in the pregnant population. These new infectious diseases include West Nile virus, monkeypox, severe acute respiratory syndrome, and bioterrorism agents.[62] The effects on pregnant mothers and possible vertical transmission to the fetus in utero and/or during labour and later via breastfeeding are currently only speculative.

Urinary Tract Infection

Epidemiological association

Morphological and physiological urinary tract changes during pregnancy make women more vulnerable to urinary tract infections (UTIs).[63] UTI is common during pregnancy. The incidence has been reported to be 17% to 20% of pregnant women. Infection leads to preterm labour and preterm, prelabour rupture of the membranes.[64] Women harbouring bacteria in the urinary tract are symptomatic or asymptomatic. Asymptomatic bacteriuria results in pyelonephritis in approximately 30% of untreated women.[65]

Intervention

Evidence from systematic and other reviews

Vazquez and Villar,[65] in a systematic review of nine RCTs that assessed the impact of treating symptomatic UTI on pregnancy outcomes, reported that the studies were of small sample size and included oral, intramuscular, or intravenous treatment. A high cure rate was reported in all studies. There were no differences noted in the incidences of preterm births for outpatient therapy versus in-patient therapy (RR 1.04, 95% CI 0.37, 2.89); intravenous cefazolin versus ampicillin and gentamicin (RR 1.9, 95% CI 0.48, 7.55); intramuscular ceftriaxone versus intravenous ampicillin and gentamicin (RR 1.10, 95% CI 0.23, 5.19); intramuscular ceftriaxone versus intravenous cefazolin (RR 0.58, 95% CI 0.15, 2.29); and cephalosporins once per day versus multiple doses (RR 1.1, 95% CI 0.44, 2.72).

Smaill and Vazquez,[66] in a systematic review of 14 RCTs comparing antibiotic treatment with placebo for asymptomatic bacteriuria, reported that marked heterogeneity was present among the studies for antibiotic of choice, time of treatment onset, dose, and duration of treatment. The methodological quality of the studies was poor. However, there was a reduction in the risk of LBW births in the treatment group (RR 0.66, 95% CI 0.49, 0.89) versus no treatment. The OR for preterm births was 0.37 (95% CI 0.10, 1.36). There was a decreased risk of LBW births in patients who received continuous antibiotic therapy versus no treatment for asymptomatic bacteriuria (RR 0.56, 95% CI 0.33, 0.96). The RR for preterm births was 0.36 (95% CI 0.14, 0.95).

Conclusions

UTI is a well-recognized cause of preterm/LBW births, but the exact contribution is not well known. Treatment of mothers with symptomatic or asymptomatic infections is indicated. Further research is needed from larger RCTs for management of asymptomatic UTI. Identifying which women will benefit from the treatment of asymptomatic bacteriuria is important in order to avoid the development of bacterial resistance to antibiotics in the population.

Periodontal Infections

Periodontal infections are commonly due to Gram-negative anaerobic organisms. These organisms are believed to be similar to those colonizing the genital tract. Acute infection with these organisms is suspected to release lipopolysaccharides and inflammatory mediators that react with the fetoplacental unit. This interaction may result in preterm/LBW births.[67]

Epidemiological association

Evidence from systematic and other reviews

Xiong et al.[68] examined the existing evidence on the association between periodontal disease and adverse pregnancy outcomes from observational studies (i.e., case-control, cross-sectional, and cohort), non-randomized controlled studies, and randomized controlled studies that examined periodontal disease as a risk factor for adverse pregnancy outcome. Twenty five studies (13 case-control, nine cohort, and three controlled trials) were identified. Of the included studies, 18 suggested an association between periodontal disease and increased risk of adverse pregnancy outcome (ORs ranging from 1.10 to 20.0) and seven studies identified no evidence of an association (ORs ranging from 0.78 to 2.54). Results from seven observational studies (three case-control and four cohort) suggested that periodontal disease is a risk factor for preterm births (ORs and RRs ranging from 2.12 to 20.0). However, four studies (two case-control and two cohort) failed to find an association. Results from six studies (four case-control and two cohort) suggested that periodontal disease is a risk factor for LBW births (ORs and RRs ranging from 1.1 to 7.2). However, a large cohort study failed to show an association.

In another review, Shub et al.[69] identified 16 studies that reported an adverse effect of periodontal disease on preterm/LBW births and 10 studies that did not. The authors proposed that it might be inappropriate to perform any type of meta-analysis of these studies because of the heterogeneity in study design, diagnostic tests, patient populations, and outcome measures. Three ongoing large randomized controlled intervention studies were identified.

Evidence from other study designs

Boggess et al.[70] prospectively evaluated dental heath starting from <26 weeks' gestation by standard examiners. Of the cohort of 1017 women, 284 (28.0%) had no periodontal disease, 588 (57.8%) had mild periodontal disease, and 145 (14.3%) had moderate/severe periodontal disease. Mild periodontal disease was not statistically significantly associated with an increased risk of SGA births (adjusted RR 1.3, 95% CI 0.7, 2.5). Moderate/severe periodontal disease was statistically significantly associated with an increased risk of SGA births (adjusted RR 2.3, 95% CI 1.1, 4.5). The risk of SGA births among women with moderate/

severe periodontal disease with a serum C-reactive protein level at >75th percentile in the model was increased (adjusted RR 2.7, 95% CI 1.1, 6.8).

Farrell et al.[71] prospectively studied 1793 women for their dental health from 12 weeks' gestation. A total of 7.3% gave birth preterm and 0.9% had a late miscarriage. There was no increased risk for either preterm or LBW births in women with poorer periodontal health.

Intervention

Evidence from systematic and other reviews

No systematic review on the topic was identified.

Evidence from other study designs

Michalowicz et al.[72] randomly assigned pregnant women between 13 and 17 weeks of gestation to undergo scaling and root planing either before 21 weeks (413 patients) or after giving birth (410 patients). In addition, the women in the treatment group underwent monthly tooth polishing and received instruction in oral hygiene. Preterm birth occurred in 12.0% of the treatment group and in 12.8% of the control group ($p = 0.70$). There were no significant differences in BW (3239 g versus 3258 g, $p = 0.64$) or in the rate of SGA births (OR 1.04, 95% CI 0.68, 1.58).

Offenbacher et al.,[73] in a pilot study, reported that periodontal intervention (second trimester scaling and root planing) resulted in a significantly decreased risk of preterm births (OR 0.26, 95% CI 0.08, 0.85).

Jeffcoat et al.,[74] in a three-arm RCT, assessed the efficacy of scaling and root planing for pregnant women at 20 to 25 weeks' gestation with periodontal infection. Providing scaling and root planing to pregnant women with periodontal disease may reduce preterm births (RR 0.5, 95% CI 0.2, 1.3) and very preterm births at <35 weeks (RR 0.2, 95% CI 0.02, 1.4).

Conclusions

An association between periodontal disease and adverse pregnancy outcomes has been documented in some case-control and cohort studies, which were mostly of poor quality. A well-conducted intervention study did show an improvement in periodontal disease and that the treatment is safe, but it did not alter rates of preterm/LBW/IUGR births. Further research is needed to confirm the possible association between periodontal disease and adverse pregnancy outcomes and the effectiveness of interventions aimed at improving periodontal disease and pregnancy outcomes.

Threatened Preterm Labour

One of the reasons for preterm onset of labour is infection. When a woman presents with threatened preterm labour, a clinical dilemma arises regarding whether to consider overt or covert infection and whether to treat the mother or not. Threatened preterm labour can occur with or without rupture of fetal membranes. Preterm, prelabour rupture of the membranes occurs in approximately one third of preterm births. The break in the gestational sac acts as a portal of entry for microorganisms to travel from the lower genitourinary tract.[11] In this section, we describe these scenarios.

Intervention

Increased predisposition to infections in women with preterm, prelabour rupture of the membranes has prompted physicians to use prophylactic antibiotics. In certain cases, administration of antibiotics may provide a vital 48-hour period before the birth that is needed for the action of the glucocorticoids given to the mother to promote maturation of fetal lungs.[75] There is a concern, however, that maternal antibiotics may cure the mother but may not be effective against fetal infection and may cause deleterious consequences and drug-resistant strains.

Administration of antibiotics for preterm births has been studied from different perspectives.

1. Inter-conception antibiotics to prevent spontaneous preterm births

Andrews et al.[76] studied the role of antibiotic administration during the inter-pregnancy interval in non-pregnant women with a previous preterm birth at <34 weeks' gestational age in reducing the rate of spontaneous preterm births in the following pregnancy. Women were randomly assigned at 4 months postpartum to receive either 1 g of azithromycin twice (4 days apart) plus 750 mg of sustained-release metronidazole daily for 7 days or identical-appearing placebos. This regimen was repeated every 4 months until the subsequent pregnancy. A total of 241 women were randomly assigned; 124 conceived a subsequent pregnancy and were available for study, including 59 in the antibiotic group and 65 in the placebo group. In the antibiotic group, neither the rates of subsequent spontaneous preterm births (52% versus 46%, p = 0.568) nor of preterm births at <32 weeks (31% versus 23%, p = 0.376) or miscarriage at <15 weeks (12% versus 14%, p = 0.742) were significantly different from the placebo group. Although not statistically significant, mean gestational age at birth in the subsequent pregnancy was 2.4 weeks earlier in the antibiotic versus the placebo group (32 weeks (standard deviation (SD) 7.9) versus 34.4 weeks (SD 6.3), p = 0.082), and mean BW was lower in the antibiotic group (2046 g (SD 1209) versus 2464 g (SD 1067)).

2. Prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality in the second trimester

Morency and Bujold[77] systematically reviewed the effect of prophylactic antibiotic administration in high-risk women during the second trimester. Compared with placebo, macrolides were associated with a lower rate of preterm births (OR 0.72, 95% CI 0.56, 0.93), as was clindamycin (OR 0.68, 95% CI 0.49, 0.95). Metronidazole use was not associated with significant changes in preterm births (OR 1.1, 95% CI 0.95, 1.29). A higher rate of preterm births was identified when mid-trimester metronidazole was the only antibiotic administered (OR 1.31, 95% CI 1.08, 1.58).

3. Prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality in the second and third trimester

Thinkhamrop et al.[78] systematically reviewed the effect of prophylactic antibiotics during the second and third trimester of pregnancy. Antibiotic prophylaxis in unselected pregnancies reduced the risk of prelabour rupture of the membranes (OR 0.32, 95% CI 0.14, 0.73). In women with previous preterm births, there was a reduction in the risk of LBW births (OR 0.48, 95% CI 0.27, 0.84) and postpartum endometritis (OR 0.46, 95% CI 0.24, 0.89). There was a reduction in the risk of preterm births (OR 0.48, 95% CI 0.28, 0.81) in women with a previous preterm birth associated with BV during the current pregnancy, but there was no risk reduction in pregnant women with previous preterm births without BV during pregnancy.

4. Antibiotics for inhibiting preterm labour with intact membranes

King and Flenady[79] systematically reviewed the role of antibiotic treatment for women in preterm labour with intact membranes (identified between 20 and 36 weeks' gestational age). There was no reduction in the risk of preterm births (RR 0.99, 95% CI 0.92, 1.05) or LBW births (RR 1.04, 95% CI 0.95, 1.13). There was no statistically significant effect on perinatal mortality (RR 1.22, 95% CI 0.88, 1.70). The risk of neonatal death showed a borderline increase (RR 1.52, 95% CI 0.99, 2.34) in the antibiotic group. The authors concluded that antibiotics are not recommended for pregnant women in preterm labour without rupture of the membranes, and concerns were raised about increased neonatal mortality for those who received antibiotics.

5. Antibiotics for inhibiting preterm labour with rupture of the membranes

Kenyon et al.[80] systematically reviewed the role of antibiotics for women with preterm labour and rupture of the membranes. Antibiotics were associated with a statistically significant reduction in maternal infection and chorioamnionitis. There was a reduction in the number of infants born within 48 hours (RR 0.57, 95% CI 0.37, 0.86; number needed to treat 9, 95% CI 6, 20) and 7 days (RR 0.80, 95% CI 0.71, 0.90; number needed to treat 7, 95% CI 5, 15). There

was no significant effect on perinatal mortality (RR 0.91, 95% CI 0.75, 1.11). A combination of amoxicillin and clavulanate was associated with a highly significant increase in the risk of necrotizing enterocolitis (RR 4.60, 95% CI 1.98, 10.72; number needed to harm 50, 95% CI 33, 100). The authors concluded that antibiotic administration after prelabour rupture of the membranes (PROM) is beneficial for both women and neonates, but a combination of amoxicillin and clavulanate should be avoided.

Conclusions

Macrolides and clindamycin, given during the second trimester of pregnancy, are associated with a lower rate of preterm births, whereas second-trimester metronidazole use is linked with a greater risk of preterm births in a high-risk population. The evidence suggests that antibiotics should be prescribed only to women with preterm PROM, but not to women with threatened preterm labour with intact membranes. Further long-term follow-up studies are needed.

Conclusions for Infections

Infection has a role in the onset of preterm labour and subsequent preterm/LBW births. Biological evidence suggests the interplay of multiple mechanisms. Epidemiological evidence suggests that genital tract infections and UTIs are common causes of spontaneous onset of preterm labour. Once the infection is identified or suspected, treatment should be a priority from maternal and neonatal perspectives. The lack of evidence for a reduction in preterm/LBW births in intervention studies for certain infections may be due to small sample size or inadequate methodological quality of the studies. Screening and prevention of infection should be a public health priority. Potential gains could be obtained by screening particularly high-risk populations such as women with a history of preterm birth. Routine serological screening for commonly encountered viral infections in the first trimester (including HIV) and early identification and treatment of bacterial infection, including UTI, are helpful to mother and fetus. In malaria-prone areas, infection can lead to LBW births; intermittent prophylaxis and insecticide-treated nets are beneficial in reducing the incidence of LBW births.

