

Part 2: Determinants and primary prevention

A. Maternal factors:

1. History:

a. Parity:

Biological plausibility:

The biological mechanism of how parity may influence the incidence of preterm/LBW births is not clear.

Epidemiological association:

No primary review on the influence of parity on preterm/ LBW births was identified. The following reflects the derived effects of parity observed in various studies aimed at studying different variables. In most of the studies the estimates were unadjusted for confounders.

Kramer et al²³ in an analysis of births between 1978 – 1996 in Montreal, Canada reported no increased risk for preterm birth in primiparous women compared to multiparous women (adjusted OR 1.038, 95% CI 0.949, 1.135).

Henriksen et al,²⁹ in a prospective cohort study of singleton pregnancies assessing the relation of work to preterm births, reported a 4.3% incidence of preterm birth in primiparous working women and a 4.4% incidence in multiparous working women.

Shiono et al,³⁰ in a cohort study assessing ethnic differences in LBW, observed no mean birth weight difference in nulliparous women and women with history of previous childbirth (3326g vs. 3388g, $p < 0.1$).

Kesmodel et al,³¹ in a prospective cohort study to assess the impact of alcohol on preterm delivery, observed that among nulliparous women the rate of preterm birth was 4.5%, in women who had one previous child the rate was 3.6% (RR 0.80, 95% CI 0.68, 0.93) and among mothers of higher parity it was 4.2% (RR 0.94, 95% CI 0.76, 1.15). Thus there was a marginally lower risk of preterm birth for the second born child.

Frisbie et al³² in a cohort study of racial and ethnic differences reported increased risk of IUGR for primiparous women (OR 1.7, 95% CI 1.4, 1.9) compared to multiparous women. The risk for preterm birth for primiparous women compared to multiparous women was not increased (OR 1.1, 95% CI 0.6, 2.0).

Conclusion:

There is a trend towards an increased risk of preterm birth and IUGR for the first child compared to subsequent children in some studies but this trend is not well confirmed in other studies. This topic needs further research in the form of observational studies.

b. 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 conception of the next child) and pregnancy outcome.³³

- Short interpregnancy interval may result in inadequate replenishment of maternal nutrient stores and reduced fetal growth.³⁴
- Short interpregnancy interval can lead to increased stress and preterm/LBW births.³⁴
- Women with short interpregnancy interval are more likely to have associated risk factors such as young age, high parity, previous history of preterm/LBW births, inadequate education, minority race and tobacco use.^{33;35}
- A mother's ability to facilitate growth of the fetus in-utero declines gradually over the years after the first pregnancy. After a few years following the first pregnancy mothers may acquire the same physiological status as a true primigravida. This may lead to preterm/LBW births in mothers with long interpregnancy intervals.³⁴
- Unidentified metabolic and anatomic factors may play a role in the interval period of infertility in women with long interpregnancy intervals. These factors can possibly influence the risk for preterm/LBW births.³⁴

Epidemiological association:

No review specifically looking at birth interval and its effect on preterm/LBW births was identified. Good quality evidence from large cohort studies is referred to below.

Zhu et al³³ studied a 7-year birth cohort involving 173,205 infants from Utah, US. Women who became pregnant within 6 months after a live birth were at an increased risk of giving birth to a LBW (OR 1.4, 95% CI 1.3, 1.6), preterm (OR 1.4, 95% CI 1.3, 1.5) and SGA (OR 1.3, 95% CI 1.2, 1.4) infant compared to women who became pregnant between 18 – 23 months following a previous birth. Women who became pregnant 120 months after a live birth were also at an increased risk of giving birth to a LBW (OR 2.0, 95% CI 1.7, 2.4), preterm (OR 1.5, 95% CI 1.3, 1.7) and SGA (OR 1.8, 95% CI 1.6, 2.0) infant compared to women who became pregnant between 18 – 23 months. These results were after adjusting for 16 confounding variables. The authors suggested a “J” shaped response between interpregnancy interval and pregnancy outcomes with the optimal outcome with interpregnancy interval between 18 to 23 months.

Zhu et al³⁴ studied 435,327 infants from Michigan, US. A similar “J” shaped pattern was observed for preterm, SGA and IUGR births for both the white and the black population. Again, an interpregnancy interval of 18 to 23 months was suggested to have the lowest risk.

Fuentes-Afflick et al³⁵ studied 289,842 births in the US. The adjusted ORs for very preterm births (23 – 32 weeks) and moderately preterm births (33 – 37 weeks) were 1.47 (95% CI 1.30, 1.65) and 1.20 (95% CI 1.15, 1.26) respectively for an interpregnancy interval of < 6 months; 1.39 (95% CI 1.25, 1.54) and 1.14 (95% CI 1.10, 1.18) respectively for an interpregnancy interval of 6 - 11 months;

1.26 (95% CI 1.13, 1.41) and 1.15 (95% CI 1.10, 1.19) respectively for an interpregnancy interval of 12 - 17 months and 1.45 (95% CI 1.31, 1.60) and 1.12 (95% CI 1.08, 1.15) respectively for an interpregnancy interval of > 59 months compared to an interpregnancy interval of 18-59 months.

Rawlings et al³⁶ studied military families of white and black races to assess the impact of the interpregnancy interval on two races. Short interpregnancy intervals were more common among black women. An interpregnancy interval of < 9 months was associated with increased risk of preterm and LBW (combined incidence 11.6% vs. 4.4% in women with ≥ 9 months interpregnancy interval, $p = 0.020$) in black women. An interpregnancy interval of < 3 months was associated with an increased risk of preterm and LBW births in white women (11.8% vs. 2.8% for an interpregnancy interval ≥ 3 months, $p < 0.001$).

Ekwo et al³⁷ studied 293 black women and 468 white women to assess the impact of the interpregnancy interval on birth outcomes. For black women an additional pregnancy within 6 months was associated with a tendency for an increased risk of preterm births (35.8% vs. 25.8%, OR 1.6, 95% CI 0.34, 2.86). After controlling for confounders there was no significant difference between pregnancy within 6 months or beyond.

Conclusion:

Several epidemiological data sources indicate an impact of the interpregnancy interval on the risk of preterm birth/SGA/IUGR/LBW births. Both short (<18 months) and long (>60 months) intervals are associated with preterm/SGA/IUGR/LBW births. Interpregnancy interval could be a significant modifiable factor for preterm/SGA/IUGR/LBW births. All mothers should be informed about the advantages of an interpregnancy interval of approximately 18 – 23 months. This may reduce the risk of preterm/SGA/IUGR/LBW births.

c. History of previous preterm/LBW/IUGR birth:

Biological plausibility:

Preterm birth and LBW tend to repeat in families. Medical or non-medical factors responsible for preterm/SGA/IUGR/LBW births in a previous pregnancy may operate during subsequent pregnancies leading to increased risk.

Epidemiological association:

Studies have evaluated the risk of preterm birth or IUGR in families with a previous history of preterm/SGA/IUGR/LBW births. No reviews were identified.

Bloom et al³⁸ reviewed consecutive births at their institution during 1988 - 99. Women who delivered a singleton infant before 35 weeks gestation in their first pregnancy were at an increased risk of recurrence (OR 5.6, 95% CI 4.5, 7.0). The risk for recurrent spontaneous preterm birth was increased in women presenting with either intact membranes (OR 7.9, 95% CI 5.6, 11.3) or rupture of membranes (OR 5.5, 95% CI 3.2, 9.4). Of those women with recurrent preterm

births, 49% delivered within 1 week of the gestational age of their first delivery and 70% delivered within 2 weeks.

Carr-Hill et al³⁹ reported the recurrence of preterm birth in an escalating manner. The risk of preterm birth in women with a history of one previous full term infant was 5%, with one previous preterm infant it was 15%, with a previous history of a full term and a preterm birth it was 24% and with a history of two previous preterm births it was 32%.

Mercer et al⁴⁰ in a prospective study of prediction of preterm births reported that mothers with a previous history of a spontaneous preterm birth had a 2.5 fold increased risk of a repeat spontaneous preterm birth compared to women with no previous history of preterm births (21.7% vs. 8.8%; $p < 0.001$).

Bratton et al⁴¹ in a retrospective cohort study evaluated the risk of VLBW offspring in women with and without the first child being a VLBW infant. The risk was significantly increased for a repeat VLBW infant (RR 11.5, 95% CI 5.4, 24.4).

Villar et al⁴² performed a randomized controlled study of psychosocial support during the antenatal period to women with high-risk pregnancies. Women with a previous history of a preterm/LBW birth or a fetal death or an infant death had a 16.6% incidence of repeat preterm birth compared to 14.8% incidence in the control group. The incidences of repeat LBW births were 14.0% and 15.3% in the control and the intervention groups respectively.

Shiono et al³⁰ in a cohort study found that the mean birth weight was 3,117g for infants born to women with a history of a previous LBW birth while 3,429g for infants born to women with no history of a LBW birth ($p < 0.001$).

Kesmodel et al³¹ in a prospective cohort study to assess the impact of alcohol on preterm birth reported that the rate of preterm birth was 3.8% in mothers with no previous history of a preterm birth and 14.2% in women with such a history (RR 3.78, 95% CI 3.11, 4.61).

Conclusion:

The epidemiological evidence indicates an increased risk of preterm/LBW births in a subsequent pregnancy for women with a previous history of such outcomes. It is possible that the factors responsible for preterm/LBW/IUGR births in the previous pregnancy may be operative. These factors may or may not be modifiable. Prevention programs should provide special attention to this group of mothers.

2. Demographic factors:

a. Race/Ethnicity:

Biological plausibility:

The biological mechanisms underlying the effects of race are not completely understood. Several hypotheses have been suggested.

- The most commonly held hypothesis is that of stress. Corticotrophin releasing hormone (CRH) is elevated in women who deliver preterm.^{43;44} Acute experiences of racism (defined as racial prejudice or discrimination) have

been shown to be associated with increase in heart rate and blood pressure, indicating release of stress hormones. Chronic exposure to stress such as racial discrimination and other factors experienced by minority groups causes an incremental effect of wear and tear on the hypothalamic pituitary axis prior to conception. This probably results in altered endocrine homeostasis and hormonal interaction.⁴³ Associated factors such as psychological disturbance, poor self esteem, alcohol use and abuse aggravate the impact. Both acute and chronic stresses have been implicated to increase release of CRH and act as a trigger for the cascade resulting in preterm labor.

- An alteration of Vitamin D metabolism in black women is proposed. Being a person with heavily pigmented skin at high latitudes such as in certain areas of the US may prevent the conversion of prohormone to active Vitamin D due to blockade of ultraviolet B rays. This results in changes in calcium homeostasis, which may lead to higher incidences of hypertension, IUGR and preterm births.⁴⁵
- Geronimus⁴⁶ proposed the hypothesis of a “weathering” effect on the health of black women living in poverty. It was observed that there is deterioration in the general health of black women living in poverty as age advances. This has not been fully established for other races. This may be an explanation of the increased risk of LBW/preterm birth in this population. Further research into physiological mechanisms at extremes of age is needed.

As our understanding of the biological impact of social stressors is unclear further research is warranted. The “Project Viva” being undertaken in Boston, US⁴⁷ is expected to provide further insight on this topic. The primary objectives are to assess the impact of maternal experiences of racism and violence on CRH levels and risk of preterm births. Approximately 6,000 women are planned to be recruited at their first antenatal visit (8 – 10 weeks). Questionnaires will be completed during the first trimester and at mid-gestation. Personal interviews will be conducted at mid-gestation. Postpartum and follow up visits at 6 months, 12 months, 2 years and 3 years are also planned. Maternal blood will be collected twice antenatally and cord blood will be collected at birth to measure hormonal status.

Epidemiological association:

No systematic reviews on the differences in the risk of preterm/LBW births were identified. Narrative reviews have derived conclusions from selected studies. The following describes studies representing associations.

Collins et al⁴⁸ in a population-based study conducted in Chicago, US found that the incidence of LBW was 14% in the Afro-American population compared to 6% in the white population. Thirty one percent of Afro-American mothers who had LBW infants were living in census areas that indicated an average household income of less than \$10,000/year compared to 4% of white women who had LBW infants. The range of relative risks for having a LBW infant varied from 1.92 to 2.26 for 4 income strata (< \$ 10,000, 10,001 - 20,000, 20,001 - 30,000 and 30,001 - 40,000/year).

Dubay et al⁴⁹ compared one cohort from 1980 - 86 to a second cohort from 1987 - 93 and found that there was a reduction in the percentage of late initiation of prenatal care (by 6 - 7.8%) in the recent time period. There was a reduction in the incidence of LBW infants in white women by 0.26 - 0.37% in the later time period. However, there was no difference in the incidence of LBW infants in Afro-American women over the two time periods, denoting widening of the gap between the two communities.

The impact of race has been investigated from the aspect of country of birth. Cabral et al⁵⁰ in a retrospective review found that foreign born African-American women were less likely to have a preterm birth (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) compared to US-born African-American women.

A similar pattern was observed in the US-born Mexican population compared to the foreign-born Mexican population. There was an increased risk of IUGR births in US born Mexican mothers compared to foreign-born Mexican mothers (RR 1.5, 95% CI 1.1, 2.1).⁵¹

The probable explanation for this difference in the US born population in these two studies was acculturation. Acculturation is defined as adoption of the cultural orientation of the place of giving birth. This includes adoption of unhealthy behaviors such as tobacco use, alcohol intake and illicit drug use, the frequency of which is higher in the US than in the native countries.

Shiono et al³⁰ in a population based study of ethnic differences in birth weight found that maternal ethnic group was a strong correlate of birth weight (the mean birth weight for African-American infants 3231g, Chinese infants 3272g, Dominican infants 3484g, Mexican infants 3431g, Puerto Rican infants 3341g and White infants was 3503g; $p < 0.001$).

Local perspectives:

Fifty-eight percent of the residents in Toronto in 1996 indicated non-British or non-Canadian origin.⁵² Chinese, Italian, East Indian, Portuguese, Jamaican and Jewish were the most common ethnic origins. As the incidences of adverse pregnancy outcomes vary markedly between different countries (being significantly higher in developing countries)¹⁸ race of the mother and country of birth play key roles.

Data regarding mother's place of birth from Toronto suggest variation in the rates of LBW according to mother's place of birth (table 1). Further studies are required to understand this variation.

Table 1. Toronto Residents, Live Births, 1997				
Mother's Place of Birth				
(World Bank Regions)	Total	Singleton	Singleton <2500g	
			Count	%LBW
East & Southern Africa	1,512	1,470	71	4.8
West Africa	377	368	46	12.5
East Asia & Pacific excluding China	3,326	3,267	215	6.6
China	1,878	1,851	75	4.1
South Asia excluding India	2,595	2,549	154	6.0
India	1,425	1,399	122	8.7
Eastern Europe & Central Asia	1,193	1,174	46	3.9
Rest of Europe	1,887	1,847	76	4.1
Middle East	763	740	34	4.6
North Africa	172	168	7	4.2
Americas excluding Canada	4,718	4,609	326	7.1
Canada	11,233	10,923	514	4.7
Unknown	351	349		
Total	31,430	30,714		

Source: Live Birth Database, Health Planning System (HELPS), Ministry of Health & Long Term Care (MOHLTC)
 Data Limitations: A number of live births are not reported in the Ontario vital statistics each year. This number increased in 1996 and again in 1997. It is estimated that 2.3% of Ontario live births and 3.2% of Toronto live births were not reported in 1997. The number under-reported is disproportionately higher among mothers under 20 years of age, low birth weight births and pre-term births. Therefore, the number of low birth weight births in 1997 may be higher than reported. Provided by: Health Information, Toronto Public Health.