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CHAPTER 14:

Antenatal Care and Early Detection of At-Risk Fetuses

Main Summary Points

- Prenatal care can identify at-risk pregnancies and provide counselling and further management. The effectiveness of prenatal care in reducing adverse pregnancy outcomes is debatable. A reduced visit model was as effective as a standard care model for lowering the incidence of preterm births. The content of these care programs requires study to identify the most effective components and to identify the best way to deliver these programs.
- Educational programs directed towards high-risk women do not prevent preterm births. Any such intervention would have to strike a balance between adequate information and the excessive stress induced by provision of such information.
- Cervical changes observed before the onset of preterm labour are not highly predictive for preterm labour.
- Cervical length of <30 mm and funnelling of the cervix have been shown to be associated with preterm birth. The measurement of cervical length as a screening tool is not justified.
- Abnormal uterine artery Doppler and high resistive indices are predictive of pre-eclampsia and subsequent intrauterine growth restriction; however, further studies are needed to identify appropriate target populations.
- The opinions of experts regarding the use of home uterine activity monitoring are variable. In a low-risk population, home uterine activity monitoring does not seem to confer any benefits in reducing preterm/low birth weight births.
- The absence of fetal fibronectin is a strong indicator of women not having preterm labour and the presence of fetal fibronectin in cervical-vaginal secretions is a moderate predictor for preterm labour within the next 14 days.
- Other biomarkers for the prediction of preterm/low birth weight births need further studies.

In this chapter we review the effects of antenatal care and the early detection of at-risk fetuses on the incidence of preterm/low birth weight (LBW) births.

Antenatal care

Throughout the world, antenatal care is provided to most pregnant women. The emotional component attached to the provision of antenatal care prevented researchers for years from testing its efficacy. In this section, we describe the evaluation of the medical component of antenatal care.

Biological plausibility

There is no known direct biological mechanism by which antenatal care directly influences pregnancy outcomes.[1] Screening of mothers, identification of medical maternal or fetal problems, appropriate nutritional advice, counselling against substance use, psychosocial support, and early intervention are the key components of antenatal care. Studies in multiple pregnancies have revealed promising results of improved perinatal outcomes with individualized or intensive care. The results include reduction in perinatal mortality,[2] improved birth weight (BW),[2,3] and reduced incidence of very low birth weight (VLBW) births.[4] However, these results were reported in retrospective studies with inherent limitations. The biological plausibility related to certain specific components is addressed in the relevant sections of this chapter.

Epidemiological association

Antenatal care has been studied from three perspectives: timing of initiation and frequency of antenatal visits, content of antenatal care, and continuity of antenatal care. The following section presents reviews, or studies if no reviews have been identified in specific areas, that address these components.

Timing of initiation and frequency of antenatal care

Evidence from systematic and other reviews

Carroli et al.[5] systematically reviewed seven randomized controlled trials (RCTs) of routine antenatal care. There was no difference in the risk of LBW births (odds ratio (OR) 1.04, 95% confidence interval (CI) 0.93, 1.17) between a model with a reduced number of prenatal visits and a traditional model. Two studies had high attrition rates. A sensitivity analysis excluding these two trials did not change the results. There was no difference in perinatal mortality (OR 1.06, 95% CI 0.82, 1.36). The studies were of high quality; however, in some, there was a mild to moderate degree of bias due to unmasked ascertainment of outcomes, co-intervention, protocol deviation, and unclear intention-to-treat analysis.

Evidence from other study designs

Villar et al.,[6] in an RCT, assigned mothers (n = 20,000) to either standard prenatal care or a "new model" with a reduced number of prenatal visits based on risk assessment. A significant reduction in the number of prenatal visits in the new model was observed compared with the traditional model without any significant

difference in maternal satisfaction. There was no statistically significant difference in the rate of LBW births (adjusted OR (AOR) 1.06, 95% CI 0.97, 1.15).

Reichman and Teitler[7] evaluated the impact of prenatal care and the timing of its initiation on pregnancy. The incidence of preterm births was 8.2% in mothers who initiated prenatal care in the first trimester, 8.7% in those who initiated it in the second trimester, 10% in those who initiated it in the third trimester, and 10.8% in those who did not receive any prenatal care. The incidence of LBW births was 7.5% in mothers who initiated prenatal care in the first trimester, 8.1% in those who initiated it in the second trimester, 8.2% in those who initiated it in the third trimester, and 10.0% in those who did not receive any prenatal care. These differences were statistically insignificant. Initiation of care in the first trimester was associated with a 56 g increase in BW ($p = 0.01$) compared with no prenatal care.

Goldani et al.[8] reported the results of a survey of maternity units conducted in 1978/1979 and 1994. The proportion of women who had no antenatal care was reduced from 7.3% to 2.6% between these two cohorts. The risk of LBW was higher in the 1978/1979 cohort (adjusted risk ratio (RR) 1.88, 95% CI 1.38, 2.56) and in the 1994 cohort (AOR 2.21, 95% CI 1.42, 3.42) for women who had no prenatal care compared with women who had prenatal care.

Orvos et al.[9] compared the outcomes of pregnancies of women who gave birth after prenatal care and the outcomes of those who gave birth after no prenatal care. One percent of births occurred following no prenatal care. There was a higher incidence of preterm births (OR 3.1, 95% CI 1.4, 6.8) and lower mean BWs ($p < 0.001$) in women without any prenatal care.

Hueston et al.[10] performed a retrospective review of singleton births in 1996 in the United States. The adjusted risk for LBW births was lower for women who initiated antenatal care for the first time during the second trimester (RR 0.85, 95% CI 0.83, 0.86) or the third trimester (RR 0.87, 95% CI 0.84, 0.96) compared with women who initiated care in the first trimester. This apparent paradox was suspected to have the following causes: (1) social and medical problems associated with pregnancy, rather than the timing of prenatal care, have a major role; that is, women with an adverse medical history are likely to seek early medical attention compared with those without such a history; (2) women who carry their pregnancy successfully to the third trimester are less likely to give birth to a LBW infant; and (3) the study reported only the initiation of care and did not measure the quality of care.

Content of antenatal care

Evidence from systematic and other reviews

Blondel and Breart[11] systematically reviewed eight RCTs on the efficacy of antenatal programs. Three studies reported on medical care during antenatal visits, whereas the remaining five reported on social support (reviewed in chapter

8). There was no difference in the risk of preterm births (OR 1.0, 95% CI 0.8, 1.1) between women who received home visits and those who did not.

Evidence from other study designs

White et al.[12] interviewed 1065 women (giving birth to 408 preterm infants and 657 full-term infants) who gave birth to singletons. Mothers were interviewed at 3 months postnatal age via telephone. The reported rate of receipt of various recommended procedures varied from 59% to 99%. Ultrasonography, recording of blood pressure, measurement of weight gain, urinalysis, and blood tests were the most commonly performed procedures received by >92% of women. Health advice and education were reported to have been received by 45% to 93% of women. Only 64% of women reported having discussions regarding proper weight gain. Among the smokers, only 25% received discussions regarding cessation strategies; >30% reported not receiving advice about second-hand smoke. Women who did not receive advice regarding signs and symptoms of preterm labour (OR 1.97, 95% CI 1.54, 2.52) or prelabour rupture of the membranes (OR 1.88, 95% CI 1.48, 2.39) had higher odds of preterm birth. Women who gave birth preterm were less likely to describe their care as good/excellent (92% versus 88%, $p = 0.015$) and were not satisfied with answers from healthcare providers (25% versus 18%, $p = 0.004$). Healthcare providers were meeting the care guidelines but were not meeting pregnant women's needs for health education and advice.

Panaretto et al.[13] evaluated the impact of a collaborative, shared antenatal care program for urban indigenous women. The intervention consisted of an integrated team approach, with each patient seen by aboriginal health workers, midwives, female doctors, an outreach team worker, and, if needed, an obstetric team. A pregnancy register was maintained with monthly recall to non-attendees. Daily walk-in clinics provided family orientation; care plans specifying elements of basic investigations, education, and nutritional supplementation; investigations for infections; provision of transport services; and brief teachings regarding risk factors. There was a significant reduction in the risk of preterm births in the intervention group compared with historic controls (8.7% versus 14.3%, $p < 0.01$). There was no difference in the risk of LBW births (11.1% versus 13.9%, $p = 0.07$) or mean BW (3239 g versus 3188 g, $p = 0.28$).

Ickovics et al.[14] compared group prenatal care with individualized prenatal care in a non-randomized study. Groups were facilitated by a midwife or an obstetrician. There was an increase in BW in group prenatal care (3228 g versus 3159 g, $p < 0.01$) among all infants and among preterm infants (2398 g versus 1990 g), although the latter was not statistically significant. There was no difference in the rate of preterm births (9.2% versus 9.6%), LBW (7% versus 10%), or VLBW (1.3% versus 2.6%). Several factors, such as content of prenatal care, intensity of prenatal care in the group setting, changes in social norms, avoidance of risky behaviours, opportunity to discuss these behavioural changes, and increased contact time, were reported to be the factors for success.

Tough et al.[15] evaluated the role of additional supplementary support. Women were randomly assigned to standard physician care; standard physician care plus consultation with a nurse; and standard physician care, consultation with a nurse, and consultation with a home visitor. No difference was noted in the risk of preterm (7.1%) or LBW (4.8%) births in the study population; however, individual group data were not reported.

Continuity of antenatal care

Evidence from systematic and other reviews

Hodnett[16] systematically reviewed two studies on the effect of continuity of care during pregnancy and childbirth and the puerperium. Both studies compared the type of care (continuity of care by midwives with non-continuity of care by a combination of physicians and midwives). There was a reduction in the number of admissions to the hospital during the prenatal period (OR 0.79, 95% CI 0.64, 0.97) and an increase in the attendance in educational programs (OR 0.58, 95% CI 0.41, 0.81) in the continuity of care group. There was no reduction in the risk for preterm births (RR 0.97, 95% CI 0.68, 1.39). Satisfaction with care increased among mothers in the continuity-of-care group.

Conclusions

Prenatal care is the entry point for pregnant women to the healthcare system. The medical component is capable of identifying at-risk pregnancies. Prenatal visits provide a platform to assess risk factors associated with pregnancy and to provide counselling and further management. The effectiveness of prenatal care in reducing adverse pregnancy outcomes is debatable. Performing a randomized controlled study is not ethical because women cannot be randomly assigned to prenatal care versus no prenatal care. RCTs have been conducted to compare a reduced visit model to a standard care model; these studies showed no difference in fetal growth or incidence of preterm births. However, provision of prenatal care has advantages at an individual level. The content of these care programs requires investigation to identify which components are more effective and the best way to deliver these programs (group or individualized). Moreover, future studies must focus on the evaluation of the quality of care provided and its impact on the incidence of different pregnancy outcomes. Proper mechanisms should be in place for the identification and follow up of high-risk mothers. Continuity of care by midwives has not shown any benefit for preterm/LBW births compared with care provided by several different health professionals.

Education

Programs that educate pregnant women in the early recognition of preterm labour have been proposed as a strategy for early detection and appropriate medical attention. These programs are inexpensive because they can be provided to pregnant women during routine clinical visits, so even a small gain could be advantageous.

Evidence from systematic and other reviews

Hueston et al.[17] systematically reviewed six studies that reported on the efficacy of preterm birth prevention educational programs for high-risk women. There was no difference in the risk of preterm births (RR 1.08, 95% CI 0.92, 1.27) or LBW births (RR 0.99, 95% CI 0.88, 1.11). There was an increase in the diagnosis of preterm labour (RR 1.71, 95% CI 1.41, 2.08). The studies were aimed at high-risk women, for some of whom it may not be possible to prevent preterm labour by educational interventions. The authors suggested that low-risk women are likely to have idiopathic preterm labour and programs may be of more benefit in that population. The possibility that women in the control group may have received components of the interventions cannot be ruled out.

Evidence from other study designs

Lumley and Donohue[18] randomly assigned women to a control arm (visit only to collect baseline information: 394 women) and an intervention arm (received pre-pregnancy intervention, including discussion of social, health, and lifestyle issues; preparation and timing for pregnancy; family history; rubella immunization; and a reminder card: 392 women) when they came for the newborn checkup after one pregnancy. The mean BW was lower in the intervention group (3500 g versus 3403 g). There was a trend towards an increased risk of LBW births in the intervention group (OR 1.85, 95% CI 0.91, 3.91). There was no difference in the risk of preterm births (OR 1.44, 95% CI 0.73, 2.91) or intrauterine growth-restricted (IUGR) births (OR 1.14, 95% CI 0.55, 2.38). Increased stress associated with the provision of advice, a shorter intervention-to-conception time in the intervention group, and the possibility of improvement after intervention and survival of previously non-viable fetuses may have played role in the apparent negative results.

Sprague[19] reported on the change in practice associated with supplementation of educational material to healthcare providers to give to pregnant women at the 18- to 20-week visit. Healthcare providers were told to discuss signs and symptoms of preterm labour with the expectant mothers. There was a significant improvement in the number of healthcare providers who discussed signs and symptoms of preterm labour with the mothers (56% versus 78%, $p = 0.001$). This result was confirmed by mothers on postnatal wards (44% versus 61%,

p = 0.0001). In the first year after the initiation of the program, the number of women knowledgeable about the signs and symptoms of preterm labour increased (6% versus 12%, p = 0.003); however, this improvement was lost in the subsequent 2 years. There was an increase in the number of women who received antenatal steroids among women who had preterm births between 24 and 34 weeks of pregnancy (56% versus 79%, p = 0.002).

Moore et al.[20] randomly assigned pregnant women to a control arm (baseline information and provision of a booklet about prevention of preterm labour) and an intervention arm (additional instruction about preterm labour and a twice weekly phone call from a nurse to discuss any issues that arose during pregnancy). In the intervention group, there was no reduction in the risk of preterm births (RR 0.87, 95% CI 0.62, 1.22), but there was a trend towards a reduction in the risk of LBW births (RR 0.75, 95% CI 0.55, 1.03). Among a subgroup of black women >19 years of age, there was a reduction in the risk of LBW births (OR 0.66, 95% CI 0.46, 0.94).

Conclusions

Currently, there is no evidence to suggest that educational programs directed towards high-risk women prevent preterm births. Any such intervention would have to strike a balance between adequate information and the excessive stress induced by provision of such information. Further studies are needed.

Clinical Markers

Risk factors

Attempts to identify preterm births from clinical scoring systems have yielded variable results.