Conclusion:

Though the evidence indicating race as a factor in adverse pregnancy outcomes is strong, interplay of other factors cannot be ruled out. Major factors associated with racial differences are unplanned pregnancies, nutritional deficiencies and pre-postnatal health, socioeconomic status and unhealthy behaviors.⁴³ There is a 30% higher risk of birth of a LBW infant for an Afro-American woman with an unplanned pregnancy compared to a woman with a wanted or planned pregnancy. Nutritional deficiencies and their impact on preterm/LBW births will be discussed later in the review. Insufficient or inadequate prenatal care could be an important factor for this population. Afro-American women are twice as likely to have chronic hypertension and pregnancy induced hypertension, compared to white women. Chronic stressors due to long history of exposure to discrimination may lead to accumulation of these disadvantages.⁴³ In the US, infant mortality is higher compared to other developed nations, which is attributed to an increased incidence of preterm and IUGR births in the African - American population.⁴³ Despite the strength of evidence in epidemiological studies, biological mechanisms and strategies/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
- To explore ways to reduce racism in the society
- To identify relevant modifiable factors.

b. Maternal age:

Biological plausibility:

The biological mechanisms behind the increased risk of preterm/LBW births in adolescents have been suggested as follows.

- The blood supply to the cervix and uterus has not developed completely in some adolescents. This leads to poor supply of nutrients to the developing fetus.⁵³
- Poor blood supply to the genital tract leads to an increased incidence of infections, which may act as a trigger for preterm birth.⁵⁴
- The levels of gonadal hormones are low in adolescents resulting in irregular menstrual cycles. Some adolescents may assume this irregularity as physiological when they are actually pregnant. The initiation of prenatal care is therefore delayed.⁵⁴
- A theory of nutritional competition between the immature adolescent and the fetus has been suggested. Immature pregnant adolescents who require calories for their own growth and development require increased caloric intake compared to mature adult women. Adolescents may resist a recommendation by a health care provider to increase caloric intake, as currently “slimness” is perceived as an ideal. A 150g lower mean birth weight in the offspring of physically immature adolescents compared to mature adolescents has been reported.⁵³
- There is a higher incidence of unplanned pregnancies (a risk factor for adverse outcomes) among adolescents.
- Adolescence is a time of experimenting and testing the boundaries. This may result in an increased incidence of risk behaviors.⁵³

Roth et al⁵³ have described the interplay of these factors as crucial in the higher incidence of preterm and LBW infants born to adolescent mothers.

Advanced maternal age also deserves special attention. Epidemiological studies suggest that there is a trend in developing nations to delay the age of the first pregnancy. Maternal age > 35 years for first pregnancy is associated with reduced intrauterine fetal growth. However, the independent effect of advanced maternal age is not clearly identified after controlling the confounding factors.⁵⁵

Epidemiologic association:

No review assessing the impact of maternal age on pregnancy outcomes was identified. To date most studies on the subject of maternal age have concentrated on adolescents. The following is a report of population cohort studies.

Miller et al⁵⁶ studied a cohort of adolescent (<18 years) pregnancies from 1989 - 93 and found that prenatal care was delayed in this group by an average of 8 weeks and there was an increased risk of VLBW infants (relative risk 1.7, 95% CI 1.2, 2.2).

Orvos et al⁵⁷ reviewed a 6 year cohort of pregnancies in Hungary (1991 - 96) and found that the rate of preterm birth was 18.6% in adolescents compared to 8.2% in the national cohort and the IUGR rate was 16.3% in adolescents compared to 8.6% in the national cohort.

Slap⁵⁸ reviewed pregnancies to mothers < 20 years of age and found that the OR for LBW was 1.99 (95% CI 1.52, 2.61) if there was inadequate prenatal care (defined as ≤ 5 antenatal visits) and the OR was 1.38 (95% CI 1.03, 1.84) if there was a history of maternal illness. This stresses the importance of prenatal care especially for this group.

The risk of preterm birth is shown to increase as maternal age increases above 30 years compared to 25 – 29 years (Rate ratio 1.03, 95% CI 1.00, 1.06 for mothers 30 – 34 years old; 1.24 95% CI 1.19, 1.28 for mothers 35 – 39 years old and 1.51, 95% CI 1.40, 1.63 for mothers ≥ 40 years old).⁹

Intervention:

Various interventional studies have been performed in the adolescent population. These include home visitation, clinic visits, social support, early identification, education, and special programs at school.

Brunton et al⁵⁹ systematically reviewed interventions to reduce LBW in infants born to adolescents. Of the 15 studies reviewed 13 were identified as methodologically intermediate or high quality. Five of the 13 studies reported significant improvement in birth weight and a reduction in preterm or IUGR births while 8 studies reported no significant change. There was no difference among various ethnic groups. Methodologically rigorous studies reported that a combination of home visiting and clinic services were effective. These studies provided support and health education. Early enrollment in prenatal programs showed benefit in reducing the incidence of LBW in 2 studies. Two of the studies provided one-to-one intervention whereas 3 had a class series format. Transportation to appointments was provided in 2 studies. One study also provided social support and referrals. Two studies encouraged participants to attend medical care. Interventions included a combination of multiple strategies such as transportation to appointments, health teaching, social/peer support, referrals to community services, telephone contact, and coordination of prenatal appointments. It was difficult to discern which component of intervention is more effective. Staff nurses/registrars, nurse childbirth educators, public health nurses, lay/paraprofessional home visitors, and health educators in various studies provided the support.

Local perspectives:

The rates of LBW in Toronto amongst singleton live births during the year 1997 are presented in table 2. The singleton LBW rates are highest at the extremes of maternal age. Adolescents between 15-19 years of age have the

highest rate of singleton LBW. Births to females < 20 years of age may not be declining as much as reflected by birth data. The percent of unregistered births among mothers < 20 years of age in 1997 was more than three times higher among fee charging municipalities than in years prior to the introduction of the fee.²⁶

	Age of Mother					
	15-19	20-24	25-29	30-34	35-39	40-44
Total Live Births	970	3,895	8,670	11,014	5,725	1,032
Population Estimate	66,810	85,520	115,335	121,277	111,014	97,644
Age Specific Fertility Rate/1000	14.5	45.5	75.2	90.8	51.6	10.6
Singleton Births	952	3,826	8,499	10,733	5,562	1,018
With Known Weight	952	3,824	8,497	10,731	5,562	1,017
Singleton LBW	70	237	478	516	320	72
% LBW	7.4%	6.2%	5.6%	4.8%	5.8%	7.1%

Source: Statistics Canada, Population estimates

Source: Live Birth Database, Health Planning System (HELPS), Ministry of Health & Long Term Care (MOHLTC)

Data Limitations: A number of live births are not reported in the Ontario vital statistics each year. This number increased in 1996 and again in 1997. It is estimated that 2.3% of Ontario live births and 3.2% of Toronto live births were not reported in 1997. The number under-reported is disproportionately higher among mothers under 20 years of age, low birth weight births and pre-term births. Therefore, the number of low birth weight births in 1997 may be higher than reported. Provided by: Health Information, Toronto Public Health.

Conclusion:

Extremes of maternal childbearing age have been associated with adverse pregnancy outcomes. The incidence of LBW births has been described to follow a “U” shaped curve with high numbers of LBW births at the extremes of age.⁵³

Epidemiological and biological evidence points in the direction of an increased risk of preterm/LBW births in adolescents, however the strength of the evidence is moderate and further research is needed.⁵³ The social, economic and educational challenges resulting from adolescent pregnancy are associated with intergenerational disadvantages for both the mother and the child.⁴

The interventions for adolescents that have shown benefit in terms of preterm/LBW/IUGR/SGA births are home visiting and provision of psychosocial support. Prevention of adolescent pregnancy is an important public health issue. Although beyond the scope of this review, effective interventions to prevent adolescent pregnancy would contribute to reducing preterm/LBW/IUGR/SGA rates.

Studies regarding contributory factors and effective interventions for women in their late fertile age are lacking.

c. Marital status:

Biological plausibility:

The biological mechanism of the influence of marriage on pregnancy outcomes is not clear.

Epidemiological association:

Reviews of the effects of marital status on preterm/LBW/SGA births have not been published. The following represents unadjusted effects reported from various studies aimed at different determinants.

Kramer et al²³ in an analysis of births between 1978 – 1996 in Montreal, Canada reported an increased risk of preterm birth for unmarried women compared to married women (adjusted OR 1.51, 95% CI 1.36, 1.68).

Shiono et al⁶⁰ in a population based study of ethnic differences in birth weight found a significant difference in the birth weight of offspring from married women compared to unmarried women (3403g vs. 3315g, $p < 0.01$).

Hanke et al⁶¹ found an increased incidence of SGA infants born to unmarried mothers (12/83) compared to married mothers (66/985). The risk was statistically significantly increased (OR 2.34, 95% CI 1.14, 4.71).

Frisbie et al³² in a cohort study of racial and ethnic differences reported no difference in the risk of IUGR (OR 1.0, 95% CI 0.9, 1.3) or preterm birth (OR 1.1, 95% CI 0.6, 2.3) for unmarried mothers compared to married mothers.

Kesmodel et al³¹ in a prospective cohort study to assess the impact of alcohol on preterm delivery reported the rate of preterm birth at 4% for married women compared to 6.7% for unmarried women (RR 1.67, 95% CI 1.28, 2.17).

Conclusion:

There is an indication of increased risk of preterm/IUGR births for unmarried women. The results from these studies may well be confounded by other factors. It is difficult to ascertain what proportion of these women was reported as unmarried but living with partners. The basis for protective effects of marriage may lie in social, psychological, emotional and financial support provided by the partners. Further research is needed to understand the mechanisms of the effect of marital status on pregnancy outcomes.

3. Nutritional factors/interventions:

Inadequate nutrition is the most commonly implicated cause of impaired fetal growth. The adequacy of fetal nutrition is dependent upon many factors and regulating mechanisms. These include 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. This review addresses nutritional interventions aimed at both the fetus and the mother. Maternal nutrition is examined 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 next in the review. However, it should be understood that these measures are reflective of the nutrition a pregnant woman receives.

Biological plausibility:

The role of nutrition in affecting fetal growth is clear. Animal experiments have shown that maternal undernutrition causes slowing of fetal growth following 3-4 days of malnutrition while the growth returns to normal after refeeding.⁶² The nutritional need of a woman varies according to the stages of gestation. It was observed that during the Dutch Famine at the end of the Second World War women who suffered malnutrition in the early gestation had normal size infants while mothers who starved in the late gestation had LBW infants.^{4;63}

An inter-generational effect has been observed. A malnourished mother gives birth to a growth-restricted fetus that develops into a nutritionally deprived mother and gives birth to another child at similar disadvantage. Factors associated with poor socioeconomic status aggravate the situation. The intergenerational cycle at times becomes difficult to break.⁶⁴

Malnutrition may cause stress in the fetus which is an important factor regarding preterm birth.

Independent biological plausibility of each nutrient is discussed under the section of each nutrient.

Nutritional interventions:

a. Measures to improve fetal nutrition/growth:

Biological plausibility:

- Administration of nutrient directly to fetus is a potential way of improving growth of fetus.
- Administration of nutrient to mother is attempted with a view of increasing nutrient supply eventually to fetus.
- Administration of oxygen to mother has been attempted to improve blood flow to fetus.

Epidemiological association:

Harding et al⁶² reviewed nutritional causes and interventions to improve fetal growth in a narrative review.

A fetus obtains 10% of its caloric intake from swallowed amniotic fluid. Animal experiments have shown benefit in preventing growth restriction by infusing nutrients into the fetal gut.⁶² Uncontrolled experiments of infusion of glucose and amino acids into the amniotic fluid surrounding human fetuses have shown benefit.⁶⁵ This method has not been tested in other studies.

Uncontrolled experiment⁶⁵ showed that direct infusion of nutrients into the fetal circulation is effective. This method has not been rigorously tested and the risk benefit ratio is not known.

Gulmezoglu et al⁶⁶ reviewed 3 studies assessing the impact of maternal nutrient (glucose or galactose) administration for suspected fetal growth restriction for the Cochrane Collaboration. There was no difference in the risk of SGA between the glucose supplemented and the bed rest group (RR 1.11, 95% CI 0.64, 1.92) or the galactose supplemented group (RR 0.78, 95% CI 0.39, 1.54).

Gulmezoglu et al⁶⁷ reviewed 2 studies evaluating the effects of maternal oxygen supply to improve fetal growth for the Cochrane Collaboration. There was no statistically significant difference in mean birth weight (100g, 95% CI –406, 606g) among the 25 infants in one study.

Conclusion:

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

b. Measures to improve maternal nutrition:

1. Nutritional advice:

Epidemiological association:

Kramer⁶⁸ reviewed 4 studies assessing the impact of giving advice on energy and protein intake on pregnancy outcomes for the Cochrane Collaboration. Studies providing one to one dietary counseling were included. The various methods employed in the studies included advice to improve quality of the diet, nutritional classes and counseling to experimental group. A total of 1108 women were included in these studies. Of the four studies only one reported on pregnancy outcomes. There was a reduction in the risk of preterm births (RR 0.45, 95% CI 0.22, 0.92), but no difference in the incidence of SGA births (RR 1.01, 95% CI 0.51, 1.99), mean birth weight [weighted mean difference (WMD) 15g, 95% CI – 66, 96g] or duration of gestation (WMD - 0.1 week, 95% CI – 0.44, 0.24 week). The reduction in the risk of preterm births was debatable, as there was no effect on either duration of gestation or birth weight.

Conclusion:

The impact of nutritional advice has not been studied adequately to reach a conclusion. The existing evidence for this measure is weak. Further research is needed.

2. Nutrient supplementation

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

(i). High protein diet:

Biological plausibility:

The influence of supplementation of mothers with high protein containing diets is not clear. Animal experiments have suggested an adverse effect of protein supplementation on pregnancy outcome.

Epidemiological association:

Kramer⁶⁹ reviewed two studies involving 1,076 women who were randomly assigned to a control group or an experimental group for the Cochrane Collaboration. The experimental group consumed 25% of the dietary intake as protein. The experimental group demonstrated a small increase in maternal weekly weight gain, increase in the risk of SGA births (RR 1.71, 95% CI 1.04, 2.81) and trend towards reduction of mean birth weight (WMD – 58g, 95% CI – 146g, 29g). A non-significant increase in the risk of neonatal death was reported.

Conclusion:

The available evidence to date does not support a recommendation for high protein intake during pregnancy. The underlying biological mechanisms for increased risk of SGA and reduced mean birth weight are not clear.

(ii). Isocaloric balanced protein diet:

Biological plausibility:

Nutritional requirements increase during pregnancy to support fetal growth. Adequate intake of a nutritious diet results in adequate growth in animal models and starvation, for even short periods, results in reduction in fetal growth.⁶²

Epidemiological association:

Balanced supplementation of protein and calories has shown benefit for fetal growth in some observational studies. Forced starvation during the Dutch Famine led to a reduction in the birth weight without an effect on preterm births.⁶³

Kramer⁷⁰ reviewed the impact of supplementation of a balanced protein/energy diet (where the protein content of diet was < 25% of the total energy content) on gestational weight gain and pregnancy outcomes from 13 studies for the Cochrane Collaboration. The quality of the trials varied and often the methods of randomization were not stated. It was found that there was an increase in maternal weight gain (17g/week) and a reduction in the risk of SGA births (RR 0.68, 95% CI 0.57, 0.80). There was no difference in the stratified analysis of undernourished (determined based on prepregnancy weight) and adequately nourished women in terms of difference in birth weight with supplementation of adequate nutrition (24g vs. 25g). No difference was found in the risk of preterm births (RR 0.83, 95% CI 0.65, 1.06).

Higgins et al⁷¹ reported an analysis of “Higgins Nutritional Intervention Program” participants from the “Montreal Diet Dispensary” program, who were high risk mothers from a nutritional standpoint and managed by a specific nutritional rehabilitation program depending upon need. An analysis of 525 mothers who participated in their second pregnancy but not their first pregnancy was reported. The comparison was made with the birth weight of the first and the second child and it was observed that the rate of LBW births was lower (4.9% vs. 8.9%), the mean birth weight was 107g higher in the intervention group ($p < 0.01$) and the rate of IUGR births was lower (1.4% vs. 2.4%) among participants. The authors concluded that there was a benefit of the intervention among low-income

high-risk women. This effect may represent a natural phenomenon, as second born infants are usually heavier.

Dubois et al⁷² reported on the outcomes in twin pregnancies in the same cohort as described in the “Higgins Nutritional Intervention Program” above. The LBW rate was 25% lower and the rate of preterm births was 30% lower in the intervention group among twin pregnancies.

Conclusion:

Supplementation of isocaloric balanced protein diet to mothers has been shown to reduce the risk of SGA births. There was no difference in the birth weight of the infants born to malnourished and adequately nourished mothers who received the supplementations. A potential beneficial effect of adequate nutrition to malnourished mothers is likely. No potential adverse effects were noted. Further research is needed to understand the biological mechanism for this effect. Balanced intake of protein/energy is a pre-requisite for all pregnant women and should be recommended.

(iii). 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. However, changes resulting in serious clinical implications are uncommon among women in developed countries. The relationship between maternal hemoglobin level and birth weight and preterm birth has been described as “U” shaped with high rates at the extremes of iron levels.⁷³ Several mechanisms for the association of iron deficiency and adverse pregnancy outcomes have been proposed.

- Godfrey et al⁷⁴ found that the size of the placenta had an inverse relation to maternal hemoglobin level. Maternal oxygen content influences the development of the placenta and release of growth hormones from placenta. However, its direct impact on fetal growth is unclear.
- Iron deficiency leads to release of norepinephrine, which in turn stimulates Corticotrophin Releasing Hormone (CRH) and may trigger the cascade of labor.⁷⁵
- Chronic hypoxia resulting from anemia itself can cause release of stress hormones including CRH.⁷⁵
- Iron deficiency anemia per se predisposes women to increased risk of infection.⁷⁵
- High hemoglobin leads to increased viscosity and sluggishness of circulation and reduced uteroplacental blood flow. This can lead to IUGR births.⁷⁶

Epidemiological association:

Rasmussen⁷³ reviewed 23 randomized controlled studies of iron supplementation on preterm/LBW/IUGR births. There were significant issues with the methodology of the studies. The author reported false-positive bias in one

(randomization by centres and analysis by individuals), false negative bias in 19 studies (women not anemic at the start of studies), bias of unknown direction in 6 studies, confounding in 3 studies (improper randomization) and insufficient information in 1 study. The range of RR for preterm birth among various studies for moderate anemia was 0.6 to 2.63 and for severe anemia it was 1.10 to 4.01. The range of RR for LBW was 0.76 to 2.96 for moderate anemia and 1.0 to 6.33 for severe anemia. An uncontrolled estimate of a 200 - 400g reduction in birth weight was noted in women with severe anemia (< 80g/dl).

Mahomed⁷⁷ reviewed the effects of iron supplementation on pregnancy outcomes and hematological parameters from 20 studies for the Cochrane Collaboration. It was found that there was improvement in the maternal hematological parameters but there was no statistically significant difference in the birth weight between placebo and treatment groups (30g, 95% CI – 90, 150g). There was no reduction in the rate of LBW (RR 1.12, 95% CI 0.72, 1.73), SGA (RR 1.09, 95% CI 0.8, 1.49) and preterm birth (RR 1.40, 95% CI 0.94, 2.09) when iron was used selectively vs. routinely. These results were reported in only one study. Authors concluded that iron supplementation was effective in elevating maternal iron status but there was not enough information available to assess the impact on pregnancy outcomes.

Cuervo et al⁷⁸ reviewed randomized controlled studies assessing the impact of treatment of iron deficiency anemia during pregnancy for the Cochrane Collaboration. Only one study comparing the oral iron vs. intravenous iron examined the effect on SGA births. There was no statistically significant change in the risk for SGA births with either mode of therapy (RR 1.6, 95% CI 0.56, 4.56).

Ramkrishnan et al⁷⁹ reviewed observational studies of iron supplementation and LBW/preterm births. Similar conclusions as in other reviews were made. Due to recommendations from WHO/UNICEF in support of routine supplementation during pregnancy the authors acknowledged ethical difficulties in performing a randomized controlled trial.

de Onis et al⁸⁰ reviewed nutritional interventions during pregnancy and their impact on IUGR. Two studies of iron supplementation were reviewed. Mahomed excluded one of the studies included in the above-mentioned review due to high attrition rate. There was no difference between the two groups (risk for IUGR, OR 0.92, 95% CI 0.59, 1.43).

Conclusion:

The epidemiological studies from various parts of the world suggest that supplementation of iron is associated with improvement in maternal iron status. There is no evidence that supplementation reduces the incidence of preterm/LBW/IUGR births. Methodological problems in the studies may have been responsible for not showing a significant reduction. The current approach of supplementation of 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.

(iv). Folic acid:**Biological plausibility:**

During pregnancy there is an increased turnover of cells and rapid cell division in the fetus that requires increased amount of folate. This has led to a routine practice of supplementing folic acid to pregnant women. Willoughby et al⁸¹ reported megaloblastic anemia in 3.4% and folate deficiency in one third of pregnant women.

Epidemiological association:

Mahomed⁸² reviewed 21 randomized and quasi-randomized controlled studies assessing the impact of additional folic acid supplementation on pregnancy outcomes for the Cochrane Collaboration. The trials were of variable quality. Supplementation with folate improved the biochemical parameters of folic acid status. There was no difference in the risk of preterm birth (RR 1.03, 95% CI 0.71, 1.49) or LBW (RR 0.75, 95% CI 0.50, 1.12) between the two groups. The author concluded that there is no evidence for or against the supplementation of folate to pregnant women in relation to preterm/LBW births.

Ramkrishnan⁷⁹ reviewed five prospective follow up studies and six randomized controlled studies and concluded that the effect of folic acid supplementation on fetal growth is not conclusive. There was lack of well-designed randomized controlled studies assessing effect of folic acid supplementation in reducing preterm/IUGR/LBW births.

de Onis et al⁸⁰ reviewed five randomized controlled studies (4 included in Mahomed's review, one excluded from Mahomed's review) of folate supplementation and reported a reduction in the risk of IUGR (OR 0.60, 95% CI 0.37, 0.97). However, the authors acknowledged poor quality of the studies, especially lack of proper documentation of randomization.

Conclusion:

The quality of the studies assessing the impact of folate is poor. The conclusive efficacy in improving hematological status was not translated into significant reduction of preterm/IUGR births. Further research is needed to identify a group of women who will benefit the most. This review does not include the assessment or efficacy of folic acid supplementation on neural tube defects.

(v). Calcium:**Biological plausibility:**

Deficiency of calcium leads to release of parathormone and renin. High levels of parathormone increase intravascular calcium concentration and lead to vasoconstriction. This may result in pregnancy induced hypertensive disorders and preterm/IUGR births.⁸³

Epidemiological association:

Pregnancy induced hypertensive disorders are among the contributors to preterm births and fetal growth restriction. An association was observed in epidemiological studies from Ethiopia where the high calcium content in the diet has led to reduced incidence of preeclampsia and eclampsia.

Atallah et al⁸⁴ reviewed 11 high quality studies of supplementation of calcium to prevent hypertensive disorders of pregnancy for the Cochrane Collaboration. A reduced risk of high blood pressure was noted with calcium supplementation (RR 0.81, 95% CI 0.74, 0.89) in all women, women at risk of hypertension (RR 0.45, 95% CI 0.31, 0.66) and women with low calcium intake (RR 0.49, 95% CI 0.38, 0.62). However, no effect was noticed on the risk of preterm birth in all women (RR 0.95, 95% CI 0.82, 1.10). There was a reduction in the risk of preterm birth in women at high risk of hypertension including teenagers, women with previous pre-eclampsia, women with increased sensitivity to angiotensin II and women with pre-existing hypertension (RR 0.42, 95% CI 0.23, 0.78). A reduction in the risk of LBW was noted (RR 0.83, 95% CI 0.71, 0.98) in the combined high risk and low risk groups.

de Onis et al⁸⁰ in their review included five studies of calcium supplementation and concluded that routine supplementation of calcium did not reduce the risk of IUGR (OR 0.77, 95% CI 0.51, 1.16). However, in their review methodological assessment was not rigorous. There was a discrepancy regarding inclusion of one study between the two reviews.

Conclusion:

Epidemiological evidence indicates that supplementation of calcium may be beneficial to women particularly at risk of developing pregnancy induced hypertensive disorders or with low dietary intakes of calcium in reducing preterm/LBW births. Assessment of dietary intake of calcium or biochemical assessment during prenatal visits may help to identify at risk populations.

(vi). Magnesium:

Biological plausibility:

Magnesium is required for synthesis of proteins and regulation of electrical activity across cell membranes. Epidemiological studies have indicated that magnesium has a beneficial effect on fetal growth.⁷⁹

Epidemiological association:

Makrides et al⁸⁵ reviewed seven studies assessing the impact of supplementation of magnesium on pregnancy outcomes for the Cochrane Collaboration. Six studies were randomized controlled studies and one used cluster randomization (randomized by center). There was a reduction in the risk of preterm birth for the trials supplementing magnesium before 25 weeks gestation (RR 0.73, 95% CI 0.57, 0.94), LBW (RR 0.67, 95% CI 0.46, 0.96) and SGA (RR 0.70, 95% CI 0.53, 0.93) compared to placebo. However, analysis without inclusion of the trial with cluster randomization revealed no difference.

There were major concerns regarding the quality of the studies and the authors acknowledged the lack of high quality studies.

Conclusion:

In conclusion, the biological mechanism of action of magnesium supplementation is not clear. The available evidence from studies of variable quality suggests benefit of magnesium supplementation on reduction of preterm/LBW/SGA births. However, this requires further studies.

(vii). Vitamin D:

Biological plausibility:

The requirement of vitamin D is increased during pregnancy. It is not clear whether supplementation is associated with any effect on pregnancy.

Epidemiological association:

Mahomed et al⁸⁶ reviewed two randomized controlled studies of Vitamin D supplementation on pregnancy outcomes for the Cochrane Collaboration. The trials were of small sample size. There was no difference in the risk of LBW (RR 0.55, 95% CI 0.24, 1.25) and SGA (RR 0.54, 95% CI 0.26, 1.10). Based on the small sample size the authors concluded that the evidence was insufficient.

Similar conclusions were reported by de Onis et al⁸⁰ and Ramkrishnan et al⁷⁹ from their reviews.

Conclusion:

There is not sufficient evidence to support supplementation of Vitamin D during pregnancy. Further research is needed.

(viii). Zinc:

Biological plausibility:

Zinc plays a vital role in cellular function. Deficiency of zinc has been reported to be associated with several pregnancy complications such as LBW, pregnancy induced hypertension, prolonged labor, and postpartum hemorrhage.⁷⁹ The biological mechanism is not clear.

Epidemiological association:

Mahomed et al⁸⁷ reviewed seven studies assessing the impact of zinc supplementation on pregnancy outcomes for the Cochrane Collaboration. A reduction in the risk of preterm delivery (RR 0.74, 95% CI 0.56, 0.98) with zinc supplementation was noted. However, there was no reduction in SGA (RR 0.90, 95% CI 0.64, 1.28), LBW (RR 0.77, 95% CI 0.56, 1.06), change in birth weight (24g, 95% CI – 46, 95g) and duration of gestation (WMD 0.37 week, 95% CI - 0.10, 0.85 week). The reduction of preterm births was debatable, as it did not explain lack of difference in the length of gestation. The authors recommended further studies.

Similar conclusions were reported by de Onis et al⁷⁹ and Ramkrishnan et al⁸⁰ from their reviews.

Osendarp et al⁸⁸ performed a randomized controlled study of zinc supplementation from 12 - 16 weeks to the end of the pregnancy in Bangladesh. The overall incidence of LBW was 43% in the cohort; however, there was no difference between the two groups. LBW infants born in the zinc-supplemented group had lower incidence of childhood morbidities.

Conclusion:

The epidemiological evidence indicates that zinc deficiency may play a role in preterm birth. However, further research is needed to confirm these results and to understand the exact underlying biological mechanism.

(ix). Multivitamins:

Biological plausibility:

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

Epidemiological association:

Supplementation with multivitamins is a common practice during pregnancy. This has not been adequately assessed for the effects on the rates of preterm or LBW births.

Ramkrishnan et al⁷⁹ reviewed 2 observational studies and 2 experimental studies. Apart from the reduction in the incidence of neural tube defects due to the folic acid component there were no significant effects on preterm/LBW births. This was probably due to lack of study power. According to the authors a randomized controlled trial was ongoing in Mexico comparing multiple micronutrients and iron supplementation.

Czeizel et al⁸⁹ performed a randomized controlled trial of supplementation of multivitamins (containing vitamins and minerals) and trace elements (no vitamins) 4 weeks prior to attempts for conception to until 12 weeks after conception. There was no difference in the incidence of LBW (4.3% vs. 3.5%) or preterm births (7.5% vs. 7.2%) between the two groups. An unexplained higher rate of multiple births (3.8% vs 2.7%) was noted in the multivitamin group.