Evidence from systematic and other reviews

Honest et al.[21] systematically reviewed the accuracy of various risk scores in predicting preterm births from 19 studies. Twelve different scoring systems were used in these studies, but the most common scoring system used was that developed by Creasy et al.[22] There was marked heterogeneity among studies and the overall quality of studies was moderate. Among the three high-quality studies that used Creasy's scoring system, the positive likelihood ratio varied from 1.0 (95% CI 0.6, 1.4) to 7.1 (95% CI 5.0, 10.2) and the negative likelihood ratio varied from 0.5 (95% CI 0.3, 0.6) to 1.0 (95% CI 0.9, 1.2) for preterm births. Between the two studies that used statistical methods to calculate risk scoring, the positive likelihood ratio varied from 1.5 (95% CI 1.1, 2.1) to 2.0 (95% CI 1.3, 3.2) and the negative likelihood ratio varied from 0.8 (95% CI 0.6, 1.0) to 0.9 (95% CI 0.7, 1.0) for preterm births.

Evidence from other study designs

Creasy et al.[22] reported a scoring system that was based on risk factors in maternal medical and social history. The positive predictive value of this scoring system was 38% for preterm births. Further studies that use this scoring system have yielded poor results.

Tekesin et al.[23] studied the use of a scoring system called the CLEOPATRA (clinical evaluation of preterm delivery and theoretical risk assessment). This system was developed on the basis of potential risk factors, individual patient risk factors, results of a rapid fibronectin assay, and sonographic measurement of cervical length. History of preterm birth (OR 4.56, 95% CI 0.93, 22.4) and fetal fibronectin (OR 17.9, 95% CI 5.10, 62.7) were the significant predictors of preterm birth in the current pregnancy (area under the receiver-operating characteristic curve = 0.81).

Conclusions

Although some risk factors are known to be significantly associated with preterm births, their role in predicting it is not well established because of the relatively weak strengths of association.

Cervical Changes

Before the onset of labour, certain changes occur in the cervix of the uterus.

Evidence from systematic and other reviews

No reviews on the role of detection of cervical changes and its association with preterm births were identified.

Evidence from other study designs

Papiernik et al.[24] evaluated serial weekly observations of cervical changes. Cervical changes were observed 3 to 4 weeks before the onset of labour. Cervical dilatation of >1 cm was associated with a two- to three-fold increase in the risk for preterm labour. The false-positive values were not reported, which makes it difficult to assess the findings.

Mortensen et al.[25] examined cervical changes at 24, 28, and 32 weeks. In the low-risk group (no associated risk factors), the positive predictive value for preterm births was 4%, and in the high-risk group it was 25% to 30%.

Conclusions

Cervical changes observed before the onset of preterm labour are not highly predictive for preterm labour. Additionally, in a low-risk population, monitoring of cervical changes requires additional testing visits. Monitoring may have a role in a high-risk situation such as threatened preterm labour; however, more information can be gained non-invasively with the use of modern technology.

Ultrasound in the assessment of cervical changes preceding labour

Evidence from systematic and other reviews

Honest et al.[26] systematically reviewed 46 studies (33 studies in asymptomatic women and 13 studies in symptomatic women) on the accuracy of cervical length measurement in predicting preterm labour. Various studies have used different cut-offs and measured cervical length at different times in gestation. The most commonly reported measure in asymptomatic women was to assess cervical length at <20 weeks' gestation and use the cut-off of 25 mm. In this group, the likelihood of spontaneous preterm births at <34 weeks' gestation yielded a positive likelihood ratio of 6.3 (95% CI 3.3, 12.0) and a negative likelihood ratio of 0.79 (95% CI 0.65, 0.95). In symptomatic women, the degree of cervical funnelling was more predictive of spontaneous preterm births.

Ultrasonography is used for assessment of fetal well-being and changes in the maternal lower genital tract. With labour, changes in the cervix start at the internal os. The cervical canal shortens as labour advances and at the same time, the internal os opens. This process continues distally until the external cervical os joins the internal os and completes the effacement.[27] Investigators have attempted to predict preterm labour on the basis of cervical changes shown by ultrasonography.

Kagan et al.[28] reviewed studies of transvaginal ultrasound scanning for cervical length in predicting preterm births. For asymptomatic singleton pregnancies, the detection rate for preterm births before 35 weeks by measuring cervical length at 20 to 24 weeks of gestation was 34%, for a false-positive rate of 5%. For asymptomatic twin pregnancies, cervical length measured at 21 to 24 weeks was inversely related to the risk of preterm births at <32 weeks (66% for 10 mm, 24% for 20 mm, 12% for 25 mm, and <1% for 40 mm). Among women with singleton pregnancies and spontaneous preterm labour, preterm births within 7 days occurred in 49% of women with a cervical length of <15 mm and in 1% of women with a cervical length of >15 mm. Among twins, the cut-off for birth within 7 days of presentation for spontaneous preterm labour was 25 mm.

Colombo and Iams[27] reviewed two studies that evaluated cervical length in women with symptoms suggestive of preterm labour. Cervical length of >30 mm was associated with a low risk of preterm labour. The presence of cervical funnelling was associated with a 100% chance of preterm labour. For women with multiple pregnancies, the use of cervical length for predicting preterm labour was beneficial in restricting the use of interventions.

Evidence from other study designs

To et al.[29] retrospectively evaluated data on maternal factors, cervical length, and

a combination of both for the prediction of preterm births at <32 weeks. At a fixed false-positive rate of 10%, the detection rate was 38% for maternal factors, 55% for cervical length, and 69% for combined testing.

Jenkins et al.[30] reported that dynamic cervical changes were noted in 47% of pregnancies. Minimum cervical length was predictive of preterm labour (OR 3.0, 95% CI 1.1, 8.3).

Pires et al.[31] reported that non-detection of the cervical gland area was a statistically significant predictor (OR 111.0) of preterm births, with a positive predictive value of 67% and a negative predictive value of 98%.

Severi et al.[32] compared the predictive accuracies of two-dimensional ultrasonography and three-dimensional ultrasonography for the assessment of cervical length to predict preterm births in singleton women. With a cut-off level of 35 mm for prediction of preterm births, three-dimensional ultrasonography had a sensitivity of 71%, a specificity of 85%, a negative predictive value of 98%, and a positive predictive value of 26% compared with two-dimensional ultrasonography, with a sensitivity of 57%, a specificity of 76%, a negative predictive value of 96%, and a positive predictive value of 15%. Receiver-operator characteristic curves yielded an area under the curve of 0.95 for second-trimester examinations and 0.81 for third-trimester examinations for three-dimensional ultrasonography.

The risk for preterm birth increased at a cervical length of <30 mm. Women with a cervical length of ≤30 mm at 24 weeks' gestation had an increased risk of preterm labour (RR 6.19, 95% CI 3.84, 9.97) compared with women with a cervical length of 40 mm.[33]

Taipale and Hiilesmaa[34] evaluated women between 18 and 22 weeks' gestation and reported that women with a cervical length of ≤29 mm had an increased risk of preterm births (RR 8, 95% CI 3, 19). Dilatation of the internal os of >5 mm in addition to a cervical length of ≤29 mm was associated with a significantly increased risk (RR 28, 95% CI 12, 67) for preterm births before 35 weeks' gestation. The sensitivity of this finding was only 29%. The presence of cervical funnelling had a negative predictive value of 97%, which may be an important finding in the clinical context.

Conclusions

The risk of spontaneous preterm birth seems to increase as the cervical length is reduced. A cervical length of <30 mm and funnelling of the cervix have been shown to be associated with preterm births. The measurement of cervical length as a screening tool is not justified. The finding of a short cervix should be considered in the context of history, physical examination, and biochemical markers.

Routine ultrasound Doppler in identifying an at-risk fetus

Aberrant trophoblastic invasion of spiral arteries is associated with an increased risk of pre-eclampsia, placental abruption, and IUGR. Assessment of uterine artery flow velocity has been used as an indicator of placentation.

Evidence from systematic and other reviews

Bricker and Neilson[35] systematically reviewed the role of routine ultrasound Doppler in low-risk pregnancy. There was no difference in the risk of preterm births (RR 1.08, 95% CI 0.89, 1.32), mean gestational age at birth [weighted mean difference (WMD) -0.02 weeks, 95% CI -0.19, 0.15], mean BW (WMD -27 g, 95% CI -74, 20), BW at <10th centile (RR 0.97, 95% CI 0.77, 1.23), or BW at <3rd centile (RR 1.17, 95% CI 0.80, 1.70) when routine Doppler ultrasound was compared with no/concealed/selective Doppler ultrasound. One study reported increased perinatal mortality in the intervention group; however, meta-analysis of three studies reported no significant difference in perinatal mortality. One study in the review compared serial ultrasound and Doppler ultrasound versus selective ultrasound examination. There was no difference in mean gestational age at birth (WMD -0.10 weeks, 95% CI -1.21, 1.01), mean BW (WMD -25 g, 95% CI -68, 18), or risk for LBW births (RR 1.14, 95% CI 0.85, 1.52). There was, however, an increase in the risk of BW at <10th centile (RR 1.36, 95% CI 1.10, 1.68) and BW at <3rd centile (RR 1.66, 95% CI 1.10, 2.51) in the intervention group.

Bricker and Neilson[36] systematically reviewed the role of routine ultrasound Doppler performed after 24 weeks' gestational age in low-risk pregnancy. There was no difference in the risk of preterm births (RR 0.96, 95% CI 0.85, 1.08), mean BW (WMD -0.5 g, 95% CI -15, 14), LBW births (RR 0.92, 95% CI 0.71, 1.18), BW at <10th centile (RR 1.07, 95% CI 0.91, 1.25), or BW at <5th centile (RR 1.18, 95% CI 0.81, 1.74) when routine Doppler ultrasound was compared with no/concealed/selective Doppler ultrasound.

Fayyad and Harrington[37] reviewed studies on the use of uterine arterial Doppler. Three studies were identified that evaluated the role of uterine Doppler examination in selected populations of women who were at high risk for pre-eclampsia. A resistive index of >0.57 had a sensitivity of 44%, and a resistive index of >0.68 had a sensitivity of 56% for the prediction of pre-eclampsia. In an unselected population, there was marked variability in the technique, measurement, gestational ages of the study population, and baseline prevalence of pre-eclampsia. When used as a one-stage screening test (nine studies), the positive predictive value of a high resistive index ranged from 7% to 31% and the negative predictive values ranged from 76% to 99% for the prediction of pre-eclampsia. When used as a two-stage screening test (screening test initially and repeated in later gestations in selected groups) in four studies, the positive predictive value ranged from 10% to 22% and the negative predictive value was 99% for high resistive indices in predicting the development of pre-eclampsia.

The presence of bilateral uterine artery Doppler notches and a resistive index of >0.55 had the highest sensitivity (88%) and specificity (83%).

Alfirevic and Neilson[38] systematically reviewed the role of Doppler ultrasonography of the umbilical artery in high-risk pregnancy from RCTs. There was a statistically significant reduction in perinatal deaths (OR 0.62, 95% CI 0.45, 0.85) with the use of Doppler ultrasonography. There was no significant reduction in preterm births (OR 1.36, 95% CI 0.93, 1.98), preterm births at <34 weeks' gestation (OR 2.28, 95% CI 0.87, 6.01), or BW at <10th centile (OR 1.04, 95% CI 0.73, 1.48).

Conclusions

Abnormal uterine artery Doppler and high resistive indices are predictive of pre-eclampsia and subsequent IUGR births; however, further studies are needed to identify appropriate target populations. The use of uterine Doppler in low-risk, unselected women before or after 24 weeks gestation is not beneficial. One study reported an increase in perinatal mortality with the routine use of Doppler ultrasonography. However, this association was not identified in other studies. Further research is warranted.

Ultrasound assessment of fetal breathing movements

Evidence from systematic and other reviews

Honest et al.[39] systematically reviewed the accuracy of the absence of fetal breathing movements detected on ultrasonography in predicting preterm births from eight studies. The studies were lacking in one or more aspects of typical diagnostic accuracy studies. Absence of fetal breathing movement had a positive likelihood ratio of 14.8 (95% CI 6.3, 34.8) for predicting birth within the next 7 days, and 7.8 (95% CI 1.1, 55.0) for predicting birth within the next 48 hours for women with threatened preterm labour. The negative likelihood ratio was 0.5 (95% CI 0.4, 0.6) for predicting preterm birth within 7 days and 0.3 (95% CI 0.1, 0.5) for predicting birth within the next 48 hours.

Conclusions

Assessment of fetal breathing movement could be helpful in predicting preterm birth within the next 48 hours and within the next 7 days in women with threatened preterm labour. High-quality studies are needed.

Home uterine activity monitoring

Uterine activity is reported intermittently throughout pregnancy and is increased in the third trimester. Monitoring of uterine activity has been proposed to predict preterm labour.[40]

Biological plausibility

Before labour (term or preterm), a pregnant woman experiences increased frequency in uterine contractions. Investigators have used an arbitrary cut-off of four to six contractions per hour as predictive of preterm labour. There is no recognizable consistent pattern of uterine contractions and progression of preterm labour.[40]

Epidemiological evidence

Devoe and Ware[40] reviewed six published meta-analyses or reviews of the major trials on home uterine activity monitoring (HUAM). These meta-analyses included five to seven studies. The results or conclusions differed depending on the primary objective of the review and the studies included. All of the individual studies included in those meta-analyses lacked power. Two larger studies were published after these reviews. The intervention group in the studies received monitoring of uterine activity one to three times per day. Some trials had a component of home visits by a nurse, making it difficult to assess which component was effective. HUAM was associated with increased frequency of referral for threatened preterm labour. The criteria for the diagnosis of preterm labour varied between the studies. Devoe and Ware[40] included the latest RCTs in their assessment and performed another meta-analysis of nine studies. There was no difference in the risk of preterm births in either group (OR 0.93, 95% CI 0.75, 1.08) or in the risk of birth before 34 weeks' gestation (OR 0.98, 95% CI 0.74, 1.19).

Newman[41] reviewed all of the RCTs on HUAM, previous meta-analyses, and practice statements from the American College of Obstetricians and Gynecologists (Bulletins from 1992, 1996, and 2001). The author argued that of 10 RCTs on HUAM, eight have shown benefit for early diagnosis of preterm labour, reduction in preterm births, and benefits to neonates. Use of HUAM in high-risk pregnancies resulted in earlier admission of mothers with less cervical dilatation. However, when analyzed in the context of intention to treat with the entire randomized cohort as a baseline, HUAM failed to show benefit.

Morrison and Chauhan[42] reviewed all clinical trials (n = 22) on the use of HUAM. Seventeen studies identified benefits of prolongation of pregnancy and early diagnosis of preterm labour with the use of HUAM. The authors separated the trials of tertiary prevention, that is, the use in women who have threatened preterm labour. All six studies identified various benefits, including prolongation of pregnancy, reduced neonatal complications, and cost savings. The data were not synthesized.

Conclusions

The opinions of experts regarding the use of HUAM are variable. In a low-risk population, HUAM does not appear to confer any benefit in reducing preterm/LBW births, thus precluding its routine use. However, for high-risk preterm

labour, HUAM may be useful in prolonging pregnancy and reducing the number of preterm births.

Biochemical markers

Several biochemical markers have been used to detect early onset of preterm labour in order to intervene in its progress.

Evidence from systematic and other reviews

Goldenberg et al.[43] conducted a review of biochemical markers for the prediction of preterm births. Biological fluids that have been used as sources for tests include serum, plasma, amniotic fluid, urine, vaginal and cervical secretions, saliva, and periodontal fluid. In these fluids, researchers have looked for organisms, cytokines, enzymes, and hormones as predictors for preterm births. There are many issues related to the timing of the test, the cost, and the ease of fluid collection and processing. Studies need to be designed that test an intervention with the biological plausibility of reducing preterm births in women whose test results are positive in the specific test under study. *"Only when the use of a marker and subsequent treatment have been shown to result in a significant reduction in preterm birth should any single or multiple marker test for spontaneous preterm birth be introduced as part of routine prenatal care."* [43]

In the following section, we review commonly used and experimental markers for the prediction of preterm births.

Fetal fibronectin

Fibronectin is a glycoprotein found in malignant tissues, fetal tissues, the placenta, and amniotic fluid. It is produced by the chorion. Disruption of the choriodecidual surface leads to its release in cervical and vaginal secretions. It is present in the secretions from the vagina at up to 21 weeks of gestation. Recent intercourse, or digital examination, can result in a false-positive test. A careful collection of a specimen by speculum examination is necessary.[44]

Evidence from systematic and other reviews

Leitich and Kaider[45] updated a previously published meta-analysis that included 40 studies on the use of cervico-vaginal fibronectin as a marker of preterm births. Marked clinical and statistical heterogeneity was noted. Overall sensitivity for prediction of preterm births was 52% and specificity was 85%. The test had a sensitivity of 53% and a specificity of 89% for prediction of preterm births at <34 weeks' gestation. For the outcomes of births within 7, 14, and 21 days, the sensitivities were 71%, 67%, and 59% and the specificities were 89%, 89%, and 92%, respectively. For the subgroup of women with symptoms of preterm labour, the sensitivity for preterm births was 54% and the specificity was 85%; the

sensitivity for births at <34 weeks' gestation was 63% and the specificity was 86%; and the sensitivities for births within 7, 14, and 21 days were 77%, 74%, and 70% and the specificities were 85%, 87%, and 90%, respectively.

Andersen[44] reviewed five studies that reported the use of fetal fibronectin for the diagnosis of women with symptoms of labour. Three studies reported on the prediction of labour within the next 14 days and all five studies reported predictive values for preterm labour before 37 weeks. In the three studies reporting predictive values for births within the next 14 days, sensitivity ranged from 69% to 83%, specificity ranged from 79% to 83%, positive predictive value ranged from 17% to 41%, and negative predictive value ranged from 95% to 99%. The RR ranged from 7.4 to 20.4. The results for the predictive values for labour before 37 weeks were a sensitivity range of 41% to 82%, a specificity range of 81% to 96%, a positive predictive value range of 45% to 83%, and a negative predictive value range of 76% to 92%. The ORs ranged from 2.5 to 9.1. The CI for the OR in all studies was >1, indicating usefulness of the test. Fetal fibronectin is a valuable tool in predicting women who are unlikely to give birth within 7 to 14 days of the test.

Andersen[44] reviewed eight double-blind studies that reported on the risk of preterm births in women without symptoms of labour. Women were assessed for fibronectin levels biweekly from 22 to 24 weeks' gestation. The RR of preterm births between 24 and 31 weeks, if a woman was found to be positive for fetal fibronectin at 24 weeks, was 21 (95% CI 14.3, 31.4). The test was found to be more predictive for early preterm (<28 weeks) births. The predictive values for labour before 37 weeks from another seven studies had a sensitivity range of 18% to 93%, a specificity range of 52% to 96%, a positive predictive value range of 15% to 64%, and a negative predictive value range of 79% to 97%. The RR ranged from 1.0 to 7.6.

Evidence from other study designs

Combinations of factors such as history of preterm birth, short cervix on ultrasound scan, and presence of fetal fibronectin[33] suggested that a woman with a history of a preterm birth with a normal cervical length had a 7% risk of preterm birth if the fibronectin result was negative. Fetal fibronectin combined with other tests may provide better predictive accuracy.

Interventions based on fetal fibronectin results

Claims regarding the predictive accuracy of a diagnostic test should be supplemented with results that indicate a change in the outcomes. Two studies have used the fetal fibronectin test to apply therapeutic manoeuvres to change the outcome. The interventions used are not proven therapies for prevention of preterm labour; however, the results are a guide to the utility of the test.

Shennan et al.[46] randomly assigned women who were at high risk of preterm birth and who had fetal fibronectin in their vaginal secretions in the second

trimester to receive either oral metronidazole (400 mg three times a day) or a placebo for 1 week. The study was stopped prematurely when 11 of the 53 women given metronidazole and 5 of the 46 placebo recipients gave birth at <30 weeks' gestation (RR 1.9, 85% CI 0.72, 5.09). The risk for preterm births was higher in the metronidazole group compared with the placebo group (RR 1.6, 95% CI 1.05, 2.40). The positive and negative predictive values for fetal fibronectin for early preterm births, estimated at 24 weeks for the risk of giving birth at <30 weeks, were 26% and 99%, respectively. BWs averaged 366 g lower for infants whose mothers received metronidazole, and 56% more infants in this group were of LBW at birth compared with those whose mothers received placebo. Metronidazole has been shown to have adverse effects on fetal outcomes; however, this study indicates utility (high negative predictive value) of the fetal fibronectin test in predicting preterm labour.

Elliot et al.[47] randomized women in preterm labour (cervical dilatation ≤3 cm) and receiving magnesium sulphate, who also had a negative result for fetal fibronectin at 23 to 33 weeks' gestation, to activity restriction (n = 36) versus no activity restriction (n = 37). The overall preterm birth rate was 40% (44.4% in the activity restriction group and 35.1% in the no-activity restriction group, p = 0.0478). Activity restriction or bed rest has been evaluated in chapter 15 and the evidence is inadequate to confirm its effects. An interesting finding is that the incidence of preterm births in symptomatic women whose test results were negative for fetal fibronectin was higher than previously reported.

Conclusions

The absence of fetal fibronectin is a strong indicator of women not having preterm labour in the next 7 to 14 days. The presence of fetal fibronectin in cervical-vaginal secretions is a moderate predictor for preterm labour within the next 14 days. The presence of fetal fibronectin is a good marker for preterm labour at 24 to 28 weeks. Because results appear to be heterogeneous among the studies, caution should be taken when results are applied to a specific population. A rapid test kit has been developed. Intervention studies based on fetal fibronectin results have been disappointing, although the therapies attempted were not proven. Further studies of the utility of fetal fibronectin to reduce adverse fetal outcomes are needed.

Estriol

The level of estrogen increases before parturition. Rising levels of estrogen can be detected in mothers to predict labour.

Evidence from systematic and other reviews

Nielson and Cloherty[48] systematically reviewed the effects of performing biochemical tests of placental function in high-risk, low-risk, or unselected

pregnancies in general; however, only one trial of poor quality was identified. Women with high-risk pregnancies were allocated to have their estriol results revealed or not on the basis of their hospital record number. There were no important differences in perinatal mortality (RR 0.88, 95% CI 0.36, 2.13) between the groups. The possible impact on preterm/LBW births was not reported in the review.

Evidence from other study designs

McGregor et al.[49] noted a rise in salivary estriol levels 3 weeks before women gave birth in a prospective study. A threshold of 2.3 ng/dl had a sensitivity of 71% and a specificity of 77% for prediction of preterm labour. The same group of investigators[50,51] reported that serial salivary estriol predicts preterm births 91% of the time. The risk ratios for preterm births in women with an estriol level of $\geq$2.1 ng/dl were 4.0 ($p \leq 0.05$) in the low-risk population and 3.4 in the high-risk population ($p = 0.05$).

Conclusion

Estriol may be useful for prediction of preterm labour; however, further studies are needed.

Corticotropin-releasing hormone

Corticotropin-releasing hormone (CRH), the principal regulator of the hypothalamic-pituitary-adrenal axis, and its receptors have been isolated in most female reproductive tissues, including the uterus, the placenta, and the ovaries.[52] Endometrial, placental, and ovarian CRH may participate in decidualization, implantation, parturition, ovulation, and luteolysis, as well as the physiology of pregnancy. The hypercortisolism of the latter part of pregnancy can be explained by high levels of placental CRH in plasma and is presumed to play a role in the initiation of parturition.[52,53] Investigators have postulated that CRH receptor antagonism in the fetus can delay parturition.[54]

Evidence from systematic and other reviews

Ramsay and Goldenberg[55] reviewed studies that reported on CRH for predicting preterm labour. Three studies found a positive association and one study found no association. Leung et al.,[56] using a cut-off value of 1.9 multiples of the median, found a sensitivity of 73%, a specificity of 78%, a positive predictive value of 4%, and a negative predictive value of 100% for preterm labour.

Conclusions

Further research is needed to establish the exact role of CRH in the early detection of preterm labour.

Metalloproteinases

The matrix metalloproteinases (MMPs) form a specific class of proteolytic enzymes. MMP8 is an enzyme that degrades fibrillar collagens, imparting strength to the fetal membranes, and is expressed in leukocytes and chorionic cytotrophoblast cells.[57] The breakdown of the chorioamniotic membrane results in the release of MMPs in the amniotic fluid and blood.

Evidence from other study designs

A case-control study[57] reported a statistically significant association between the three minor allele haplotypes, which display the highest MMP8 promoter activity in trophoblast cells, and prelabour rupture of the membranes (PROM) (OR 4.63, $p < 0.0001$), whereas the major allele promoter appeared to be protective (OR 0.52, $p < 0.0002$). Single nucleotide polymorphism haplotypes in the MMP8 gene have functional significance and are associated with obstetrical outcomes.

A study noted a significant increase in total MMP9 in saliva from women with prelabour rupture of the membranes before preterm birth compared with any other group.[58]

Conclusions

The presence of MMP8 and MMP9 has been investigated for correlation with preterm labour. The predictive power of MMP is limited.

Cytokines

Infection is one of the precipitating events for preterm labour. Patterns of expression of cytokines in the fetal membranes and decidua suggest that inflammatory activation occurs modestly with term labour but much more prominently in preterm births, particularly in the presence of intrauterine infection.[59]

In high-risk pregnancy, a correlation between levels of tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) and the fetal middle cerebral artery pulsatility index (PI) was reported. Abnormal uterine artery PI and the presence of a "notch" were highly significantly associated with high TNF-α and IL-6 levels, indicating a correlation with uteroplacental blood flow.[60]

Elevated levels of cytokines such as interleukins, ferritin, and lactoferrin in various body fluids have been tested for their association with preterm labour.[56]

Conclusions

Not all hospitals that deal with labour and birth have the capacity to assess the level of cytokines, particularly in a rapid fashion, which has prevented its widespread use. In addition, there have been inconsistencies in the results among various studies. Further research is needed.

Other Markers

Numerous other markers have been studied in association with preterm/LBW and IUGR births. Some of these markers are listed below.

- Elevated maternal testosterone levels have been associated with IUGR births.[61]
- Total activin A concentrations are higher in a low-risk population of women who experience preterm births.[62]
- Serum relaxin levels decrease less rapidly in women who subsequently give birth preterm; this process results in elevated serum relaxin levels in the second and third trimester.[63]
- C-reactive protein is sensitive but non-specific.[64]
- Elevated levels of alpha-protein in amniotic fluid may help with the early detection of a fetus at risk of developing IUGR.
- Low levels of nitric oxide in the amniotic fluid during the early second trimester may represent an impaired stimulus to vascular formation and endothelial regulation, inducing placental disease and subsequent fetal growth restriction.[65]
- Raised serum human chorionic gonadotropin has a better predictive value for adverse pregnancy outcome than does raised alpha-fetoprotein.[66]
- The risk of giving birth to a LBW infant at term after an uncomplicated pregnancy varies with maternal circulating concentrations of a placental protein or pregnancy-associated plasma protein A in the first week of conception. Poor fetal growth may therefore already have been determined by the time obstetric monitoring begins.[67]

Conclusions for Early Diagnosis

Several methods have been used for early diagnosis of preterm births. A combination of history, physical examination, biochemical tools, and sonography may provide better prediction. Efficacy of educational programs is questionable and the anxiety generated from information overload could be detrimental. Risk factor-based scoring systems may provide borderline predictive accuracy; however, further research is needed. Measurement of cervical length on ultrasonography in a symptomatic woman probably provides a better indication of preterm birth in the next 48 hours to 7 days. Abnormal uterine Doppler and high resistive indices in the uterine artery are predictive of pre-eclampsia and IUGR births; however, the role of these tests in screening the general population is questionable. The absence of fetal breathing movement predicted preterm births within 48 hours and the next 7 days with reasonable accuracy; however, the role of this method in screening the general population has not been studied. The opinion of experts on the use of HUAM is contentious. Its role in the general

population is not justified. The fibronectin assay is a useful predictor of preterm births in high-risk women at 24 to 28 weeks' gestation; however, a positive result may generate significant anxiety in women. The use of other biochemical markers in the prediction of preterm labour is in the initial phase of evaluation. The use of a test to predict preterm labour or IUGR births should be supplemented by interventions or measures that prevent abnormal outcomes; however, research in this area is preliminary.