Conclusion:

The information from the literature on supplementation of multivitamins during pregnancy to reduce preterm/LBW/SGA births is inadequate. Further research is warranted. However, there is an unequivocal reduction in neural tube defects with supplementation of folic acid.

(x). Salt intake:

Biological plausibility:

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

Epidemiological association:

Duley et al⁹⁰ reviewed 2 studies advising change in salt intake during pregnancy and its effect on pregnancy outcome for the Cochrane Collaboration. A total of 603 women were advised to reduce salt intake. There was no difference in the risk of IUGR (RR 1.5, 95% CI 0.73, 3.07), LBW (RR 0.84, 95% CI 0.42, 1.67) or preterm birth (RR 1.08, 95% CI 0.46, 2.56). The authors concluded that there was insufficient evidence to support the practice of reducing salt intake.

Conclusion:

There is no evidence supporting the restriction of salt during pregnancy for reduction in pregnancy induced hypertension.

(xi). Thiamine:

Ramakrishnan et al⁷⁹ reviewed the literature related to thiamine deficiency in pregnancy. Thiamine deficiency was associated with IUGR in rats but no human studies have confirmed this finding. Further research in women deficient in thiamine is needed.

(xii). Vitamin B₆:

Vitamin B₆ is an important co-enzyme for protein metabolism. Ramkrishnan et al⁷⁹ reviewed one randomized controlled study of 50 mothers who received 7.5 mg of Vitamin B₆ or placebo. There was no difference in the birth weight of these infants. The study lacked power. Further research in women deficient in B₆ is needed.

(xiii). Vitamin B₁₂:

Vitamin B₁₂ is involved in metabolic functions and DNA synthesis. Ramkrishnan et al⁷⁹ reviewed 2 observational studies of Vitamin B₁₂ status and risk of preterm labor. Both studies revealed an association of low Vitamin B₁₂ and preterm labor. No interventional studies have been performed to date.

(xiv). Vitamin C:

Vitamin C is linked with preterm prelabor rupture of membranes due to its function in collagen integrity. Ramkrishnan et al⁷⁹ reviewed 2 observational studies, which found an association of a low level of Vitamin C and preterm prelabor rupture of membranes, which often result in preterm labor. No intervention studies were identified.

(xv). Vitamin E:

Vitamin E plays a role in normal reproduction. Ramkrishnan et al⁷⁹ reviewed observational studies and found that Vitamin E values were either lower

or normal in different studies of pregnant women. No interventional studies were identified.

(xvi). Copper and selenium:

Ramkrishnan et al⁷⁹ reviewed observational studies assessing the level of copper and selenium for their association with LBW. Conflicting results were obtained. Further research is warranted.

(xvii). Vitamin A:

Vitamin A is essential for normal growth and development. Observational studies provide conflicting results regarding an association of low Vitamin A levels and birth weight. Ramkrishnan et al⁷⁹ reviewed four experimental studies of supplementation of Vitamin A and found conflicting results. The authors concluded that there is a need for a well-designed randomized controlled study to examine whether improving Vitamin A status can alter birth weight. The teratogenic effects of high doses of Vitamin A should be kept in mind.

(xviii). Fish oil:

Biological plausibility:

- Fish oil contains long chain n-3 fatty acids.⁹¹
- Prostaglandins are essential for the onset of labor. Long chain n-3 fatty acids may postpone onset of parturition by down regulating the formation of prostaglandins (PGE₂ and PGF_{2α}) involved in the triggering of parturition.⁹¹
- Long chain n-3 fatty acids increase the formation of PGI₂ and PGI₃ leading to relaxation of myometrium and prolongation of the gestation.⁹¹
- Long chain n-3 fatty acids lower the thromboxane/prostacyclin ratio and blood viscosity leading to improved placental blood flow and subsequently fetal growth.⁹¹
- N-3 fatty acids are believed to protect against preeclampsia and pregnancy induced hypertension.⁹¹

Epidemiological association:

de Onis et al⁸⁰ reviewed 3 studies of fish oil supplementation and its effect on IUGR. Prophylactic fish oil was given in one randomized controlled trial to women with pregnancy induced hypertension or asymmetrical IUGR. There was no reduction in the rate of infants born with mean birth weights below the third centile in either group (OR 0.89, 95% CI 0.48, 1.64). A three arm randomized controlled study was reviewed involving placebo, fish oil and olive oil groups. There was no difference in the birth weight between the placebo and the fish oil group (WMD 67g, 95% CI -44, 178g). There was an increase in the mean birth weight in the fish oil group compared to olive oil group (WMD 126g, 95% CI 19, 233g).

Olsen et al⁹¹ performed a randomized controlled study of fish oil supplementation to high-risk pregnancies. Women with high risk pregnancies (previous preterm/IUGR births, pregnancy induced hypertension, twin

pregnancies, threatening preeclampsia or suspected IUGR in this pregnancy) were randomized to receive either fish oil or olive oil as prophylaxis (from 20 weeks gestation) or as therapy (33 weeks gestation). Fish oil reduced the recurrence of preterm birth from 33% to 21% (OR 0.54, 95% CI 0.30, 0.98). There was no reduction in the incidence of IUGR (OR 1.26, 95% CI 0.74, 2.12). There was no reduction in the rate of preterm birth in twin pregnancies.

Olsen et al⁹² in a prospective cohort study reported that the rate of preterm delivery was 7.1% in the group of patients who never consumed fish compared to 1.9% in the group of women who reported consuming fish as a hot meal and/or an open sandwich with fish at least once a week. Adjusted OR for preterm delivery was 3.6 (95% CI 1.2, 11.2) in the no consumption group compared with the high consumption group.

Conclusion:

Biological and epidemiological evidence indicates benefits of fish oil consumption for women with a previous history of preterm labor. The evidence is not strong for its benefit for all women. Most studies have been undertaken by one group of investigators. Further research from different centres is warranted to confirm the effectiveness in the prevention of preterm births.

(xix). Interaction of micronutrients:

Ramkrishnan et al⁷⁹ reviewed the studies on interaction of various micronutrients. Zinc was found to interfere with availability and absorption of iron. Vitamin A deficiency was found to inhibit utilization of iron. Combined tablets of iron and folic acid make it difficult to assess the individual impact. Vitamin C was found to enhance iron absorption. Interaction between vitamin A and zinc is not well studied in humans. Folic acid supplements were found to reduce zinc absorption. The evidence is derived either from small studies or animal studies. Further research is needed.

National perspectives on nutritional supplementation during pregnancy:

Canadian programs relating to provision of nutrients and/or nutritional advice exist throughout the country.⁹³ The review of Canadian Prenatal Nutrition Programs by Health Canada⁹⁴ identified 8 programs in the country with a nutritional focus. These included the Halifax “Milk and Orange Juice Ticket Program for Pregnant and Breast feeding Women” on social assistance, the “Vancouver Healthiest Babies Possible Program”, the “Prince Edward Island Nutritional Intervention Program”, the “Montreal Diet Dispensary - Higgins Nutrition Intervention Program”, the “Toronto Healthiest Babies Possible Program”, the “British Columbia Pregnancy Outreach Program”, the “Daybreak Healthy Baby Club” in Newfoundland and the “*Programme integre de prevention en perinatalite (PIPP) Natre egaux-Grandir en sante*” in Quebec. These programs offer nutritional interventions to low-income women. In addition, all programs counsel against tobacco and alcohol use. The objectives of these programs include individualized counseling and nutritional assessment.⁹⁵

Local perspectives:

The “Toronto Healthiest Babies Possible Program (HBP)” was launched in Toronto in 1979 and is still ongoing.^{96:97} The aim of the program is to reduce the incidence of LBW. It provides education on childbirth and nutrition to high-risk women. Dietitians and public health nurses provide the counseling. Nutritional assessment is undertaken after an individual home visit, which is followed up at regular intervals. Women are provided with a coupon to purchase 1 liter of milk per day and given a multivitamin mineral supplement. The dietitian and the nurse perform one postnatal visit. In 3 published reports from this program, in an uncontrolled comparison, there was a steady decline in the incidence of LBW. There have been several concerns raised regarding the data collection, which has prevented proper evaluation of this program.⁹⁵ The preceding described the HBP program at the time of evaluation. The program has evolved since these reports and changes have been made. No further evaluation has occurred to date.

Healthy Beginnings started as a joint community program in 1988. The program includes provision of supplementary food, health education, nutritional education, social support, and improvement of self-esteem. Drop-in centers supply food to the whole family based on family size. A typical program includes serving of snacks, cooking demonstrations for healthy food preparation, and provision of education materials. Public health nurses and dietitians are available during the sessions to answer questions regarding pregnancy and nutrition. Uncontrolled results suggest that there was a marked variability in the reported number of women from the total number of enrolled women due to a large number of dropouts.⁹⁵ From an epidemiological standpoint the results reported so far lack methodological rigor.⁹⁵ There is a need to design proper measures for the assessment of this program, to formalize the approach to some extent, to reduce the number of missing data points and to evaluate the effectiveness of the program.

Currently, there are over 40 ongoing weekly prenatal nutrition and support programs for pregnant women at risk for poor pregnancy outcomes occurring in Toronto. The Canada Prenatal Nutrition Program (CPNP) provides funding for the programs, in part, and program evaluation is being undertaken through Health Canada.

Conclusion for nutritional factors/interventions:

Nutrition is a significant determinant for fetal growth. Luke et al⁶⁴ suggested that even an increase in birth weight of 40 grams could have a significant impact on the population in terms of neonatal mortality and morbidity. An understanding of the biological mechanisms of the interaction of certain micronutrients and pregnancy outcomes are evolving. The major nutritional factors that can affect pregnancy outcomes are the intake of nutrients and the uptake and regulation of nutrients by the feto-placental unit.

Interventions directly aimed at the fetus are not studied adequately to make suggestions for their routine use. The one intervention that is suggestive of

having a beneficial effect in reducing SGA births is supplementation of a balanced nutritious diet. Certain supplementations such as iron, calcium, magnesium and zinc have shown improvement in physiological parameters and a trend towards a reduced rate of either 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.

The factors that may affect the nutritional status of pregnant women are multiple including socioeconomic status, life style behaviors 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 to have limited resources to meet the demands of pregnancy may help to break the inter-generational cycle of LBW.

4. Anthropometric factors:

Three anthropometric factors associated with preterm/LBW/SGA/IUGR births include: gestational weight gain, maternal prepregnancy weight and maternal height. The US Institute of Medicine recommends gestational weight gain according to maternal BMI prior to the pregnancy (for BMI < 19.8 recommended weight gain during pregnancy 28 – 40lb, for BMI 19.8 - 26 recommended weight gain during pregnancy 25 – 35lb, for BMI 26.1 – 29 recommended weight gain during pregnancy 15 – 25lb and for BMI > 29 recommended weight gain during pregnancy 15lb).⁹⁸

a. Gestational weight gain:

Weight gain during pregnancy reflects increase in the uterine tissue, the fat stores, the plasma volume, the placenta, the fetus and the breast tissue. Prepregnancy body mass and its effect on pregnancy outcome have been studied.

Biological plausibility:

Several hypotheses have been proposed for the mechanism underlying the effects of weight gain during pregnancy on outcomes.

- Maternal weight gain reflects adequacy of caloric intake and micronutrients. Poor weight gain may reflect deficiency of these substrates, which are required for the growth of the fetus.⁹⁹
- Zinc deficiency has been particularly linked to poor weight gain as it can cause suppression of appetite leading to perpetuation of existing deficient caloric intake. In addition, it impairs the synthesis of prostaglandins and collagen and affects uterine contractility.⁹⁹
- Early nutritional insult can result in poor plasma volume expansion and insufficient development of maternal tissues for support of the fetus.⁹⁹
- Some of the mechanisms described under the section of nutrition are applicable.

A combination of factors is probably operating simultaneously in mediating the effects of gestational weight gain on fetal weight and duration of gestation.

Epidemiological association:

Carmichael et al⁹⁹ reviewed 13 epidemiological studies reporting 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” while some followed the recommendation of body mass index (BMI). Rate of weight gain is also affected by the duration of gestation. Weight gain pattern probably provides a better description of the nutritional status than 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 while in some instances the reason for 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 out of these 7 reported a protective effect (reduced incidence of IUGR/LBW) in the presence of adequate weight gain. All five studies reporting the pattern of weight gain (slow weight gain in the initial phase and rapid weight gain the later stage) showed a protective effect. Most of the studies reported an increased risk of preterm birth by approximately 50-100% 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 with respect to weight gain patterns and proper assessment of gestational age.

Luke et al⁶⁴ in a review concluded that an adequate weight gain provided a similar protective effect. They suggested that cultural differences in metabolism of various substrates are important. Chinese mothers, despite lower prepregnancy weight, were found to have similar size infants as white mothers. This was attributed to higher mean blood sugar levels during gestation in Chinese women compared to other races, which may be responsible for increased birth weight.

Conclusion:

Biological and epidemiological evidence indicates that adequate weight gain during pregnancy has a protective effect on LBW/preterm births. No rigorously conducted intervention studies were identified as it is not ethical to perform randomized controlled trials. Adequate weight gain should be the target for each pregnancy.

b. Maternal height:**Biological plausibility:**

Maternal height is a result of genetic factors, environmental effects and nutrition. The exact mechanism of how maternal height influence pregnancy outcomes is not clear.

Epidemiological association:

The influence of maternal height has been studied in various epidemiological studies. An inter-generational effect has been noted. Preventive measures to break this intergenerational cycle include nutritional interventions during pregnancy and childhood to allow each fetus to reach its maximum genetic potential.⁶⁴

Luke et al⁶⁴ reviewed the studies of the effects of maternal height on birth weight. The authors found that in most of the studies reviewed taller women gave birth to heavier infants. The explanation for this phenomenon was probably due to higher prepregnancy weight and higher weight gain.

Conclusion:

Maternal height is a determinant for birth weight. The impact of maternal height is not clearly established in relation to preterm/LBW/IUGR births.

c. Maternal prepregnancy weight:

Biological plausibility:

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

Epidemiological association:

No review was identified examining prepregnancy weight and pregnancy outcomes. The following represents 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 al¹⁰⁰ in a study of Austrian and West German mothers found that prepregnancy weight had a major influence on birth weight compared to pregnancy weight gain.

Kirchengast et al¹⁰¹ studied the effect of prepregnancy weight and pregnancy weight gain on newborn size in 10,240 infants in Austria. A higher prepregnancy weight was associated with higher birth weight and head circumference. The incidence of LBW was significantly higher in underweight women compared to women with normal weight, overweight and obese women.

Hickey et al¹⁰² studied ethnic groups and prepregnancy weight in the US. Low prepregnancy BMI was associated with an increased risk of preterm birth between 33 – 36 weeks in the black population (OR 1.4, 95% CI 1.1, 1.8 for BMI 16.5 - 19.7) and the white population (OR 1.5, 95% CI 1.1, 2.0 for BMI 16.5 - 19.7) but not in the Hispanic population (OR not reported).