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CHAPTER 15:

Secondary Prevention for Preterm Birth and Fetal Growth Restriction

Main Summary Points

- Bed rest, hospitalization, or hydration of women with threatened preterm labour is not effective in reducing the risk of preterm/low birth weight births.
- Tocolytics are widely used for prevention of preterm births.
    - Betamimetics reduce the number of women who give birth within 48 hours and within 7 days but have no effects on perinatal/neonatal deaths or other neonatal outcomes. Adverse effects in mothers are common.
    - Magnesium sulphate is ineffective in delaying births or preventing preterm births.
    - Calcium channel blockers are preferable to other tocolytics (especially betamimetics).
    - There is insufficient evidence for the effectiveness of cyclo-oxygenase inhibitors, nitric oxide donors, and oxytocin inhibitors for women in preterm labour, and these agents may cause harm to the fetus.
    - The use of progestational agents and 17α-hydroxyprogesterone caproate reduces preterm and low birth weight births in high-risk pregnancies. Progestational agent therapy should be recommended to women at high risk for preterm births.
- Cerclage in women with a short cervix diagnosed by ultrasound may reduce preterm births in a subgroup of singleton pregnancies, particularly in women with a previous preterm birth.
- Measures to improve fetal growth by administration of oxygen, plasma, hormones, calcium channel blockers, and betamimetics have not been studied adequately. Antiplatelet agents have shown small to moderate benefit for mother and infant.
- Multicomponent preterm birth prevention programs are based on interventions that promote education, recommend avoidance of exertion, teach women early signs of preterm labour, encourage women to seek medical attention, and promote the administration of medical interventions to reduce the risk of initiation of labour. These programs have variable results for reducing the rate of preterm/low birth weight births.

The aims of management for threatened preterm labour are: (1) to prevent contractions; (2) to control contractions to allow maximum time to birth; and (3) to improve fetal maturation before birth. Gestational age plays a vital role in decision making because a number of therapies given to the mother, but directed at the fetus, can cause side effects and pose risks to the mother. In this chapter we review the role of various interventions for mothers with threatened preterm labour, for mothers with an intrauterine growth-restricted (IUGR) fetus, and for low- or high-risk mothers.

Interventions for Threatened Preterm Labour

Various interventions such as bed rest, hospitalization, hydration, tocolytics, cervical cerclage, and antibiotics have been tried to either delay or prevent preterm births. Antibiotics are discussed in detail in chapter 13.

Bed rest

Bed rest in hospital or at home is a widely prescribed intervention for pregnancy complications.

Biological plausibility

- Hard work and physical activity can be associated with preterm births. Bed rest has been suggested to reduce activity that could precipitate possible uterine contractions.
- The side effects of bed rest include increased risk of venous thrombosis, muscle atrophy, weight loss, stress to the mother, and cost to the healthcare system.[1]

Epidemiological association

The practice of bed rest during the antenatal and postnatal period has continued since the 17th century.[2]

Intervention

Evidence from systematic and other reviews:

Sosa et al.[3] reviewed one randomized controlled trial (RCT) on bed rest for singleton pregnancy that included 174 women and found that there was no reduction in the risk of preterm births (risk ratio (RR) 0.92, 95% confidence interval (CI) 0.62, 1.37).

Crowther[4] reviewed six RCTs of bed rest for multiple pregnancies and reported that there was no difference in the risk of preterm births (odds ratio (OR) 1.14, 95% CI 0.82, 1.58), births before 34 weeks (OR 1.37, 95% CI 0.85, 2.21), low birth weight (LBW) births (OR 0.83, 95% CI 0. 67, 1.07), or very low birth weight

(VLBW) births (OR 1.36, 95% CI 0.82, 2.25) between the bed rest and control groups. There was no difference in the risk of preterm births (OR 1.31, 95% CI 0.92, 1.89) or LBW births (OR 0.83, 95% CI 0.65, 1.06) for twin pregnancies. For triplet pregnancies, the author found no reduction in the risk of preterm births (OR 0.13, 95% CI 0.01, 2.33) but noted a tendency towards reduction in the rate of LBW births (OR 0.13, 95% CI 0.02, 1.01). There was no difference in the risk of LBW births (OR 0.91, 95% CI 0.56, 1.47) or preterm births (OR 0.69, 95% CI 0.32, 1.50) among women who had cervical dilatation.

Schroeder[5] reviewed the reasons for continuing to prescribe bed rest in pregnancy. Because little harm is done to the fetus with bed rest, the practice of prescribing bed rest in high-risk pregnancies continues. Suggestions from textbooks and colleagues influence many healthcare workers in this regard.

Evidence from other study designs

Maloni et al.[6] compared data from 141 singleton women who had threatened preterm labour and were prescribed strict bed rest (bathroom privileges only) to matched data available from a US reference cohort from 1994 to 1996. There was no significant difference in the number of small for gestational age (SGA) births (8.5% in the study sample versus 9.3% in the national sample).

Conclusions

Any advantage of bed rest may lie in the degree of supervision, but there is little evidence of a reduction in preterm/LBW births.

Hospitalization

Hospitalization is intended for monitoring and provision of bed rest, depending on the need. The topics of bed rest and hospitalization are interrelated. Here we present the information from two RCTs not included in the bed rest reviews that include hospitalization as their study intervention.

Intervention

Evidence from other study designs:

Goulet et al.[7] randomly assigned 250 women between 20 and 35 weeks of gestation who had attended a clinic with an acute episode of preterm labour to either home care or hospitalization. There was no difference in the risk of preterm births (42% in the home care group versus 44% in the hospital group, $p = 0.8$), birth weight (BW) (mean 2,974 g in the home care group versus 3,020 g in the hospital care group, $p = 0.60$), or gestational age at birth (mean 37.5 weeks in both groups, $p = 0.96$).

Yost et al.[8] randomly assigned 101 women with singleton pregnancy and arrested labour to home care or hospital management between 24 and 33 weeks and 4

days of gestation. There was no difference in the risk of LBW births (31% in hospital group versus 43% in home care group, p = 0.26), VLBW births (9% in hospital group versus 2% in home care group, p = 0.15), extremely low birth weight births (BW < 1000 g) (0% in hospital group versus 2% in home care group, p = 0.33), preterm births at <36 weeks (29% in hospital group versus 28% in home care group, p = 0.89), or preterm births at ≤34 weeks (22% in hospital group versus 24% in home care group, p = 0.77). The study was terminated after interim analyses.

Conclusion

Hospitalization of women with threatened preterm labour is not effective in reducing the risk of preterm/LBW births.

Hydration

Hydration with either oral fluids or intravenous fluids is a common practice for a mother who is admitted with a diagnosis of threatened preterm labour.

Biological Plausibility

The biological mechanism is not clear.

- Plasma volume expansion leads to increased uterine blood flow, which in turn stabilizes lysosomes and reduces prostaglandin (PG) production.[9]

Intervention

Stan et al.[10] reviewed two studies (228 women) of hydration for preterm birth and reported that there was no difference in the risk of preterm births (RR 1.09, 95% CI 0.71, 1.68), preterm births at <34 weeks (RR 0.72, 95% CI 0.20, 2.56), or preterm births at <32 weeks (RR 0.76, 95% CI 0.29, 1.97).

Conclusion

There is no evidence that hydration reduces the risk of preterm births in mothers with threatened preterm labour.

Tocolytics

The use of tocolytics is widespread for women with threatened preterm labour. The primary goal of tocolytic therapy is to prevent uterine contractions and thus delay the onset of labour and ultimately reduce neonatal morbidity and mortality. Coleman et al.[11] reported a higher risk of respiratory distress, need for intubation, and infection in neonates exposed to tocolytics compared with neonates not exposed to tocolytics. Various tocolytic agents have been used.

Mechanism of action

Different tocolytics have different mechanisms of action.[12]

- Betamimetics act on β_2 receptors in the uterus and increase cyclic adenosine monophosphate in smooth muscles, leading to a reduction in free calcium and thus inhibiting uterine contractions.
- Magnesium sulphate acts as a competitive antagonist to calcium entry into the myocyte and decreases myometrial contractility.
- Calcium channel blockers inhibit the influx of calcium ions through the muscle membrane and inhibit contractions.
- PG synthetase/cyclo-oxygenase (COX) inhibitors inhibit COX and decrease PG synthetase enzymes. This prevents the conversion of free arachidonic acid to PGs, which are mediators of uterine contractions.
- Nitroglycerin acts as a potent smooth muscle relaxant and relaxes the uterus.
- Oxytocin antagonists inhibit oxytocin, which is believed to stimulate uterine contractions.
- Progestational agents (progesterone) play a role in maintaining pregnancy and are thought to act by suppressing smooth muscle activity in the uterus.

Epidemiological evidence

Several systematic reviews have been performed on various tocolytics. For nitric oxide donors, four studies have been performed since the most recently published systematic review. These reviews and studies are summarized in Tables 15.1 and 15.2.

Table 15.1: Summary of results of systematic reviews of tocolytics reporting on important maternal and neonatal outcomes

Study	Tocolytic	Outcome	Number of studies, patients	Results	Remarks
Anotayanonth et al.[13]	Betamimetics for tocolysis	Births within 48 hours	Ten studies, 1209 women	RR 0.63 (95% CI 0.53, 0.75)	Higher rate of withdrawal from treatment because of adverse effects
		Births within 7 days	Five studies, 911 women	RR 0.78 (95% CI 0.68, 0.90)	
		Perinatal mortality	Eleven studies, 1332 infants	RR 0.84 (95% CI 0.46, 1.55)	
		Neonatal mortality	Six studies, 1174 infants	RR 1.00 (95% CI 0.48, 2.09)	
Dodd et al.[14]	Betamimetics for maintenance of tocolysis	Perinatal mortality	Six studies, 681 women	RR 2.41 (95% CI 0.86, 6.74)	Tachycardia more frequent
		Preterm births	Four studies, 384 women	RR 1.08 (95% CI 0.88, 1.32)	

Study	Tocolytic	Outcome	Number of studies, patients	Results	Remarks
Nanda et al.[15]	Terbutaline pump for maintenance of tocolysis	Gestational age	Two studies, 79 women	WMD at birth -0.1 weeks (95% CI, -1.7, 1.4)	
		Preterm births	Two studies, 79 women	RR 1.17 (95% CI 0.79, 1.73)	
Yamasmit et al.[16]	Oral betamimetics for tocolysis in twin pregnancy	Preterm labour	One study, 50 twin pregnancies	RR 0.40 (95% CI 0.19, 0.86)	
		Preterm births	Four studies, 276 twin pregnancies	RR 0.85 (95% CI 0.65, 1.10)	
		Preterm births at <34 weeks	One study, 144 twin pregnancies	RR 0.47 (95% CI 0.15, 1.50)	
		LBW births	Two studies, 366 twin pregnancies	RR 1.19 (95% CI 0.77, 1.85)	
		SGA births	Two studies, 178 twin pregnancies	RR 0.92 (95% CI 0.52, 1.65)	
		Neonatal mortality	Three studies, 452 neonates	RR 0.80 (95% CI 0.35, 1.82)	
Crowther et al.[17]	Magnesium sulphate for tocolysis	Births within 48 hours	Eleven studies, 881 women	RR 0.85 (95% CI 0.58, 1.25)	
		Preterm births	Six studies, 424 women	RR 0.91 (95% CI 0.75, 1.11)	
		Preterm births at <34 weeks	One trial, 80 women	RR 0.82 (95% CI 0.45, 1.54)	
		Gestational age at birth	Four studies, 361 women	WMD -0.43 weeks (95% CI -1.72, 0.87)	
		Mortality in children	Seven studies, 727 participants	RR 2.82 (95% CI 1.20, 6.62)	
Crowther and Moore[18]	Magnesium sulphate for maintenance of tocolysis	Preterm births	Three studies, 303 women	RR 0.85 (95% CI 0.47, 1.51)	Magnesium sulphate vs. placebo
				RR 0.98 (95% CI 0.56, 1.72)	Magnesium sulphate vs. ritodrine or terbutaline

Study	Tocolytic	Outcome	Number of studies, patients	Results	Remarks
King et al.[19]	Calcium channel blockers	Births within 7 days	Four studies, 453 women	RR 0.76 (95% CI 0.60, 0.97)	
		Preterm births at <34 weeks	Six studies, 619 women	RR 0.83 (95% CI 0.69, 0.99)	
		Side effects requiring cessation of medication	Ten studies, 833 women	RR 0.14 (95% CI 0.05, 0.36)	
Gaunekar and Crowther[20]	Calcium channel blockers for maintenance of tocolysis	Preterm births	One study, 74 women	RR 1.00 (95% CI 0.73, 1.37)	
King et al.[21]	Cyclo-oxygenase inhibitors for tocolysis	Preterm births	One trial, 36 women	RR 0.21 (95% CI 0.07, 0.62)	vs. placebo
		Preterm births	Three studies, 168 women	RR 0.53 (95% CI 0.31, 0.94)	vs. other tocolytic
		Gestational age at birth	Two studies, 67 women	WMD 3.5 weeks (95% CI 1.1, 5.9)	
		Mean BW	Two studies, 67 women	WMD 716 g (95% CI 426, 1007)	
		Maternal side effects requiring cessation	Five studies, 355 women	RR 0.07 (95% CI 0.02, 0.29)	
Duckitt and Thornton[22]	Nitric oxide donors	Preterm births	Three studies, 391 women	RR 0.69 (95% CI 0.53, 0.88)	Fewer side effects (other than headache) for nitroglycerin compared with other tocolytics
		Preterm births at <34 weeks	Two studies, 365 women	RR 0.69 (95% CI 0.52, 1.10)	
		Preterm births at <32 weeks	One study, 233 women	RR 1.00 (95% CI 0.40, 2.06)	
Papatsonis et al.[23]	Oxytocin receptor antagonists	Infant deaths	One study, 583 women,	RR 6.15 (95% CI 1.39, 27.22)	
		BW	Two studies, 692 women	WMD -138 g (95% CI -249, -28)	
		VLBW births (compared with other tocolytics)	Two studies, 575 women	RR 1.96 (95% CI 1.15, 3.35)	

Study	Tocolytic	Outcome	Number of studies, patients	Results	Remarks
Coomarasamy et al.[24]	Progesterone	Preterm births	Eight studies, 3369 women	OR 0.42 (95% CI 0.31, 0.57)	
		Preterm births at <34 weeks	Three studies, 1830 women	OR 0.51 (95% CI 0.34, 0.77)	
Dodd et al.[25]	Progesterone given by any route	Preterm births	Six studies, 988 women	RR 0.65 (95% CI 0.54, 0.79)	
		Preterm births at <34 weeks	One study, 142 women	RR 0.15 (95% CI 0.04, 0.64)	
		LBW births	Four studies, 763 infants	RR 0.63 (95% CI 0.49, 0.81)	
		Perinatal mortality	Five studies, 921 women	RR 0.66 (95% CI 0.37, 1.19)	

BW: birth weight; CI: confidence interval; LBW: low birth weight; OR: odds ratio; RR: risk ratio; SGA: small for gestational age; VLBW: very low birth weight; WMD: weighted mean difference.