Conclusion:

The effects of prepregnancy weight can only be assessed by cohort epidemiological studies. Available evidence suggests that low prepregnancy body weight is associated with an increased risk of preterm/LBW births. Improvement in the nutritional status in women of childbearing age and its effects on preterm/LBW/IUGR/SGA births need further research.

5. Medical factors:

Maternal general health and altered hemodynamic status due to pregnancy can affect the fetus in several ways.

a. Maternal general medical conditions:

Nutrients and oxygen are the key factors for fetal growth. Maternal conditions altering this environment can result in altered fetal growth. Maternal infection with organisms transmitted through the placenta can affect growth. Maternal conditions affecting oxygen carrying capacity, uteroplacental blood flow and size of the uterus can affect the growth of the fetus and the duration of the gestation.^{1;7;15;103-105}

Chronic maternal hypertension resulting either from renal parenchymal diseases or essential hypertension can reduce fetal growth by a factor of 2 - 3.¹⁰³ This may be due to a reduction in blood flow or an increased risk of developing preeclampsia. The mechanism is unclear.¹⁰³ Treatment of hypertension has shown no effect on either fetal growth or growth restriction.

Maternal diabetes can cause long-standing changes in the microvasculature of the placenta and cause fetal growth restriction.¹⁰³

Other chronic conditions reported to have an effect on fetal growth are asthma, collagen vascular disorders, cystic fibrosis, starvation, short bowel, pancreatitis, malabsorptive states, cyanotic heart disease, sickle cell anemia and living at a high altitude.^{1;7;15;103-105}

b. Pregnancy associated conditions:

Pregnancy induced hypertension is the most commonly encountered disorder in which fetal growth may be impaired. Uteroplacental insufficiency and placental infarcts are frequently seen in mothers with pregnancy-induced hypertension.¹⁰⁶

Misra et al¹⁰⁷ reviewed epidemiological studies undertaken from 1931 onwards reporting 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. (3) Most studies failed to adjust for covariates, especially smoking. Biological plausibility was not consistently reflected in the epidemiological studies and further research is needed.

Gestational diabetes usually results in large for date infants. If the mother has previous glucose intolerance, superimposed gestational diabetes can lead to growth restriction.

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.¹⁰⁸

Maternal infection with rubella, cytomegalovirus, malaria, syphilis, varicella, herpes, *Listeria*, Epstein-Barr virus and Chagas disease can cause fetal growth restriction.^{1;15;103-105} 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 the growth of the fetus.¹⁰⁴

c. Infections:

Biological plausibility:

Several theories have been proposed to explain the exact pathogenesis of infection and preterm labor. The maternal genital tract is colonized predominantly with acidophilic lactobacilli and a very scant amount of other organisms such as staphylococci, streptococci and *Gardnerella vaginalis*.¹⁰⁹ Estrogen affects the distribution of these organisms through out the life of a woman.¹¹⁰

Infection of the vagina can act as a starting point in the cascade of ascending infection, rupture of fetal membranes, infection of the chorio-amniotic sac and subsequent preterm labor.¹¹¹ The evidence supporting¹¹²⁻¹¹⁵ the trigger for the onset of labor from biochemical studies is as follows:

- Infection triggers the release of various compounds locally and systemically.¹¹⁶
- The organisms release proteases, which hydrolyze the cervical mucus barrier, and promote the entry of the microorganisms.^{113;114}
- Proteases released by these microorganisms weaken the collagen content of fetal membranes.¹¹⁷
- The organisms release sialidase, which affects the sialic acid component of the cervical mucus and breaks the protective barrier.^{113;114}
- Most of these organisms are anaerobic and produce fatty acid salts, which are inhibitory to the fibroblasts and weaken the fetal membranes.^{109;113;114}
- Phospholipase A2 is released following infection, which initiates the synthesis of prostaglandins. Prostaglandins are known to cause uterine contractions.^{118;119}
- Infection of the chorio-amniotic sac leads to release of cytokines and inflammatory mediators. Higher levels of interleukin 1 β and interleukin 6 have been found in the amniotic fluid of women in preterm labor.¹²⁰
- A mechanism involving sperms acting as a vector for the transport of bacteria from the vagina to the uterus has been proposed.¹¹⁰

It is unclear why there is a difference in the latent period between onset of infection and onset of labor.

Epidemiological association:

The role of infection in preterm labor and delivery has been examined in three ways.¹²¹

1. In animals, experimental administration of bacteria or bacterial toxins in the blood results in abortion or labor
2. Maternal systemic infections such as pneumonia, pyelonephritis, malaria and typhoid fever are associated with preterm labor
3. Intrauterine infection leads to labor

Romero et al¹²¹ reviewed the role of infection in preterm labor from an epidemiological standpoint. Biological plausibility was reviewed above. The association of infection and preterm labor lacks a high degree of specificity because preterm labor can occur without microbiological or pathological evidence of infection. High degree of specificity is rare in biological systems. The evidence suggests a temporal relationship as 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 was suggestive of a moderate correlation (RR of 1.4 – 2.0). Studies have indicated a dose response gradient eg. the concentrations of bacterial endotoxins have been found to be higher in patients in preterm labor compared to patients not in labor. The authors concluded that the evidence was strongly supportive of the role of infection in preterm births.

1. Bacterial vaginosis (BV):

Epidemiological association:

BV occurs due to changes in the prevailing flora in the lower genital tract.^{110;114} Gardnerella vaginalis, Bacteroides, Peptostreptococcus, Ureaplasma or Mycoplasma species replace the normal flora.^{109;110;113;114} The incidence of BV among pregnant women in general is reported to be 10 - 41% and more than 50% in high-risk populations.¹⁰⁹ The method of ascertainment of BV is important in detecting the prevalence of BV. Krohn et al¹²² 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, those who had initiated sexual activity at an earlier age and those who had other sexually transmitted diseases.

Flynn et al¹²³ reviewed case control and cohort studies reporting on the outcome of mothers with BV. Eleven cohort studies were included. The risk of preterm birth was increased in women with BV (OR 2.05, 95% CI 1.67, 2.50). Subgroup analysis of only cohort studies revealed similar findings (OR 1.75, 95% CI 1.34, 2.29). Significant heterogeneity among studies reporting the risk of preterm birth was found. The risk of LBW was increased in 6 studies reporting on birth weight (OR 1.73, 95% CI 1.11, 2.69). Subgroup analysis of 3 cohort studies revealed similar findings (OR 1.43, 95% CI 1.10, 1.87).

McGregor et al¹⁰⁹ reviewed case control and cross sectional studies of BV. The range of RR for preterm birth in various studies was 1.8 to 2.7. The studies documenting presence of BV earlier in the gestation were associated with increased risk of preterm/LBW births even when BV was documented to be absent later in pregnancy.

Oleszchuk et al¹¹⁰ reviewed studies of vaginal infection and obstetric outcomes. They concluded that these infections were linked to preterm/LBW births.

Yost et al¹¹⁴ reviewed the impact of BV on preterm birth. The RR for preterm birth ranged from 1.4 to 1.9 and 5.0 to 7.5 in mothers with BV after 26 weeks and before 16 weeks gestation respectively.

Morris et al¹¹⁵ in a recent review reported that the risk factors for BV were tobacco use, black ethnic group and use of intrauterine contraceptive devices. The authors concluded that there was an increased risk of preterm birth and maternal morbidities in women with BV.

The epidemiological evidence is highly suggestive of BV in causation of preterm labor and subsequent LBW.

Intervention:

Due to the high prevalence of BV in the general population and comparatively low incidence of adverse pregnancy outcomes, it has not been established whether all women with BV should be treated with antibiotics.

Brocklehurst et al¹²⁴ reviewed 5 randomized controlled trials that assessed the efficacy of antibiotic therapy in BV for the Cochrane Collaboration. The studies were of high quality. Three studies compared metronidazole with placebo, one study compared amoxicillin with placebo and one study compared clindamycin vaginal cream with placebo. The treatment was effective in eliminating infection (OR 0.22, 95% CI 0.17, 0.27) in pregnant women. There was a trend towards reduction in the risk of preterm birth (RR 0.78, 95% CI 0.60, 1.02). There was a reduction in the risk of preterm birth in the subgroup of mothers with previous preterm birth (OR 0.37, 95% CI 0.23, 0.60). The authors recommended that, as there was no difference in the risk of preterm birth, antenatal screening is not justified for all women.

Carey et al¹²⁵ performed a randomized controlled trial of 1,953 women and found that metronidazole was effective in clearing the infection. The women were treated in the second trimester of pregnancy and the therapy was of a short duration. There was no difference in the risk of preterm birth (RR 1.0, 95% CI 0.8, 1.2) or LBW (1.0, 95% CI 0.7, 1.2).

McGregor et al¹⁰⁹ in their review of cohort and randomized controlled trials concluded that screening and treatment of BV might prevent a significant proportion of preterm births. The range of RR among the studies for preterm birth in women with BV was 0.4 to 1.0. The studies reviewed were identical to those reviewed by Brocklehurst et al¹²⁴ described above. The study comparing intravaginal cream with placebo did not show any benefit.

Conclusion:

Bacterial vaginosis is a recognized cause of adverse pregnancy outcomes. Biological and epidemiological evidence confirms its role in the causation of preterm/LBW births. However, intervention studies have failed to establish the role of treatment in the prevention of preterm/LBW births. A select group of pregnant women with history of previous preterm/LBW births may benefit from routine screening and treatment. Further research is needed to establish the effectiveness of routine screening and early treatment.

2. Trichomoniasis:

Epidemiological association:

Trichomoniasis is a common infection during pregnancy. Its role in causation of adverse pregnancy outcomes is not clearly established.

Cotch et al¹²⁶ reported from the “Vaginal Infection and Prematurity Study Group” that the prevalence rate of trichomoniasis among all women at midpregnancy in 6 urban clinic centres was 12.6%. The rate was higher in smokers, unmarried and less educated women.

Intervention:

Gulmezoglu et al¹²⁷ reviewed the only randomized controlled study of Benzoylmetronidazole versus no treatment. There was no difference in the incidence of LBW between the two groups (12% in the treatment group versus 11% in the no treatment group). There was no increase in the duration of gestation (38.5 ± 1.5 weeks in the treatment group vs. 39.8 ± 1.3 weeks in the control group).

Klebanoff et al¹²⁸ performed a randomized controlled trial of 315 women in the Metronidazole group and 289 women in the placebo group. Preterm delivery occurred in 19% of the treatment group compared to 10.7% in the placebo group (RR 1.8, 95% CI 1.2, 2.7). The incidence of spontaneous preterm labor was higher in the treatment group. There was no difference in the risk of LBW (RR 1.4, 95% CI 0.9, 2.1).

Conclusion:

More research is needed to establish the relationship of trichomoniasis and preterm/LBW births and the effects of Metronidazole in reducing preterm/LBW births.

3. Chlamydia infection:

Chlamydia is a sexually transmitted disease. Its relation to adverse pregnancy outcome has not been well studied. Chlamydia infections can result in severe conjunctivitis and pneumonia in neonates.¹²⁹

Intervention:

Brocklehurst et al¹²⁹ reviewed eleven good quality randomized controlled trials comparing treatment of chlamydia infection with different antibiotics versus placebo for the Cochrane collaboration. Amoxicillin was found to be the treatment

of choice for chlamydia. There was no difference in the risk of preterm birth between the placebo and the antibiotic group (RR 0.9, 95% CI 0.56, 1.46), however this outcome was reported in only one study. There was no difference in the risk of preterm birth between the Azithromycin and the Erythromycin group (RR 0.75, 95% CI 0.28, 2.04).

Conclusion:

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

4. Syphilis:

Syphilis is a sexually transmitted disease. Following a decline in the incidence in the previous two decades, an increase from 1990 - 2000 has been reported in the US. The effects of syphilis during pregnancy include abortions, still births and congenital syphilis.¹³⁰ Fiumara et al¹³¹ in 1952 observed that 4 infants were born preterm or with LBW among 7 untreated mothers with syphilis.

It is routine practice to screen and treat mothers who test positive for syphilis.

Intervention:

Walker et al¹³⁰ reviewed 26 studies for inclusion in a review for the Cochrane Collaboration. No randomized controlled trial was identified. With the established effectiveness of penicillin in the treatment of syphilis it is not justified to perform a randomized controlled study.

5. Urinary tract infection:

Urinary tract infection is common during pregnancy. The incidence has been reported to be 17-20% in pregnant women. It leads to preterm labor and preterm rupture of the membranes.¹³² Women harboring bacteria in the urinary tract are symptomatic or asymptomatic. Asymptomatic bacteriuria results in pyelonephritis in approximately 30% of untreated women.¹³³

Intervention:

Vazquez et al¹³⁴ reviewed five randomized controlled studies assessing the impact of treating urinary tract infection on pregnancy outcomes for the Cochrane Collaboration. The studies were of small sample size and included oral, intramuscular or intravenous treatment. A high cure rate was reported in all the studies. There were no differences noted in the incidences of preterm births (outpatient therapy vs inpatient therapy RR 0.33, 95% CI 0.01, 8.02; intravenous Ceftazidime vs Ampicillin and Gentamicin RR 1.9, 95% CI 0.48, 7.55; intramuscular Ceftriaxone vs intravenous Ampicillin and Gentamicin RR 1.1, 95% CI 0.23, 5.19; intramuscular Ceftriaxone vs. intravenous Ceftazidime RR 0.58, 95% CI 0.15, 2.29 and Cefazolin once a day vs. Cefazolin multiple doses RR 1.1, 95% CI 0.44, 2.72). The authors concluded that, as there was no difference

among various treatment regimens in eradication of urinary tract infection, it is justified to use the simplest and cheapest locally available treatment.

Smaill et al¹³³ reviewed 14 randomized controlled studies comparing placebo versus antibiotic treatment for asymptomatic bacteriuria for the Cochrane Collaboration. There was marked heterogeneity among the studies in terms of antibiotic of choice, time of onset of treatment, dose and duration of treatment. The sample sizes of the studies were small. The methodological quality of the studies was poor. However, there was a reduction in the risk of preterm/LBW in the treatment group (RR 0.64, 95% CI 0.50, 0.82) in a meta-analysis of 10 studies reporting this outcome. There was a decreased risk of preterm/LBW infants in patients who received continuous antibiotic therapy vs no treatment (RR 0.67, 95% CI 0.48, 0.94).

Conclusion:

Urinary tract infection is a well-recognized cause of preterm birth and/or LBW. Treatment of mothers with symptomatic or asymptomatic infections is indicated. Further research is needed from larger randomized-controlled studies for management of asymptomatic UTI. In order to avoid the development of bacterial resistance to antibiotics it is necessary to identify which women will benefit from the treatment of asymptomatic bacteriuria.