Table 15.2: Recent studies of nitric oxide donors for threatened preterm labour

Study	Intervention	Population	Results
Smith et al.[26]	RCT of transdermal nitroglycerine vs. placebo	Threatened preterm labour between 24 and 32 weeks (153 women)	Risk of preterm births at <28 weeks' gestation (RR 0.50, 95% CI 0.23, 1.09) Composite outcome of common neonatal morbidities or mortality (RR 0.29, 95% CI 0.08, 1.00)
Bisits et al.[27]	RCT of β2 sympathomimetics vs. glyceryl trinitrate	Threatened preterm labour with positive fetal fibronectin test (238 women)	No difference in time to delivery ($p = 0.451$) At 2 hours, 27% of women receiving β2 sympathomimetics had moderate or stronger contractions compared with 53% in the glyceryl trinitrate group ($p < 0.001$) Gill et al.28 found no difference in psychomotor performance of children (n=156) randomly assigned in the Bisits et al.27 study
Schleussner et al.[29]	RCT of transdermal glyceryl trinitrate vs. fenoterol	Women in preterm labour between 27 and 35 weeks' gestation (50 women)	The mean (SD) BW was 3245 g (560) in the glyceryl trinitrate group and 2846 (480) in the fenoterol group ($p < 0.01$) The mean (SD) duration of pregnancy was 269 days (12) in the glyceryl trinitrate group and 257 days (15) in the fenoterol group ($p < 0.003$)

BW: birth weight; CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation

Additional evidence

Oei et al.,[30] in a review of calcium channel blockers for tocolysis, identified a number of reports of severe maternal adverse events (pulmonary edema and dyspnea) and one fetal death ascribed to nifedipine. The authors recommended that all serious adverse events of all tocolytics be reported to a central registry and critically reviewed.

Two studies assessing the effects of oxytocin inhibitors have been published since the systematic review. Shim et al.[31] randomly assigned 128 women to receive atosiban or ritodrine. Tocolytic efficacy after 7 days was significantly better in the atosiban group than in the ritodrine group (60.3% versus 34.9%, OR 2.83, 95% CI 1.37, 5.84) but not at 48 hours (68.3% versus 58.7%, OR 1.51, 95% CI 0.73, 3.14). Maternal adverse events related to therapy were reported less frequently in the atosiban group (7.9% versus 70.8%, $p = 0.0001$). Serious neonatal morbidities such as infection and intraventricular hemorrhage occurred more frequently in the atosiban group compared with the ritodrine group.

Al-Omari et al.[32] randomly assigned 63 women with threatened preterm labour to receive either atosiban or nifedipine. There were no significant differences in the effectiveness of tocolysis between the two groups. Women with a history of preterm labour responded significantly better to atosiban than did those without such a history. Women at <28 weeks gestation responded significantly better to nifedipine, whereas those at >28 weeks gestation showed an equal response in the two groups. Nifedipine achieved uterine quiescence in a significantly shorter time than did atosiban, but the maternal side effects were higher with nifedipine.

Neither of these trials had the power to identify any meaningful differences in important neonatal outcomes.

Similar to oxytocin, vasopressin is produced by the fetus from the posterior pituitary during stressful conditions. It has strong effects on the uterus via vasopressin V_{1a} receptors.[33] Steinwall et al.[34] reported an RCT on relcovaptan (vasopressin V_{1a} receptor antagonist) in 18 women (12 in the intervention group and 6 in the control group) who presented with preterm labour. There was a reduction in uterine contractile activity in the intervention group from 30 to 120 minutes after dosing compared with the placebo group. There was no difference in the mean gestational age or BW of the infants. Further studies are needed.

Surveys of current practices of the use of tocolytics

Hui et al.[35] conducted two cross-sectional surveys of Canadian obstetricians to examine their use of tocolytics, antenatal corticosteroids, and progesterone for women at increased risk of preterm labour and birth, and to ascertain whether these practices changed between 1997/1998 and 2004. Response rates were 46% in 1997/1998 and 43% in 2004. Tocolytics were prescribed for women with signs and symptoms of preterm labour by 97.4% of respondents in 1997/1998 and by 92.2 % in 2004 ($p < 0.001$). Use of tocolytics for >48 hours decreased from 20.0%

in 1997/1998 to 9.6% in 2004 ($p = 0.06$). In 1997/1998, the most frequently prescribed tocolytic was magnesium sulphate (40.6% of respondents) and in 2004 it was indomethacin (47.5% of respondents). In 2004, 7% of the respondents prescribed progesterone for women at increased risk of preterm births.

Ness et al.[36] conducted a follow-up survey on the use of progesterone to prevent preterm births. The response rate was 45%. In 2005, 67% of respondents used progesterone compared with 38% in 2003 ($p < 0.001$). Among the users, 38% recommended progesterone for indications other than previous spontaneous preterm births.

Conclusions

Tocolytics are widely used for prevention of preterm births.

- Betamimetics reduce the number of women giving birth within 48 hours and within 7 days, but have no effects on perinatal/neonatal deaths or other neonatal outcomes. Adverse effects in mothers are common. There are insufficient data to support the use of a specific betamimetic. Current evidence does not support the routine use of betamimetics for maintenance therapy after threatened preterm labour for singletons or twins.
- Magnesium sulphate is ineffective in delaying birth or preventing preterm births and its use is associated with an increased mortality for the infant.
- Calcium channel blockers are preferable to other tocolytics (especially betamimetics). Women receiving calcium channel blockers should be carefully monitored for adverse effects (i.e., dyspnea, pulmonary edema). Evidence is lacking for the use of calcium channel blockers for maintenance therapy for preventing preterm births.
- There is insufficient evidence on which to base decisions about the role of COX inhibition for women in preterm labour and it may cause harm to the fetus.
- There is insufficient evidence to support the routine administration of nitric oxide donors in the treatment of threatened preterm labour.
- The oxytocin inhibitor atosiban is not superior to betamimetics or placebo for tocolysis. The finding of an increase in infant deaths in one placebo-controlled trial raises concerns.
- The use of progestational agents and 17α-hydroxyprogesterone caproate reduces the incidence of preterm and LBW births in high-risk pregnancies. Progestational agents are cost-effective in this population. Progestational agent therapy should be recommended to women at high risk of preterm births.
- Other tocolytics have not been studied adequately.

Cervical cerclage

Cervical incompetence is a cause of preterm labour and preterm, prelabour rupture of the membranes. With the advent of ultrasonography and measurement of cervical length, prophylactic cerclage, in which a suture is placed around the cervix in an attempt to block the progress of labour, has been used in certain cases.

Evidence from systematic and other reviews

Berghella et al.[37] conducted an individual patient meta-analysis of four trials (607 women) of cerclage for short cervix diagnosed by ultrasound. Preterm births at <35 weeks gestation (including multiple pregnancies) occurred in 29.2% of the cerclage group, compared with 34.8% of the no-cerclage group (RR 0.84, 95% CI 0.67, 1.06). There was a significant reduction in preterm births at <35 weeks in the cerclage group compared with the no-cerclage group in singleton gestations (RR 0.74, 95% CI 0.57, 0.96); in singleton gestations with prior preterm birth(s) (RR 0.61, 95% CI 0.40, 0.92); and in singleton gestations with prior second trimester loss (RR 0.57, 95% CI 0.33, 0.99). There was a significant increase in preterm births at <35 weeks gestation in twin pregnancies (RR 2.15, 95% CI 1.15, 4.01). There was no statistically significant effect on perinatal mortality in singletons (RR 0.94, 95% CI 0.54, 1.64) or in twins (RR 2.66, 95% CI 0.83, 8.54).

Bachmann et al.[38] reviewed seven trials in which the effectiveness of elective cerclage was evaluated compared with no cerclage in women at risk of preterm births at <34 weeks gestation. In the largest trial of good quality, cerclage was shown to prevent preterm births at <34 weeks' gestation (one study, 1292 women, OR 0.72, 85% CI 0.53, 0.97). The findings of the other trials (of lower quality) were consistent with the larger trial.

Belej-Rak et al.[39] systematically evaluated six studies on the effectiveness of cerclage for a shortened cervix, as determined by transvaginal ultrasound scanning, in terms of preterm birth. There were no statistically significant effects on the rates of preterm births at <37, <34, <32, and <28 weeks gestation, preterm labour, neonatal mortality or morbidity, gestational age at birth, or time to delivery.

Drakeley et al.[40] reviewed the effectiveness and safety of emergency cerclage inserted during mid-trimester via an abdominal or vaginal route to treat threatened preterm labour, as well as the superiority of one technique over the other. There was no significant reduction in preterm births (four trials, 2062 women, RR 0.88, 95% CI 0.76, 1.03) with prophylactic cerclage. A small reduction in preterm births at <33 weeks gestation was seen in the largest trial (one trial, 1292 women, RR 0.75, 95% CI 0.58, 0.98). Cervical cerclage was associated with mild pyrexia, increased use of tocolytic therapy, and hospital admissions, but not with serious morbidity. Two trials examined the role of therapeutic cerclage when ultrasound examination revealed short cervix. Pooled

results failed to show a statistically significant reduction in preterm births at <28 weeks gestation (one trial, 35 women, RR 0.12, 95% CI 0.01, 2.19) or at <34 weeks gestation (two trials, 148 participants, RR 0.70, 95% CI 0.44, 1.12) in women assigned to cervical cerclage.

In a prospective controlled study conducted in Greece[41] over a 6-year period, all cases of cervical dilatation and bulging membranes were detected through a transvaginal ultrasound screening for preterm births between 18 and 26 weeks. Women were offered emergency cervical cerclage and those who refused were prescribed bed rest. Twenty-nine women underwent cervical cerclage and 17 women who refused cerclage formed the bed rest group. The mean prolongation of pregnancy was 8.8 weeks (standard deviation (SD) 3.9) in the cerclage group and 3.1 weeks (SD 2.6) in the bed rest group ($p < 0.001$). Preterm births at <32 weeks gestation occurred in 9 of 29 treated women and in 16 of 17 women who chose bed rest ($p < 0.001$). The mean BW was 2101 g (SD 699) in the cerclage group and 739 g (SD 487) in the bed rest group.

Conclusions

Cervical cerclage should not be offered to women at low or medium risk of mid-trimester loss, regardless of cervical length by ultrasound. The role of cervical cerclage for women who have a short cervix diagnosed by ultrasound remains uncertain, as the numbers of women included in the trials are too few to draw firm conclusions. Although promising, the results of emergency cerclage in women who have a dilated cervix and bulging membranes need to be confirmed in RCTs. The highest quality review[37] concluded that cerclage in women with a short cervix diagnosed by ultrasound may reduce preterm births in a subgroup of singleton pregnancies, particularly in women with a previous preterm birth.

Interventions for suspected impaired fetal growth

Various interventions have been attempted after identification of a fetus that is growth restricted.

1. Oxygen

Fetal growth impairment is often associated with fetal hypoxemia, and thus investigators have hypothesized that providing continuous oxygen to the mother might promote growth.

Say el al.[42] reviewed the role of oxygen administration to the mother for improving pregnancy outcomes. Oxygen therapy was associated with a lower perinatal mortality rate (three studies, 94 women, RR 0.50, 95% CI 0.32, 0.81). The longer gestational age in the oxygenation group may explain the difference. There was no statistically significant effect on BW (two studies, 57 women, WMD 85 g, 95% CI -54, 223). Further research is warranted as the total number of patients in these studies is small.

2. Plasma volume expansion

In pregnancy, the maternal plasma volume expands. A failure of this normal expansion is associated with impaired fetal growth and pre-eclampsia. No study has properly evaluated the role of maternal plasma volume expansion to improve fetal growth.[43]

3. Hormones

Estrogens may improve fetal growth secondary to an increase in nutritional supply to the fetus from increased uterine blood flow. No study has evaluated this intervention.[44]

4. Calcium channel blockers

Calcium channel blockers have been prescribed in an attempt to improve blood flow to the fetus. Gulmezoglu and Hofmeyr[45] systematically reviewed one study on the role of calcium channel blockers for suspected impaired fetal growth. There was no difference in the rates of preterm births at <38 weeks gestation (RR 0.55, 95% CI 0.22, 1.36) or of perinatal mortality (RR 0.33, 95% CI 0.01, 7.99). The mean BW was significantly higher in the group receiving calcium channel blockers (3291 g) versus the group receiving placebo (3011 g) ($p = 0.0024$).

5. Betamimetics

Betamimetics may promote fetal growth by decreasing vascular resistance and increasing nutrient transfer across the placenta. Say et al.[46] reviewed two studies that assessed the effects of betamimetics for suspected impaired fetal growth. There was no statistically significant difference in the risk of LBW births (RR 1.17, 95% CI 0.75, 1.83) between the betamimetic groups and the control groups.

6. Antiplatelet agents

Pre-eclampsia is an important cause of fetal growth restriction. Platelet aggregation is increased in women with pre-eclampsia.[47] Antiplatelet agents have been used to reduce platelet aggregation. Leitich et al.[48] performed a systematic review and meta-analysis of 13 published RCTs of an antiplatelet agent (low-dose aspirin) for prevention of IUGR births. Aspirin was associated with a significant reduction in IUGR births (13 studies, 13,234 participants, OR 0.82, 95% CI 0.72, 0.93), but perinatal mortality (13 studies, 13,234 participants, OR 0.84, 95% CI 0.66, 1.08) was not significantly reduced.