6. Threatened preterm labor:

Biological plausibility:

- Threatened preterm labor can occur with or without rupture of fetal membranes. Preterm prelabor rupture of 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.¹²¹
- A certain proportion of women is admitted with threatened preterm labor without rupture of membranes. Overt infections by organisms such as ureaplasma and mycoplasma have been implicated as the triggers for the onset of preterm labor.¹³⁵

Increased predisposition to infections in women with preterm prelabor rupture of membranes has prompted physicians to use antibiotics prophylactically. In certain cases administration of antibiotics may provide a “vital 48 hours” prior to the birth needed for the action of the glucocorticoids given to the mother to promote the maturation of fetal lungs.¹¹² There is a concern however, that maternal antibiotics may cure the mother but at the same time may not be effective against fetal infection and cause deleterious consequences.

Epidemiologic association:

Kenyon et al¹¹² reviewed 13 randomized controlled trials assessing the effectiveness of antibiotic versus placebo in preterm prelabor rupture of the membranes for the Cochrane Collaboration. A significant reduction in the risk of maternal infection was noted (RR 0.85, 95% CI 0.76, 0.96). There was a

significant reduction in the number of infants born within 48 hours of initiation of antibiotics (RR 0.77, 95% CI 0.72, 0.83) and within 7 days (RR 0.88, 95% CI 0.84, 0.92). Authors concluded that there was sufficient evidence in favor of the use of antibiotics for women with preterm prelabor rupture of membranes. Erythromycin was found to be superior to Amoxicillin due to concerns of an increased incidence of necrotising enterocolitis associated with Amoxicillin. No long-term follow up is available on the neonates.

King et al¹³⁶ reviewed 10 randomized controlled trials of antibiotic treatment for women in preterm labour with intact membranes (identified between 20-36 weeks gestational age) for the Cochrane Collaboration. Pregnancies were prolonged by 5.4 days in the antibiotic group compared to placebo or no treatment (95% CI 0.9- 9.8 days). However, there was an increase in perinatal mortality in the antibiotic group (OR 3.36, 95% CI 1.21, 9.32). There was no reduction in the risk of preterm (defined for the studies included in the review as < 36 or < 37 weeks) birth (RR 0.94, 95% CI 0.84, 1.05). The authors concluded that antibiotics are not recommended for pregnant women in preterm labor without rupture of the membranes.

Kenyon et al¹³⁷ performed a randomized controlled trial of 6,295 women in preterm labor with intact membranes randomized to Erythromycin, Co-amoxiclav, both or placebo. There was no difference in the composite outcome of neonatal death, chronic lung disease or major cerebral abnormalities among the groups.

Stetzer et al¹³⁸ reviewed prospective controlled trials of the effectiveness of antibiotics for treatment of preterm labor (with or without rupture of membranes). Seven studies reported that there was no difference while six studies reported an increase in the latency period between antibiotic administration and onset of labor.

Conclusion:

The evidence suggests that antibiotics should be prescribed only to women with threatened preterm labor and preterm prelabor rupture of membranes but not to women with threatened preterm labor with intact membranes. Further long term follow up studies are needed.

7. HIV (human immunodeficiency virus) infection:

Epidemiological association:

Human immunodeficiency virus infection may be transmitted from mother to infant. Brocklehurst et al¹³⁹ reviewed 31 prospective cohort studies comparing 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 (OR 2.09, 95% CI 1.86, 2.35) and IUGR (OR 1.7, 95% CI 1.43, 2.02). Observer bias could be an important factor as observers were blinded in only 6 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:

Brocklehurst et al¹⁴⁰ reviewed 3 studies assessing the impact of antiviral medication for HIV infection on pregnancy outcomes. There was no difference in the incidence of preterm birth (RR 0.89, 95% CI 0.64, 1.23) in 2 studies comparing Zidovudine vs placebo. There was no reduction in the risk of infants with LBW (RR 0.77, 95% CI 0.58, 1.04) in 3 studies comparing Zidovudine vs placebo. The sample size for each of the studies was very small.

Conclusion:

There is an association between HIV infection and preterm/LBW/IUGR births. The evidence is derived from prospective cohort studies with inadequate control for confounding factors. In the preconception phase women with HIV infection should be informed of the risks to themselves and the fetus. Women infected with HIV should be provided with sufficient information to make informed choice regarding whether or not to continue the pregnancy. The evaluation of the benefits of the treatment of mother with HIV infection during labor and its benefits to the infant are beyond the scope of this review. Further research is needed to assess the impact of antiviral therapy on preterm/LBW/IUGR births.

8. Periodontal infections:**Biological plausibility:**

Periodontal infections are commonly due to Gram-negative anaerobic organisms. Presence of these organisms, lipopolysaccharides and inflammatory mediators is proposed to react with the placenta-fetal unit. This may result in preterm/LBW births.¹⁴¹ No review addressing the outcomes of interest was identified.

Epidemiological association:

Offenbacher et al¹⁴¹ performed a case control study to assess the relationship of periodontal infection and LBW. Multivariate logistic regression, controlling for other risk factors and covariates, revealed that severe periodontal disease was a significant risk factor for preterm/LBW births (adjusted OR 7.9, 95% CI 6.27, 9.58). The authors suggested that the limited scope of the study does not enable broad generalizations. Findings need to be confirmed by larger, prospective multi center investigations.

Conclusion:

Further research is needed to confirm this association.

Conclusions for infections:

Infection plays a major role in the onset of preterm labor and subsequent preterm/LBW births. Biological evidence suggests an interplay of multiple mechanisms. Epidemiological evidence also suggests that genital tract and urinary tract infections are common causes of spontaneous onset of preterm labor. Once identified or suspected, treatment of infection 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. Prevention of infection should be a public health priority. Potential gains could be obtained by screening high-risk populations such as women with a history of previous preterm birth at regular intervals.

B. Environmental factors:

1. Psychosocial factors/Stress/Socioeconomic factors:

Racial and social differences and their impact on pregnancy outcomes are among the most extensively studied factors.¹⁴² Despite years of investigations neither the exact mechanism nor the interventions to alleviate the adverse impact are clear. Various models to understand the interplay have been described in the literature.^{143;144} Psychosocial factors are interrelated. Economic potential, occupation and educational achievement are commonly used measures of the socioeconomic status of an individual.¹⁴⁵ Disadvantaged people are exposed to long standing psychological stress and economic constraints¹⁴⁶ that lead to engaging in unhealthy life styles. Limited coping resources compound the situation. An inter-generational effect of being born in poverty has also been described.

Biological plausibility:

The exact mechanism of onset of preterm labor is not known. However, there is growing evidence of an interaction or interplay of neuro-endocrine and immunological processes.⁴⁴ Stress experienced by the individual plays a role in altering both processes.

1. Neuro-endocrine mechanisms:

Stressors, in particular chronic stressors, have been shown to increase the concentration of glucocorticoids and catecholamines in the mother.¹⁴⁷ The release of Corticotrophin releasing hormone (CRH) from the placenta due to maternal stress increases the production of prostanoids, which are implicated in the onset of labor. It was observed that mothers with onset of preterm labor in the absence of any known triggering factors had higher levels of plasma CRH compared to mothers not in preterm labor or mothers in preterm labor secondary to infection.⁴⁴ The release of CRH was observed from cultured placental tissue exposed to major biochemical substances that are released in response to stress.

Catecholamines released as a result of stress can reduce the placental blood flow and subsequently affect the growth of the fetus.¹⁴⁷

2. Immunological/ infection induced changes:

Animal experiments have indicated that stress hormones released due to chronic stress lead to immunosuppression⁴⁴ and alteration of both cellular and humoral immunity. The altered immune responses make the host susceptible to

infection. Infection is suggested as an important factor in the causation of preterm labor.¹²¹ Wadhwa et al in a review⁴⁴ identified one human study documenting depression in the activity of lymphocytes in mothers exposed to chronic stress.

3. Interaction:

Romero et al¹⁴⁸ described a systemic response to infection in the fetus which they named the “Fetal Inflammatory Response Syndrome”, triggered by fetal stress, involving activation of endocrine, immunological and hemostatic systems with release of inflammatory cytokines, cortisol and enzymes into the circulation. Preterm prelabor rupture of the membranes and preterm labor may result from this cascade of events.

There is a need for further understanding of the mechanisms of the effects of stress. A prospective cohort and nested case controlled study is underway in Montreal, Canada by Kramer et al.¹⁴⁴ A total of 5,000 women are planned to be recruited from 4 hospitals. The information collected will include a detailed history to assess acute and chronic stressors, psychological function status, blood samples for CRH and genetic mutations, vaginal examination for cervical length and fetal fibronectin assay. Further analysis of the neonates born before 37 weeks will include placental examination and hair analysis for toxic substances. This study may provide more insight into the social disparities related to preterm birth.

Epidemiological association:

A number of epidemiological studies have reported the impact of stressors on pregnancy outcomes. However, there are methodological problems with these studies.

Hoffman et al¹⁴⁷ reviewed the studies published between 1984 and 1996. Stressors were defined in two ways: acute life events and chronic stressors. The methods of evaluation of acute stress in these studies included checklists or direct interviews. Twelve studies were identified that reported the effects of acute stress on fetal growth. Only 3 studies reported an increased risk of LBW (results denote unadjusted OR 1.5 in one study, 55 gram reduction in birth weight in second study and 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 birth weight. The effect of acute stress on gestational length was assessed in 11 studies. Only one case controlled study reported an increased risk of preterm births (unadjusted OR of 3.2). Effects of chronic stress on pregnancy outcomes were examined in 7 studies. Three of these studies observed an increased risk of preterm/LBW/IUGR/SGA births (3-fold increase in the risk of preterm birth in one, reduction in birth weight of 227 grams in the second and an unadjusted OR of 2.4 for poor family functioning in the third study). These studies did not include work-related stress. Studies of work-related stress are reviewed elsewhere. The authors concluded that chronic stress could be an etiological factor that affects fetal growth more than preterm birth.

Depressive symptoms during pregnancy were associated with increased risk of preterm births in one study. This needs further study.

Kramer et al¹⁴⁵ reviewed published studies of impact of socioeconomic status on pregnancy outcomes between 1985 and 2000. Studies from the literature denoting influential factors among women from low socioeconomic status were identified. Increased incidences of short stature, low prepregnancy 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, increased incidence of abuse, depression and reduced levels of support were found among women from poor socioeconomic backgrounds. An interaction between these factors was proposed. The authors 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, illicit drugs, work related hazards and increased physical activity were different among the two 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 birth to a lesser extent.

Paarlberg et al¹⁴⁹ reviewed the studies published up to 1995 on the impact of psychosocial factors on LBW and preterm delivery. Nine of the reviewed studies reported negative impact (reduction in birth weight) of maternal stress and high workload while six studies reported no effect. Marked differences in the methodology of the studies precluded a combined estimate. An overall impression of the author was of an association between maternal stressors and birth weight. Ten studies reported an increased risk of preterm birth following stress and 3 studies reported no effect. According to the authors the evidence supporting the role of stress in triggering preterm births was more conclusive than role in LBW.

Ahluwalia et al¹⁵⁰ studied the effects of multiple risks on SGA. The hypothesis for the study was that women exposed to one risk factor are likely to be exposed to multiple risks. Tobacco use, alcohol use, weight gain during pregnancy, prenatal care, abuse, unwanted pregnancy, partner-associated stress, traumatic stress, financial stress and emotional stress were studied. A dose response relationship was observed. The adjusted OR for delivering a SGA infant increased as the number of risk factors increased from one to six. (OR 1.29, 95% CI 0.69, 2.43 for one risk factor, OR 1.86, 95% CI 1.00, 3.44 for two risks factors, OR 1.67, 95% CI 0.90, 3.10 for three risk factors, OR 2.06, 95% CI 1.10, 3.89 for four risk factors, OR 3.53, 95% CI 1.71, 7.30 for five risk factors and OR 3.82, 95% CI 1.97, 7.41 for six risk factors).

Stein et al¹⁵¹ assessed another perspective of socioeconomic disadvantage. They studied the effect of homelessness on pregnancy outcomes in Chicago, US. Homelessness is a major stressor in a woman's life. Homeless women are more likely to have an unwanted pregnancy, poor antenatal care, substance abuse, stress of day-to-day survival, poor diet and increased chances

of infection. The incidence of preterm birth among homeless women was 19% compared to the national average of 10% and LBW was 17% compared to the national average of 6%. Among homeless women, African-American women were at higher risk of adverse outcomes compared to white women.

Interventions:

Various measures have been employed to alleviate the impact of adverse psychosocial circumstances on birth outcomes. The commonly employed 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.¹⁵²

Hodnett¹⁵³ reviewed the studies reporting the efficacy of additional social support for pregnant women who are at high risk of preterm/LBW births for the Cochrane Collaboration. Fourteen randomized controlled studies of high quality were included in which the intervention group had additional support. The method of providing additional support varied among the studies. This included home visits by professionals (midwives, social workers or nurses) or specially trained lay persons at regular intervals, provision of psychosocial support, individual counseling at each visit, assessment of social support network of each mother and tangible assistance. Despite high study qualities there was heterogeneity between studies. There was no difference in the risk of preterm (RR 0.97, 95% CI 0.87, 1.08), SGA (1.05, 95% CI 0.88, 1.26) or LBW births (0.96, 95% CI 0.87, 1.07) between experimental and control groups. The author concluded that apart from maternal satisfaction there was no significant advantage of additional support during pregnancy in reducing preterm/LBW births.

Hoffman et al¹⁴⁷ reviewed observational and randomized controlled studies reporting efficacy of social support on preterm/LBW births. Among observational studies one study assessed the effectiveness of social support by support quality (a measure of network resources including number of kin, close friends, living with father of the child etc.) and concluded that, in the group of mothers who had experienced stressors, strong support quality was associated with increase in birth weight by 231g. Two other studies demonstrated a positive impact of social support on fetal growth restriction (one study reporting an OR 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, randomized controlled studies offering social support failed to provide clear benefit on either preterm or LBW births. Stratified subgroup analyses in some studies showed benefit for black women, women with previous LBW, adolescent mothers, tobacco users and women with a high degree of stress. The apparent benefit demonstrated in observational studies was not sustained in randomized controlled trials.

Blondel et al¹⁵⁴ performed a systematic review of 5 studies in which the aim was to provide social support as part of antenatal care. A total of 3,197 women were enrolled in the intervention group and 3,159 women were in the

control group. There was no difference in the risk of preterm delivery (OR 0.9, 95% CI 0.8,1.1).

Hughes et al¹⁵² in their narrative review found that prenatal care that included nutrition, health education and psychosocial assessment have met with variable results. The approaches are not completely proven to be effective.

Mamelle et al¹⁵⁵ performed a cohort study of women who were admitted with threatened preterm labor. 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 birth before 35 weeks in the intervention group (5.9% compared to 25.7%). After controlling for confounders the RR for preterm birth in the intervention group was 0.16 (95% CI 0.07, 0.37). This study approached this issue differently than the other studies as all the enrolled women were in threatened preterm labor.

National and local perspectives:

Wilkins et al¹⁵⁶ reported that in Canada the rate of preterm/IUGR births increased as the family income quintile decreased. The preterm birth rate was 5.7% and the IUGR rate was 8.0% for women in the first quintile compared to a preterm birth rate of 7.4% and an IUGR rate of 12.1% for women in the 5th quintile (lowest income group).

In Ontario 9.7% of women reported heavy stress and it was more common among adolescents, the less educated, the poor, the tobacco users and those who lacked social support.¹⁵⁷

In 1997, the singleton LBW rate in Toronto was 80% higher in the lowest income areas (6.5%) compared to 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 babies each year.¹⁵⁸ Data regarding stress experienced by pregnant women in Toronto are not available.

Conclusion:

Considerable advances have been made in the understanding of the mechanism of stress and adverse pregnancy outcomes. However, the exact triggering mechanism is still unclear. Future research is needed to delineate the complexities of the triggers of preterm birth. Available evidence does not support the role of acute stress on preterm/LBW/SGA births, however, the studies are not of high quality. The impact of chronic stressors on increasing the risk of preterm birth is indicative, but the effect on LBW is not convincing. Emerging evidence indicates that maternal depression could be playing a key role. More work is needed to identify the differential effects of socioeconomic disparities within the society.

There were several methodological differences among the studies assessing the impact of social support. Observational studies have demonstrated the beneficial effects of provision of psychological support. However, randomized controlled studies 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.

2. Life style:

a. Tobacco use:

The association of tobacco use with LBW/SGA/preterm births is the most commonly studied topic in reproductive biology. The public health importance given to this issue is appropriate considering the magnitude of the problem. Tobacco use is associated with antepartum, intrapartum and postpartum adverse consequences such as placenta previa, abruptio placentae, increased perinatal mortality and increased probability of sudden infant death syndrome.¹⁵⁹

Biological plausibility:

There have been significant advances in the field of tobacco use and the understanding of the mechanisms of how tobacco impacts on adverse pregnancy outcomes. Several mechanisms have been proposed.

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

- Nicotine is converted to cotinine in the maternal blood and transferred across the placenta.^{159;160} Nicotine is freely permeable across the placenta. The concentration of nicotine is 15% higher in the fetal blood and 88% higher in the amniotic fluid compared to the level in maternal blood.¹⁵⁹
- Cotinine in animal models exerts a number of vascular and metabolic changes. It reduces the uterine arterial blood flow, causes changes in the umbilical arterial blood flow, the fetal oxygen concentration and the acid base balance. In addition, it increases the mean arterial blood pressure and decreases fetal heart rate.¹⁵⁹
- Placental infarctions secondary to tobacco use lead to reduced uteroplacental blood flow.¹⁵⁹
- CO (carbon monoxide) released from the smoke crosses the placental barrier freely. Fetal CO concentrations are 15% higher than in the mother. This causes a leftward shift of the oxygen dissociation curve and reduces the availability of oxygen to the fetus.^{159;161}
- Newborns of mothers who use tobacco have elevated levels of erythropoietin in the cord blood. This suggests fetal response to hypoxia, which may be secondary to exposure to maternal smoking.¹⁵⁹
- Cyanide released in small concentrations following tobacco use competes with oxygen and leads to hypoxia.¹⁶²
- There is an alteration in the production of prostacyclin in smoking mothers, which may lead to an increase in adverse vascular events such as abruptio placenta.¹⁶³
- It is suggested that the disturbance in the transport of amino acids across the placenta leads to an altered nutrient environment.¹⁶⁴

- An alteration of transport of nutrients such as zinc has been reported in mothers who use tobacco.¹⁶⁴
- Mothers using tobacco have poorer quality of diet in all social classes (less protein, zinc, riboflavin, and thiamine) compared to nonsmokers.¹⁶⁵
- Mothers using tobacco eat less and have a lower weight gain during pregnancy compared to nonsmokers.¹⁶⁵
- Nutritional deficiency following tobacco use has an important effect on altered concentration of Vitamin C leading to increased risk of rupture of fetal membranes and preterm labor.¹⁵⁹
- Certain compounds in tobacco smoke alter the taste and reduce the palatability of vegetables. Smokers are likely to eat less vegetables, fruits, whole grains and lower fat milk.¹⁶⁶
- Constituents in tobacco smoke are also antagonistic to certain nutrients and smokers require higher intake of vitamins B₆, B₁₂, C, E, folate, and selenium.¹⁶⁶
- Alteration of the immunological responses following tobacco use has been reported which may lead to a higher chance of infection and subsequent preterm labor.¹⁵⁹

There are several proposed mechanisms regarding the role of tobacco use in adverse pregnancy outcomes. The pathological pathway probably results from direct effects of nicotine on uteroplacental blood flow leading to deprivation of nutrients and oxygen to the fetus. The mechanism for preterm labor is not clear. The most likely explanation is that a growth restricted stressed fetus may trigger preterm labor.

Epidemiological association:

A bio-epidemiological study by Perkins et al¹⁶⁷ found that there was a 207g reduction in birth weight of infants born to smokers. There was a 100g reduction in birth weight for every 1 microgram/litre rise in the concentration of serum cotinine.

Walsh¹⁶⁸ in a review examined the effect of maternal tobacco use on perinatal and postnatal outcomes. Several methodological issues were identified among the studies which include: 1) a lack of randomized controlled trials, 2) the confounding role of passive smoking, 3) not adjusting for other confounding factors, 4) assessment of smoking status by self reporting – issues of validity and 5) tobacco use can lead to perinatal loss due to increased incidence of abortions, which may not be reflected in the studies assessing preterm/LBW births. The author performed a critical appraisal of the literature. The evidence for smoking in causation of LBW was found to be strong. An approximate estimation of relative risk of 2 was found in observational and cross sectional studies. The association was found to be consistent and there was a strong dose response relationship.

Lumley et al¹⁶⁹ in a review including literature from 1957-1986 indicated that the results of over 100 published studies (total birth of half a million pregnancies) indicated that there is a significant reduction of birth weight among infants born to smokers compared to infants born to non-smokers.

Abel et al¹⁷⁰ pooled data from 10 studies and found that the decrease in birth weight among infants born to smokers varied between 70 - 242g among the studies. A dose response effect of smoking on birth weight was observed. There was a graded reduction in the mean birth weight by number of cigarettes smoked by white women (3399g for non-smokers, 3272g for mothers smoking 1-10 cigarettes/day, 3185g for mothers smoking 11-20 cigarettes/day and 3128g for mothers smoking > 1 pack/day).

Nordentoft et al¹⁷¹ in Denmark observed a dose response effect. Mothers smoking 0-9 cigarettes/day had an adjusted OR of 2.40 (95% CI 1.51, 3.80), those smoking 10-15 cigarettes/day had an adjusted OR of 2.68 (95% CI 1.52, 4.68) and those smoking 15 or more cigarettes/day had an adjusted OR of 2.88 (95% CI 1.36, 6.09) for IUGR births compared to nonsmokers.

Moore et al¹⁷² studied the effect of smoking in Afro-American women. There was an increased risk of LBW and preterm birth among smokers and a dose response effect was noted. Light smokers (< half pack per day) had an OR of 1.89 (95% CI 1.15, 3.13) for LBW and an OR of 1.74 (95% CI 1.0, 3.02) for preterm birth while heavy smokers (smoking > half pack per day) had an OR of 3.03 (95% CI 1.90, 4.86) for LBW and an OR of 2.60 (95% CI 1.55, 4.35) for preterm birth.

In a study controlling the confounders McDonald et al¹⁷³ found that consumption of > 10 cigarettes/day was associated with an increased risk of LBW with an OR of 1.51 (95% CI 1.44, 1.57). The risk was reduced to the level of non-smokers for women who stopped smoking before the second trimester of pregnancy.

Windham et al¹⁷⁴ studied active and passive smoking and its impact on birth weight and preterm births in 4099 births in California, US. High environmental smoke exposure (\geq 7 hours a day) was associated with an increased risk of the birth of an infant before 35 weeks (adjusted OR 2.4, 95% CI 1.0, 5.3).

Horta et al¹⁶² studied 5,166 mothers in Brazil by postnatal interviews. An increased risk of IUGR was found among smokers (adjusted OR 2.07, 95% CI 1.69, 2.53). The risk of preterm birth was also increased for mothers who continued smoking throughout pregnancy (OR 1.54, 95% CI 1.24, 1.92). An etiological fraction of 17.7% for smoking in causing LBW was reported. A positive effect of interruption of smoking during pregnancy on birth weight was observed.

Intervention:

Several authors have studied the impact of smoking cessation on preterm/LBW births. The reports indicate that most women stop smoking within 1-2 months of being pregnant. Adolescents, unmarried, less educated and heavy smokers are less likely to quit smoking. The reported rates of relapse during the postnatal period are high.¹⁵⁷

Lumley et al¹⁷⁵ performed a systematic review of 44 randomized and quasi-randomized controlled studies of interventions to decrease smoking for the Cochrane Collaboration. There were marked differences in the types of interventions and the frequency of interventions provided. The interventions

included individualized support and advice, peer support, group counseling, 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. Substantial variations in the intensity of intervention and the extent of reminders of adverse effects of smoking were noted. An estimate from 34 trials reporting the incidence of smoking showed a reduction in smoking in the intervention groups (OR 0.53, 95% CI 0.47 to 0.60). Nineteen studies which tested the biochemical validity of smoking cessation showed an OR of 0.53, 95% CI 0.45 to 0.62 for stopping smoking in the intervention group. The absolute reduction in the incidence of smoking was 7.1% (95% CI 8.8%, 5.4%). There was a reduction in the risk of LBW (OR 0.80, 95% CI 0.67 to 0.95), preterm birth (OR 0.83, 95% CI 0.69 to 0.99) and a mean increase in the birthweight of 28g (95% CI 9 to 49). Sixty-three women (95% CI 34, 333) need to be exposed to the “smoking cessation” intervention in order to prevent one infant born with LBW. This doesn’t reflect how many women actually stopped smoking in the two groups. The authors recommended that as there is benefit of smoking cessation programs in reducing smoking, attention to smoking behavior, support for smoking cessation and relapse prevention should be a part of routine antenatal care. Interventions involving additional group sessions were poorly attended, have not shown benefit and should not be recommended.

Klesges et al¹⁷⁶ in a review found that the rate of quitting smoking was higher for pregnant women compared to the general population. Overall 30-40% of mothers quit or reduce smoking during pregnancy, however, 70% continue to smoke throughout pregnancy. Important factors for successful smoking cessation were motivation, psychosocial support and lack of associated stress. Women living with partners who continue to smoke were less likely to quit compared to women living with partners who were motivated to stop. A comprehensive resource of Internet links is provided in this review for smoking cessation resources and information. The problems affecting the spread of information to the general public regarding the consequences of smoking were lack of appreciation of the extent of the damage by health workers, lack of time, and personnel in private care settings, personal beliefs on the part of health care workers and poor knowledge regarding cessation methods. Approximately 21% of mothers who stopped tobacco use relapsed before delivery. Twenty-five percent of mothers who quit smoking during pregnancy relapse within 1 month, 50% relapse within 4 months and 70-90% relapse within 1 year after giving birth.¹⁷⁷ Predictors for relapse were lack of social support and mixing with people who smoke. Measures implemented towards prevention of relapse are of public health importance. Various models of assisting patients to quit smoking have been suggested.

Dolan-Mullen et al¹⁷⁸ performed a meta-analysis of the studies aimed at smoking prevention. Eleven high quality studies were reviewed. The interventions included personalized counseling, supplementation of pamphlets, self help guides, educational videotapes, buddy-support and regular contact with reinforcement. The combined risk ratio for smoking cessation after intervention was 1.94 (95% CI 1.61, 2.34). There was heterogeneity in the treatment effect

among the studies. After removing an outlier study causing heterogeneity among the studies, the risk ratio for smoking cessation in the remaining ten studies was 1.50 (95% CI 1.22, 1.86) with intervention. Four studies reported on rates of LBW, one of them was an outlier. Higher rates of smoking cessation were related to a lower risk of LBW in the analysis of the remaining three studies. Higher quit results resulted from more intense interventions which included strategies such as intensive counseling, use of multiple contacts, provision of supportive materials and patient follow up.

Edwards et al¹⁷⁹ reviewed the studies assessing postpartum smoking relapse prevention strategies. These intervention programs were often studied in conjunction with smoking cessation interventions during the pregnancy. The authors noted that spontaneous quit rates of smoking during pregnancy have been estimated at 18-42%. Approximately 60% of women who quit smoking during pregnancy resume smoking prior to 6 months postpartum. One study of high quality and 3 studies of intermediate quality were reviewed. The prevention strategies were poorly described in most studies and consisted of brief, infrequent interventions provided in antenatal clinic settings. This 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 didn't help them to maintain cessation status during pregnancy or the postpartum period. Studies showed that a smoking partner is a strong predictor of postpartum relapse, however, no studies examined relapse prevention strategies targeting women and their partners. Further research is needed to develop effective strategies of prevention, targeting women living with partners who smoke, extending intervention and support beyond 6 months postpartum and utilizing a wider population based approach.

Benowitz¹⁶¹ 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 active smoking due to very low doses of nicotine delivered. Nicotine replacement therapies avoid the exposure to other chemicals in the smoke. There is sustained and slow absorption of nicotine from replacement therapy compared to a marked rise occurring with smoking. The authors concluded that nicotine replacement therapy could be an adjunct to smoking cessation therapy, especially in highly dependent smokers. The author justified the rationale for studying the impact of nicotine replacement therapy in heavy smokers.

Lindley et al¹⁸⁰ in an interventional study found that cessation before 32 weeks was effective in reducing the impact of smoking on the fetus.