Knight et al.[49] systematically reviewed 42 RCTs of antiplatelet agents (low-dose aspirin) for treating pregnant women at risk of developing pre-eclampsia and those with established pre-eclampsia. The risk of preterm births was reduced in women who received antiplatelet agents (23 studies, 28,268 participants, RR 0.92, 95% CI 0.88, 0.97). There was no statistically significant reduction in the risk for SGA births (25 studies, 20,349 participants, RR 0.92, 95% CI 0.84, 1.01).

Duley et al.[50] reviewed 51 trials of antiplatelet agents (largely low-dose aspirin) to prevent pre-eclampsia and its complications. The use of antiplatelet agents was associated with a reduced risk of pre-eclampsia (RR 0.81, 95% CI 0.75, 0.88) and preterm births (28 trials, 31,845 women, RR 0.93, 95% CI 0.89, 0.98). In the antiplatelet group, there was a reduction in the risk of fetal or neonatal deaths (38 trials, 34,010 women, RR 0.84, 95% CI 0.74, 0.96) and SGA births (32 trials, 24,333 women, RR 0.91, 95% CI 0.84, 0.99). There was a trend towards reduction in the risk of LBW births (RR 0.93, 95% CI 0.83, 1.05).

7. Sildenafil

Endothelium-dependent vasodilatation is decreased in myometrial vessels in women with pre-eclampsia. Phosphodiesterase 5 (PDE5) inhibitor does not affect normal pregnant myometrial vessels, but significantly improves relaxation of vessels from women with pre-eclampsia. This led to the hypothesis that PDE5 inhibitor enhances endothelial function of myometrial vessels in women with pre-eclampsia such that the behaviour of these arteries approximates those of normal women.[51] These agents therefore offer a potential therapy. An RCT of sildenafil citrate (PDE5 inhibitor) is currently being undertaken.[52]

8. Antioxidant

Lycopene is an open-chain unsaturated carotenoid that imparts a red colour to tomatoes, guava, rosehip, watermelon, and pink grapefruit. Lycopene is a proven antioxidant. Plasma levels of lycopene increase through gestation.[53] Investigators have shown that during pregnancy, plasma levels of lycopene are significantly lower in women with pre-eclampsia, and even lower in women with severe pre-eclampsia, compared with pregnant women without pre-eclampsia.[54]

Sharma et al.[55] conducted an RCT of 251 primigravida women in the second trimester (16 to 20 weeks). Women received lycopene (2 mg twice daily) or placebo. Pre-eclampsia developed in fewer women who received lycopene (8.6% versus 17.7%, $p = 0.043$). Mean BW (SD) was significantly higher in the lycopene group than in the placebo group (2751 g (316), versus 2657 g (444), $p = 0.049$). The incidence of IUGR births was significantly lower in the lycopene group compared with the placebo group (12% versus 23.7%, $p = 0.033$).

Conclusions for interventions for suspected impaired fetal growth

Measures to improve fetal growth by administration of oxygen, plasma, hormones, calcium channel blockers, and betamimetics have not been studied adequately enough to demonstrate benefit or harm. Sildenafil and lycopene for the prevention of pre-eclampsia deserve further study. Antiplatelet agents have shown small to moderate benefit for mother and infant. Mothers at risk of developing pre-eclampsia may have potential benefit. The numbers needed to treat are large; however, no significant side effects have been reported for

mothers. It is not clear when this therapy should be started. Further research is required to assess which women are most likely to benefit, as well as when treatment is best started and at what dose.

Multicomponent Preterm Birth Prevention Programs

Multicomponent programs aimed at prevention of preterm birth are undertaken in various settings. The following section presents certain preterm birth-prevention programs that have evaluated the impact of more than one intervention for the prevention of preterm births.

Evidence from other study designs

France is the only developed country that reported a reduction in the preterm birth rate in 1990s. Papiernik and Goffinet[56] reported the past 30 years of experience after implementing policies for the prevention of preterm births. Components of the policies included: (1) early and equal access to antenatal care for all women; (2) provision of information regarding lifestyle changes; (3) education and recognition of early signs of preterm labour; and (4) use of maternity leave and reduction of physical activity. The use of universally accessible, free prenatal care has steadily increased (women with more than seven prenatal visits increased from 22% in 1972 to 91% in 1995) with availability and awareness. With the help of the media (women's magazines, television shows, and newspaper articles), every woman was educated about the importance of lifestyle changes before and during pregnancy and their impact on pregnancy outcomes. The policies placed particular emphasis on work leave and reduction in physical effort at work and home. The third policy component included early recognition of warning signs of preterm labour. Obstetricians, midwives, and nurses were told to help heighten women's awareness of early warning signs of uterine contractions and to implement steps necessary to arrest threatened labour. Comparative data from 1971 to 1974, 1975 to 1978, and 1979 to 1982 from the city of Haguenau revealed preterm birth rates of 6.9%, 5.4%, and 3.8%, respectively, as the incorporation of these programs became more widespread over the years. Significant reductions were observed in preterm birth (the preterm birth rate of 12.5% in 1971 to 1974 fell to 8.3% in 1979 to 1982, $p < 0.001$). However, the preterm birth rate in 1995 was 5.4%, and in 1998 it was 6.3%. The increase in the rates was mostly due to an increase in multiple births.

Armson et al.[57] evaluated a population-based preterm birth prevention program in Nova Scotia, Canada. The program was implemented between 1995 and 1997 ($n = 24,572$) and the results were compared with a historic cohort from 1993 to 1995 ($n = 26,582$). The program consisted of an assessment of the risk of preterm births from a previously developed tool. Women were classified into high-risk and low-risk groups. The low-risk group had a risk assessment, a review of the warning signs for preterm labour, and a cervical examination at 20 to 24 weeks

and 28 to 32 weeks gestation; this group also received educational material (provided at 20 to 24 weeks' gestation). The high-risk group received educational material, an educational session with the project coordinator, modified bed rest at home, weekly prenatal visits between 24 and 34 weeks gestation, a weekly cervical examination between 24 and 34 weeks gestation, uterine activity monitoring by self-palpation, and weekly telephone contact with the project coordinator. There was no difference in the overall rates of preterm births during the intervention period compared with the historical cohort period (RR 1.10, 95% CI 0.97, 1.23).

Armson et al.[58] reported data from a nested case-control study of 210 women in the control group and 70 women in the intervention group who gave birth to preterm infants. Women in the intervention group received targeted educational strategies, bed rest for high-risk women, training on monitoring uterine contraction by palpation, and frequent pelvic examinations. Compliance was poor in all aspects of the program (only 8% of high-risk and 6% of low-risk women). There was no benefit from educational strategies or pelvic examinations in reducing preterm births in low-risk or high-risk women. Restriction of activity and uterine contraction monitoring by palpation was associated with a reduction in the risk of preterm births among low-risk women (OR 0.20, 95% CI 0.08, 0.50).

In another study, pregnant women at high risk for preterm labour were randomly assigned to intervention groups who received instructions from specially trained staff regarding early signs of labour, notification of medical staff regarding signs of labour, weekly pelvic examination from 20 to 24 weeks gestation onwards, early and frequent observation of uterine activity for brief periods of 1 to 3 hours, and prompt and aggressive tocolysis for all women experiencing labour. The control group received routine obstetric care. There was no difference in the observed rates of preterm birth in either group (16.2 versus 15.4% for <37 weeks' gestational age).[59]

Hobel et al.[60] randomly assigned clinics in Los Angeles, United States, to experimental and control groups. The control group received standard antenatal care. No education for warning signs of preterm labour was provided. The high-risk women, identified from a scoring system in the experimental group clinics, were offered a number of interventions that included clinic visits every 2 weeks and three classes on preterm birth prevention. In addition, the high-risk women were randomly assigned to one of four secondary interventions (bed rest, social support, progesterone, or placebo). The preterm birth rate was 9.1% in the control group and 7.4% in the experimental group ($p < 0.05$).

Scott et al.[61] conducted a multiphased evaluation of a community-wide preterm birth prevention program. The program consisted of visits by public health nurses to all prenatal caregivers to stress the importance of teaching all women the signs of preterm labour. The caregivers were also provided with evidence-based guidelines for the use of tocolytics and corticosteroids for the treatment of women with preterm labour. The evaluation included pre- and post-surveys

of caregivers, pre- and post-surveys of postpartum women, and pre- and post-hospital medical record review for administration of drugs and gestational age. Among women interviewed after the implementation of the program, there was a significant increase in knowledge about preterm labour ($p < 0.001$) and knowledge of the action to be taken ($p < 0.02$) in the event of signs and symptoms of preterm labour. Medical record review to ascertain the use of tocolytics and corticosteroids did not show any difference in their usage before and after the implementation of the program. There was no difference in the gestational ages of the infants born to women who experienced preterm births.

Conclusions

Multicomponent preterm birth prevention programs are based on interventions that promote education, recommend avoidance of exertion, teach women early signs of preterm labour, encourage women to seek medical attention, and promote the administration of medical interventions to reduce the risk of the initiation of labour. These programs are mostly directed towards pregnant women classified as high risk; however, a population-based report from France is encouraging even for low-risk women. These programs have reported variable results for reducing the rate of preterm/LBW births. One possible explanation for the failure may be that most of the interventions tested in these programs have not been shown to be effective in preventing preterm births when used as an isolated intervention. Compliance could also be an issue. The failure of healthcare professionals to adhere to modalities considered effective needs further exploration.

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CHAPTER 16:

Summary and Conclusions

Preterm/low birth weight (LBW) births constitute a major health problem for the individual infants, their families, and the society. The associated costs are enormous and encompass not only the initial hospital costs for mother and infant, but also the long-term costs associated with neuro-developmental impairments, learning disabilities, and the lifespan curtailing medical disorders seen in a large number of survivors.

The objectives of this synopsis were to summarize the available evidence from published systematic reviews and narrative reviews, or in the absence of reviews, primary studies, on the determinants of preterm/LBW births and to ascertain the effectiveness/efficacy of interventions and strategies to prevent or reduce the incidence of such births.

The etiology of preterm/LBW births is multifactorial. While many individual determinants were identified, most of these factors interact. The evidence categories for particular determinants and interventions have been summarized in Tables 16.1 to 16.5.

Table 16.1: Summary of determinants with strong or moderate association with low birth weight and preterm births

Low birth weight births	Preterm births
Maternal determinants	
Historical factors • Short or long birth interval • Previous history of preterm/LBW births • Maternal history of being LBW	Historical factors • Short or long birth interval • Previous history of preterm/LBW births
Demographic factors • Adolescent mothers • Minority race • Acculturation • Unmarried/cohabitating	Demographic factors • Adolescent mothers • Minority race • Acculturation • Aboriginal mothers • Unmarried/cohabitating
Nutritional factors • Iron deficiency • Lack of fish oil in diet	
Anthropometric factors • Low BMI	
Medical and pregnancy-related conditions	Medical and pregnancy-related conditions
Anatomical factors • Uterine factors • Placental factors	Anatomical factors • Uterine factors • Placental factors
Infections • Malaria • Bacterial vaginosis • Trichomoniasis • Syphilis • Gonorrhea • Urinary tract infection • Periodontal infection	Infections • Malaria • Bacterial vaginosis • Trichomoniasis • Syphilis • Gonorrhea • Urinary tract infection • Periodontal infection
Psychosocial factors • Adverse psychosocial factors	Psychosocial factors • Acute stress • Poor neighbourhood • Adverse psychosocial factors • Chronic stress
Lifestyle-related factors • Tobacco use • Heavy alcohol use • Cocaine use • Narcotic use	Lifestyle-related factors • Tobacco use • Heavy alcohol use • Cocaine use • Narcotic use
Environmental factors • Environmental tobacco exposure	
Violence/maternal abuse • Violence/abuse • Maternal trauma	Violence/maternal abuse • Violence/abuse • Maternal trauma
Infertility and IVF treatment	Infertility and IVF treatment

BMI – body mass index; IVF – in vitro fertilization; LBW – low birth weight

Table 16.2: Summary of determinants with weak or very weak association with low birth weight and preterm births

Low birth weight births	Preterm births
Maternal determinants	
Historical factors • History of induced abortion • Maternal history of being born preterm	Historical factors • Primiparity • History of induced abortion • Maternal history of being born preterm • Maternal history of being LBW
Demographic factors • Advanced maternal age • Biracial couples • Aboriginal mothers	Demographic factors • Advanced maternal age • Biracial couples
Nutritional factors • Calcium deficiency • Zinc deficiency • Vitamin B6 deficiency • Vitamin B12 deficiency	Nutritional factors • Iron deficiency • Folic acid deficiency • Calcium deficiency • Zinc deficiency • Vitamin B6 deficiency • Vitamin C deficiency
Anthropometric factors • Higher/lower than average BMI	Anthropometric factors • Higher/lower than average BMI
Medical and pregnancy-related conditions	Medical and pregnancy-related conditions
Psychosocial factors • Acute stress • Chronic stress • Poor neighbourhood • Adverse socioeconomic factors • Psychiatric disorders • Terrorism • Attempted suicide • Homelessness	Psychosocial factors • Adverse socioeconomic factors • Psychiatric disorders • Terrorism • Attempted suicide • Homelessness
Lifestyle-related factors • Heavy caffeine use • Marijuana use • Methyl-amphetamine use • Any substance use	Lifestyle-related factors • Heavy caffeine use • Marijuana use • Methyl-amphetamine use • Any substance use • Strenuous exercise • Licorice ingestion
Environmental factors • Air pollution • Water pollution • Exposure to pesticides • Ambient air temperature/season • Noise	Environmental factors • Environmental tobacco exposure • Air pollution • Exposure to pesticides • Ambient air temperature/season • Noise

Low birth weight births	Preterm births
Maternal determinants	
Occupational factors • Occupational hazards • Physically demanding work • Prolonged standing at work • Shift work	Occupational factors • Occupational hazards • Physically demanding work • Prolonged standing at work • Shift work
Prenatal care • Delayed initiation or lack thereof	Prenatal care • Delayed initiation or lack thereof
Paternal Determinants	
• Advanced paternal age • Paternal history of being LBW	• Advanced paternal age • Paternal history of being born preterm
Fetal Determinants	
• Male sex • Genetic factors	• Male sex • Genetic factors

BMI – body mass index; LBW – low birth weight

Table 16.3: Summary of determinants with no proven association with low birth weight and preterm births

Maternal Determinants
- Maternal use of electromagnetic beds - Water pollution and preterm birth - Advanced maternal age - Iron deficiency

Table 16.4: Summary of determinants for which there is a lack of information regarding association with low birth weight and preterm births

Maternal Determinants
• Alternative medicine • Herbal medicines • Vitamin E deficiency • Copper deficiency • Selenium deficiency • Influenza/avian flu infection • Exercise (LBW births)

LBW – low birth weight

Table 16.5: Evidence categories for interventions/strategies to prevent low birth weight and preterm births

Strong evidence of effectiveness

• Modification of maternal lifestyle
  - Smoking cessation and relapse prevention as a routine component of prenatal care, particularly interventions that include intensive counselling, multiple contacts, provision of supportive material and follow up
• Prevention or treatment of infections
  - Intermittent prophylaxis or insecticide-treated nets for malaria in endemic regions for primigravida and second gravida mothers
  - Treatment of infection (urinary tract infection, syphilis, gonorrhea)
  - Screening mothers with previous history of preterm/LBW births for infection and providing appropriate treatment if infection is diagnosed
• Promotion of a balanced, nutritious diet for all pregnant women
• Treatment of maternal general medical conditions
• Treatment of pregnancy-associated conditions
• Reduction of multiple births following IVF or artificial reproductive technologies
• Treatment of infection
  - Urinary tract infections
  - Gonorrhea
  - Syphilis
  - Malaria

Probable evidence of effectiveness

• Adolescent pregnancy
  - Measures to reduce adolescent pregnancy
  - Early enrolment of pregnant adolescents in prenatal programs
  - Home visits and provision of psychosocial support to pregnant adolescents
• Promotion of adequate weight gain during pregnancy
• Maternal nutrition
  - Folic acid supplementation
  - Magnesium supplementation
  - Multiple micronutrient supplementation
• Treatment of infection
  - Treatment of bacterial vaginosis
  - Treatment of human immunodeficiency virus
• Modification of maternal lifestyle
  - Measures to reduce alcohol exposure
  - Treatment of substance or narcotic use
• Improvement in occupational conditions
• Prenatal care
  - Provision of antenatal care which provides an opportunity for individual assessment, as well as diagnosis and appropriate management of maternal medical conditions
  - Improved content of prenatal care
  - Multi-component preterm birth prevention programs
• Provision of psychosocial support to high-risk women who are experiencing chronic stress
  - Legislation regarding regulation of artificial reproductive technologies

Evidence of no effectiveness

- Maternal nutrition
  - High-protein diet supplementation
  - Iron supplementation
  - Calcium supplementation
  - Salt restriction
- Treatment of infection
  - Treatment of periodontal infections
  - Administration of antibiotics for preterm labour in mothers with intact membranes
- Measures to identify and reduce violence/abuse
- Continuity of antenatal care

Lack of evidence/further research needed

- Measures to reduce pregnancies in women of advanced maternal age
- Maternal nutrition
  - Balanced energy and protein intake
  - Supplementation of multivitamins and vitamins A, B, C, D, and E
  - Supplementation of minerals
  - Nutritional advice
  - Zinc supplementation
  - Fish oil supplementation
- Treatment of infection
  - Treatment of chlamydia
- Modification of maternal lifestyle
  - Efficacy of nicotine replacement therapy for heavy smokers while pregnant
  - Identification of women using excessive alcohol during pregnancy and strategies to avoid heavy alcohol use
  - Measures to reduce cocaine use
  - Measures to reduce caffeine exposure
  - Measures to reduce marijuana use
  - Measures to reduce methyl-amphetamine and amphetamine use
  - Alternative medicines
  - Herbal medicines
  - Limitation or promotion of exercise
- Measures to reduce environmental factors
  - Measures to reduce environmental tobacco smoke exposure
  - Measures to reduce air pollution
  - Measures to reduce water pollution
  - Measures to control pesticide exposure
  - Reduction of exposure to environmental toxins
  - Reduction of exposure to noise
  - Maternal occupation-related factors
  - Reduction of work-related stress, physical exertion, and prolonged standing
  - Maternal abuse
  - Identifying and responding to abuse/violence
  - Empowering mothers against potential abuse

Evidence of harm

- Treatment of trichomoniasis with metronidazole
- Administration of metronidazole in the second trimester
- Co-amoxiclav (ß-lactam antibiotic) for women with preterm, prelabour rupture of the membranes

IVF – in vitro fertilization; LBW – low birth weight

Glossary of Terms

adjusted odds ratio
An odds ratio that has been statistically adjusted to account for the effects of confounding variables (see *odds ratio*).

allocation
The process by which an individual is assigned to a treatment or a control group in a randomized controlled trial. Ideally, to prevent selection bias the investigators should not know which comparison group individual patients have been placed into (see *randomized controlled trial; selection bias*).

association
A relationship between two characteristics such that as one changes, the other changes in a predictable way (see *positive association; negative association*).

attrition *(also called loss to follow up)*
The loss of participants during the course of a study.

bias
Defined as "systematic deviation from the truth". In studies, it refers to systematic errors in measurement or assessment that cause either an overestimation or underestimation of the results.

blinding
The process by which those involved in a study or trial (e.g. patients, caregivers, outcome assessors) are prevented from knowing which comparison group individual patients have been placed into. The term double-blind often means that patients and either outcome assessors or caregivers are 'blinded' to treatment allocation, but this term is not used consistently and may be ambiguous unless the specific participants who are blinded are listed (see *allocation*).

case
An individual with a particular disease/condition/disorder that is targeted for examination.

case-control study
A study that retrospectively compares individuals with a particular disease/condition/disorder (cases) with people from the same population who do not have the disease/condition/disorder (controls).

case series
A study describing the experiences of a number of individuals with a particular disease/condition/disorder (cases), with no control group.

centile *(also known as percentile)*
A single unit of a sample that has been divided into 100 parts, each of which contains one-hundredth of the total.

clinical trial *(also called intervention study)*
A study that compares the effects of two or more healthcare interventions.

cluster randomized study
A study in which clusters of individuals (e.g. clinics, geographical areas) rather than individuals are randomly assigned to different study groups.

cohort study *(also called an observational study)*
A study in which a group of individuals (the cohort) is followed over time. Such observational studies may involve follow up of exposed and non-exposed groups, with a comparison of disease rates across time. They may also involve follow up of case groups and control groups, with a comparison of health outcomes.

confidence interval
A statistical term for the range of values that includes the true value (usually a mean, proportion, risk ratio, or odds ratio) of the unknown quantity being measured. The interval is usually quantified as either a 90% or 95% confidence interval to represent the degree of confidence. In general, a higher degree of confidence will require a larger interval. Confidence intervals are smaller when estimates are based on larger sample sizes. There is a relationship between a 95% confidence interval and a p value such that the confidence interval for a mean difference will include zero when the p-value is > 0.05, and vice versa (see *p-value*).

confounding variable/confounder
In medical research and epidemiology, a variable that is associated with the exposure or treatment under investigation and can cause or prevent the outcome being examined. Unless these variables are measured as part of the research, their effects cannot be distinguished from those of the exposure(s) or treatment(s) being studied.

control group *(also called the comparison group)*
In a case-control study, the group of individuals without the disease or outcome of interest. In a clinical trial, the group of participants who are compared with a group of individuals who receive the intervention being evaluated (see *case-control study; clinical trial*).

cross-sectional study *(also called a survey)*
A study measuring the distribution of a particular disease/condition/disorder in a population at a particular point in time.

dose-response relationship
Originally used to describe the differences in response upon administration of differing doses of a drug or toxin. Its meaning has broadened to describe any relationship in which change in amount, intensity, or duration of an exposure is associated with a change - either an increase or decrease - in the risk of a specified outcome (see *exposure*).

double-blind study
See *blinding*.

etiologic fraction
In medical research and epidemiology, the proportion of individuals, expressed as a percentage, with a particular disease/condition/disorder (cases) as a result of an exposure in the exposed population (see *exposure*).

experimental study
A study in which investigators actively intervene to test a hypothesis.

exposure
In medical research and epidemiology, an environmental state applied to individuals either intentionally (as part of a research design, e.g. a treatment) or by chance (in the course of daily life, e.g. air pollution) which may lead to changes in health.

extremely low birth weight
By international convention, birth weight <1000 grams.

intervention study
See *clinical trial*.

intrauterine growth restriction
A fetus or infant who has not attained his/her intrauterine growth potential. Most publications measure intrauterine growth restriction as a birth weight below the 3rd centile or below the 10th centile in growth tables for gestational age.

low birth weight
By international convention, birth weight <2500 grams.

mean difference
In medical research and meta-analysis, the difference in the mean values of a variable measured in two samples from a single study (see *weighted mean difference*).

meta-analysis
A statistical technique used to combine the results from at least two primary studies that have evaluated the intervention of interest in the same way. The term is sometimes incorrectly used to refer to systematic reviews that include a meta-analysis component (see *primary study; systematic review*).

meta-regression
In meta-analysis, an advanced statistical analysis that can adjust mean differences among studies for the effects of measured confounding variables that may have differed across the studies.

narrative review
A qualitative summary of medical research findings that is broad in scope and does not use predetermined or explicit methods for identifying or selecting the included evidence (see *systematic review*).

negative association
An association where an increase in one quantity corresponds to a decrease in another (see *positive association*)

negative likelihood ratio
In screening/diagnostic tests, the probability of finding no disease in a patient with the disease divided by the probability of correctly identifying a patient without the disease ((1 - sensitivity)/specificity) (see *sensitivity; specificity*).

negative predictive value
In screening/diagnostic tests, the proportion of patients with a negative result who do not have the disease, i.e. the probability that a negative test result is correct (see *positive predictive value*).

nested case-control study
A case-control study conducted, or nested, in the population of an ongoing cohort study (see *cohort study*)

number needed to treat to harm
The number of people that need to receive a treatment before one person would experience a harmful outcome. It is the inverse of the risk difference. The smaller the number needed to treat to harm, the more common adverse events are (see *number needed to treat to benefit; risk difference*).

number needed to treat to benefit
The number of people that need to receive a treatment before one person would experience a beneficial outcome. It is the inverse of the risk difference. The smaller the number needed to treat to benefit, the more effective the treatment is (see *number needed to treat to harm; risk difference*).

observational study
See *cohort study.*

odds
In medical research, the number of individuals in a specified population who have a target disorder, or to whom a target event has occurred, divided by the number of individuals who do not have the target disorder or to whom no target event has occurred.

odds ratio
In health research, the ratio formed by dividing the odds of having the target disorder in the treated or exposed group by the odds of having the target disorder in the control or non-exposed group. For very rare disorders, the odds ratio is very close to the risk ratio and can be substituted for it (see *adjusted odds ratio; odds ratio; risk ratio*).

p value
A statistical term for the probability that the results of a particular study (e.g. a mean difference) could have been produced by chance in the absence of a real difference. By scientific convention, p-values of < 0.05 or < 0.01 indicate a low probability that the difference is by chance and are used by scientists as a guideline for determining when an observed difference can be considered real.

positive association
An association where one quantity increases as the other increases.

positive likelihood ratio
In screening/diagnostic tests, the probability of identifying the disease in patients with the disease divided by probability of obtaining the same test result in people without the disease (sensitivity/(1 - specificity)) (see *negative likelihood ratio; sensitivity; specificity*).

positive predictive value
In screening/diagnosis tests, the proportion of patients with a positive test result who actually have the disease, i.e. the probability that a positive test result is correct (see *negative predictive value*).

preterm birth
By international convention, birth occurring prior to 37 completed weeks of gestation (includes 36 weeks and 6 days).

primary study
An original study, such as a randomized controlled trial, in which data are collected (see *secondary study*).

prospective study
A study design in which one or more groups (cohorts) of individuals are monitored forwards through time to observe outcomes.

randomized controlled trial
A study design where treatment, intervention, or enrollment into different study groups is assigned by random allocation rather than by the conscious decision of clinicians or patients. If the sample size is large enough, this study design avoids problems of bias and confounding variables by ensuring that both known and unknown determinants of outcome are evenly distributed between the treatment and control groups. The most important design component for avoiding bias is concealed allocation, which ensures that the investigators cannot influence which comparison group individual patients are placed into (see *allocation; bias; confounding variable; selection bias*).

receiver-operator characteristic curve
A plot of the true positive rate (sensitivity) against the false positive rate (1 - specificity). Since a perfect diagnostic test would have a sensitivity and specificity of one, the closer the area under the receiver-operator characteristic curve is to unity, the higher the diagnostic accuracy of the test (see *sensitivity; specificity*).

retrospective study
A study design in which the outcome of interest occurred in the individuals at some point in the past. Data are collected and analyzed after the outcomes have occurred (see *prospective study*).

risk difference *(also called the absolute risk difference or absolute risk reduction)*
The absolute difference in event rates (incidence) between two groups for a particular outcome (see *number needed to harm; number needed to treat*).

risk ratio or relative risk
The ratio formed by dividing the probability of developing, in a specified period of time, an outcome among those receiving the treatment of interest or exposed to a risk factor by the probability of developing the outcome if the treatment or risk factor is not present.

secondary study
A study, such as a systematic review, in which previously collected data are re-analyzed (see *primary study; systematic review*).

selection bias
An error in choosing individuals or groups participating in a study that introduces systematic differences between the comparison groups with respect to prognosis or responsiveness to treatment (see *allocation*).

sensitivity (or true positive rate)
In screening/diagnostic tests, the proportion of diseased cases correctly identified by the test.

small for gestational age
An infant below the 10th centile for weight for his/her gestational age (some studies use the definition of an infant below the 3rd centile for weight).

spatial analysis
A data analysis technique that incorporates information about an attribute, as well as its geographic location

specificity *(or true negative rate)*
In screening/diagnosis tests, the proportion of people without the target disease who are correctly identified by the test.

synopsis
A general synthesis of information from systematic reviews and other types of studies (see *systematic review*).

systematic review
A summary of medical research findings that uses predetermined and explicit methods for identifying, appraising, and synthesizing the evidence (see *meta-analysis*).

treatment
In medical research and epidemiology, an environmental state applied to individuals intentionally as part of a study design, e.g. a medication or course of therapy.

very low birth weight
By international convention, birth weight <1500 grams.

weighted mean difference
In meta-analysis, a method of combining measures on continuous scales (such as birth weight) from different studies to correct for relevant differences (such as sample size) between the studies (see *meta-analysis*).

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