National and local perspectives:

Rates of smoking during pregnancy are available from Nova Scotia for the year 1996.⁹³ Among pregnant women 71.6% were non-smokers, 11.3% of mothers smoked 1-12 cigarettes/d, 15.3% smoked \geq 13 cigarettes/d and for 1.8% of mothers the smoking status was not known. These data have limitations because they were collected by self-reporting by mothers retrospectively up to 5 years following a pregnancy. Data from Alberta¹⁸¹ reported the smoking rate

during pregnancy to be 23.9% in 1997, 23.6% in 1998 and 23.0% in 1998. During the same period of time 2.8%, 3.2% and 2.7% of women reported quitting smoking in Alberta. According to a survey among the mothers who were smokers prior to pregnancy 90%, 92%, 92% and 84% continued to smoke during the first trimester, the second trimester, the third trimester and the entire pregnancy respectively.¹⁸²

In 2001, a survey was conducted in 3 health units in the Greater Toronto Area. A total of 1,134 mothers were interviewed in the postpartum period. The results are shown in table 3.¹⁸³

Table 3

	Overall	Canadian born	Foreign born	Ratio
% Smoking before pregnancy	17.8	25.2	9.8	2.6
% Smoking in first trimester	10.6	16.4	4.2	3.9
% Smoking in second trimester	9.6	14.9	3.8	3.9
% Smoking in third trimester	8.9	14.2	3.2	4.4
% smoking postpartum	8.1	12.3	3.4	3.6

The rates were higher among the mothers who were Canadian born compared to foreign-born mothers.¹⁸³

Conclusion:

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. Epidemiological evidence suggests that tobacco use results in approximately a 70 - 250g reduction in birth weight. Tobacco users are also at higher risk of preterm births and other perinatal and infantile adverse outcomes. The effects of tobacco use on birth weight remain significant even after controlling for appropriate confounders. The association satisfies most of the causal criteria (strength, consistency, reversibility, dose response, and biological plausibility and epidemiological sense). In an economic analysis by Lightwood et al¹⁸⁴ it was found that an annual reduction of 1% in the smoking rate would result in a reduction of LBW infants by 1,300 in US which would save 21 million dollars in direct costs for health care of these infants. Interventions for smoking cessation are effective in reducing the incidence of tobacco use and LBW. In particular interventions which include intensive counseling, multiple contacts, supportive materials and follow up are beneficial in reducing LBW rates. Screening and counseling of high-risk mothers should be a part of all routine antenatal care. Very few health care providers are prepared and trained to offer an effective strategy for pregnant women.⁶⁰

Further research needs to be done in the following areas:

- Assessing the cultural appropriateness of educational materials

- Identifying the impact of professionals' attitudes towards tobacco use on the counseling and support provided to pregnant women who smoke
- A detailed description of the program including cognitive/behavioral strategies used, their impact, and consumer perceptions
- Relapse prevention programs for specific subgroups
- Efficacy of nicotine replacement programs for heavy smokers.

b. 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 (FAE) and alcohol related neurodevelopmental disorders.^{185;186}

Biological plausibility:

The exact mechanism of alcohol induced effects on the fetus is not clear. This 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 excretion of ethanol by the fetus is ineffective. The placental barrier is freely permeable to ethanol so the fetus is directly exposed to the maternal levels of ethanol. The prolonged circulation of acetaldehyde, a breakdown product of alcohol, is fetotoxic.¹⁸⁷
- Animal research has demonstrated that the risk to the fetus appears to be related to the peak levels of blood alcohol concentrations.¹⁸⁶ In humans the threshold level above which deleterious effects will ensue is unknown. In addition, there is a wide variation in the individual metabolism of alcohol. Repeated binge drinking and its associated high levels of alcohol correlate with adverse pregnancy and neonatal outcomes in some studies.¹⁸⁶
- Alcohol use is often associated with certain nutritional deficiencies. In particular, zinc deficiency is suggested to be responsible for some of the alcohol related effects.¹⁸⁷ The effects of zinc deficiency are reported in detail elsewhere in this review.
- In animal models of fetuses exposed to high levels of ethanol there is an increased production of prostaglandins.¹⁸⁸ Prostaglandins increase the cyclic-AMP activity, which leads to a decrease in cell division and resultant LBW.¹⁸⁹

As will be revealed in detail in the subsequent section, the effect of prenatal exposure to alcohol has a "J" shaped effect on the fetus.^{31;187} A protective effect of "mild" drinking has been suggested due to an increase in the estrogen concentration¹⁸⁷ in the blood leading to an altered estrogen progesterone ratio. Mildly elevated estrogen levels have been shown to have some protective effects on overall perinatal outcomes.

Epidemiological association:

In a review of reported studies on alcohol exposure during pregnancy Abel et al¹⁹⁰ found that 26 of the 56 reported studies of prenatal exposure to alcohol demonstrated a decrease in birth weight. In a subset of 13 studies reporting actual values of alcohol consumption, more than 2 drinks per day were

associated with a reduction in mean birth weight by approximately 200g. The levels of maternal alcohol in blood were not found to have a linear relationship with preterm birth. The authors suggested that a focussed prevention of high-risk consumers is justified rather than a general public health policy.

Lundsberg et al¹⁸⁷ studied 2,714 women prospectively by conducting two interviews to assess the exposure to alcohol. Women were interviewed during the seventh month of pregnancy to assess alcohol consumption. The values for absolute alcohol consumption were derived by alcohol content of the drink multiplied by the average volume and frequency. "Mild drinking" (0.10 - 0.25 oz absolute alcohol/day during the first month of pregnancy had a protective effect on IUGR (OR 0.39, 95% CI 0.20, 0.76). A "J" shaped effect of alcohol consumption during the first month of pregnancy and birth weight was observed. The risk of adverse effects increased with consumption of > 1 oz absolute alcohol/day. There were significantly higher ORs of preterm delivery associated with alcohol consumption during the seventh 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). Binge drinking defined as the consumption of more than 5 drinks on one occasion was associated with a trend towards increased risk of IUGR (OR 1.89, 95% CI 0.93, 3.83) and preterm birth (OR 2.19, 95% CI 0.83, 5.79).

Kesmodel et al³¹ performed a questionnaire-based study of 18,228 pregnancies at sixteen weeks and 30 weeks gestation. A significantly 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) was observed. A "J" shaped effect with some degree of protective effect with small amount of consumption was observed. Assumptions were made that this phenomenon may be due to "healthy drinker effect", healthier life style or underreporting of heavy drinking. The threshold for adverse outcome in their study was observed at 10-14 drinks/week. However this has not been confirmed by other reports.

National perspectives:

In Canada 16.6% of mothers of children below 3 years of age reported use of alcohol during pregnancy.²¹ There was a higher incidence of alcohol use among women 35 years and older compared to women below 25 years of age.²¹ Prenatal alcohol consumption was reported to be 16.6% in Canada and 13.8% in Ontario in 1996-97.²¹ The self-reported incidence of alcohol consumption may be an underestimate. It has been shown that > 50% of women of childbearing age drink alcohol in the US. Among pregnant women self reported alcohol consumption has increased from 12.4% in 1991 to 16.3% in 1995 in the US. In addition there was a four-fold increase in reported episodes of binge drinking.¹⁸⁶ Thus, there is little difference in the percentage of mothers using alcohol during pregnancy between the two countries. There are no data available for the incidence of alcohol use or the amount of alcohol use among pregnant women in Toronto.

Intervention:

There are no interventional studies available on this subject. It is unethical to perform a randomized controlled trial because of the effects of maternal alcohol use on fetus.

Conclusion:

Alcohol exposure during the prenatal period can lead to adverse consequences. The biological mechanism, though 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 birth weight is protective at low levels of consumption and deleterious at high levels of consumption. However, there is no threshold level established for “safe drinking” during pregnancy. Observational studies have suggested increased tendency towards preterm birth but further research is needed. 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 based on available evidence. Due to the teratogenic effects of alcohol on the fetus the counseling should be started in the preconceptional period. Pregnant women should be informed of the risks of alcohol intake during pregnancy on the developing fetus. Interventional studies to assess the impact of such advice are needed. The American Academy of Pediatrics¹⁹¹ recommends a community wide approach.

c. Caffeine use:

Coffee is consumed widely throughout the world with certain areas having a higher consumption than others.

Biological plausibility:

The exact mechanisms of the effects of prenatal exposure to caffeine are not clear. The following theories have been proposed.

- The rate of metabolism of caffeine is 3 times slower in pregnant women compared to non-pregnant women.¹⁹²
- The placenta transfers caffeine freely.¹⁹²
- Newborns have not developed the enzyme to completely metabolize caffeine until several days after birth.¹⁹²
- Caffeine has been shown to inhibit phosphodiesterase enzyme, which results in inhibition of cyclic AMP metabolism. Increased levels of cyclic AMP interfere with cell division and may result in LBW.¹⁹³
- Increased levels of cyclic AMP induce catecholamine-mediated vasoconstriction, which results in reduced uteroplacental perfusion and adverse pregnancy outcomes.¹⁹³
- Caffeine blocks adenosine receptors, which leads to an imbalance between available oxygen and oxygen utilization. This imbalance increases the susceptibility of the cells to hypoxic insults and may cause LBW.¹⁹⁴

Though not totally clear, these mechanisms indicate a possible impact of prenatal caffeine exposure on fetal growth. Biological studies demonstrating a dose response effect are lacking.

Epidemiological association:

Christian et al¹⁹⁵ reviewed 15 studies assessing the impact of maternal coffee drinking on birth weight of the infant. Six studies demonstrated a statistically significant reduction in birth weight following excessive coffee consumption. Seven studies reported increased risk of LBW in mothers drinking coffee. Two studies showed no significant effect of coffee ingestion on birth weight. A dose response effect was observed in the studies assessing various amounts of coffee ingestion. The authors concluded that caffeine overall exerts a small but measurable effect on birth weight.

Clausson et al¹⁹⁶ prospectively studied 873 women to assess the impact of coffee use on pregnancy outcomes. Women were interviewed at 6-12 and 32-34 weeks of gestation. Caffeine intake was estimated from all sources. There was no difference in the mean birth weight (0 – 99 mg/day mean birth weight 3,660g; 100 - 299 mg/day mean birth weight 3,664g; 300 – 499 mg/day mean birth weight 3,611g and \geq 500 mg/day mean birth weight 3,647g; $p = 0.98$) or gestational age (0 – 99 mg/day mean gestational age 278.0 days; 100 - 299 mg/day mean gestational age 278.0 days; 300 – 499 mg/day mean gestational age 278.0 days and \geq 500 mg/day mean gestational age 278.2 days; $p = 0.88$) in various caffeine intake groups.

Santos et al¹⁹⁷ in an overview found that 12 out of 22 studies of caffeine use reported a lower birth weight associated with higher consumption of coffee. A dose response effect was observed in 8 studies. Twelve out of seventeen studies that controlled for smoking and alcohol use reported coffee drinking as a significant factor in the causation of LBW. Three out of eleven studies demonstrated a significant association of coffee consumption and preterm birth. No association between consumption > 300 mg/day and LBW was observed in their case controlled study (adjusted OR 0.73, 95% CI 0.48, 1.12). However, the authors claimed that the results could be due to incomplete information, recall bias or inadequate control of confounders.

Rondo et al¹⁹² performed an unmatched case controlled study in Sao Paulo City, Brazil. The amount of coffee consumption was ascertained by a food frequency questionnaire. Eighty five percent of mothers with IUGR infants and seventy percent of mothers with appropriately sized infants drank coffee during pregnancy. Adjusted OR for giving birth to an IUGR infant after controlling for smoking and alcohol drinking were significant for coffee consumption (OR 1.66, 95% CI 1.02, 2.70). A dose response effect was observed. The odds for an IUGR infant increased as the coffee consumption increased (for an average of < 1 cup/day OR 1.55, 95% CI 0.99, 2.44; for 1 - 2 cups/day OR 2.25, 95% CI 1.34, 3.78; and for > 3 cups/day OR 2.07, 95% CI 1.14, 3.78) compared to non-coffee drinkers.

Intervention:

There is no study on the interventional aspect on this subject.

Local perspectives:

Although coffee consumption is common in the Canadian population, there are no data regarding coffee consumption in the pregnant population.

Conclusion:

Coffee consumption is common in the general population. The biological evidence suggests that caffeine use has a negative impact on fetal growth. The epidemiological data indicate an association with some studies showing a dose response effect. It is advisable to suggest moderation in consumption (not more than 1 cup/day) to pregnant women. Further research is needed.

d. 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.¹⁹⁸

Biological plausibility:

The exact mechanism of the effects of cocaine is not clear. The following theories have been proposed.

- The concentration of plasma cholinesterase is reduced in pregnant women and fetuses, which hampers the excretion of cocaine.¹⁶⁰
- Cocaine crosses the placenta freely and being a weak base has been found in the same concentration in the fetal blood as in the maternal blood.^{160;198}
- Exposure of the fetus to cocaine inhibits the uptake of neurotransmitters such as dopamine and norepinephrine. The elevated concentration of norepinephrine results in vasoconstriction in the fetus and reduced nutrient uptake.^{160;199}
- Cocaine causes vasoconstriction in the uterine arteries by a similar mechanism.²⁰⁰
- Cocaine inhibits the uptake of amino acids across the placenta.¹⁶⁰
- In animal models cocaine inhibits catecholamine uptake in different tissues, which leads to stimulation of uterine contractility via alpha-receptor stimulation.¹⁹⁹
- Cocaine has an appetite suppressant effect decreasing maternal nutrient intake.¹⁹⁹
- Cocaine elevates maternal body temperature with resultant possible damage to the fetus.¹⁹⁹
- Animal studies have shown that cocaine reduces the activity of ornithine decarboxylase, which is a key enzyme in the regulation of fetal growth.¹⁹⁹
- The placenta can serve as a depot for large amounts of cocaine and therefore expose the fetus for a prolonged period to cocaine.¹⁶⁰

Epidemiological association:

The prevalence of the use of cocaine among pregnant women is difficult to establish. The study designs include self-reported questionnaires, assessment of cocaine in the urine, hair or meconium.

Holzman et al¹⁹⁹ reviewed 24 studies (in which at least 100 pregnant women were enrolled per study) reporting use of cocaine during pregnancy. Twenty-three studies showed a negative association between maternal cocaine use and birth weight. The influence of gestational age was controlled in 16 studies and the effect remained unchanged. The populations studied varied from Afro-American women, referred populations from drug treatment centers, prospectively screened mothers from prenatal care programs, women with no prenatal care and postnatal patients. Overall unadjusted analyses showed a reduction of birth weight in the range of 265 to 610g and adjusted analyses showed a weight reduction of 78 to 382g. The reported increase in the risk of preterm birth varied between the studies. The rate differed among studies adjusting for confounders and non-adjusted reports. The range in the difference in mean gestational age was 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 abruptio placentae, which may have accounted for an increased risk for preterm birth (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 lead to substance abuse, 3) multiplicity of drug usage and 4) possible publication bias.

In a cross sectional economic analysis Joyce et al²⁰¹ found that between 1980 and 1989 the incidence of LBW attributable to illicit drug use (mainly cocaine) in New York City, US increased from 3.2 to 7.3% accounting for an excess cost of \$18 - \$41 million in neonatal care.

Intervention:

There is no controlled trial directly assessing the efficacy of prevention of cocaine use.

Chazotte et al²⁰² compared cocaine using mothers who received prenatal care and those who did not receive prenatal care. They found that mothers who received prenatal care had significantly lower incidence of LBW (34.3% vs 52.3%, $p < 0.05$).

Chasnoff et al²⁰³ found that women who stopped cocaine use in the first trimester of pregnancy gave birth to infants with no difference in birth weight from that of non-cocaine users. There was a significantly higher incidence of SGA and preterm births among mothers who continued to use cocaine throughout the pregnancy.

Local perspectives:

Forman et al²⁰⁴ assessed fetal cocaine exposure using neonatal hair and urine tests for benzoylecgonine among 600 babies born in 3 nurseries in Toronto from 1990-91. 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 to 3% (12/400) from 2 suburban nurseries. The authors predicted more than 5,000 babies annually in the greater Toronto area are cared for postnatally by mothers regularly using cocaine. This high rate from a selective population needs

confirmation. Data from Alberta¹⁸¹ indicate that the use of illicit drugs during pregnancy in the province was 1.5% in 1997, 1.6% in 1998 and 1.5% in 1999.

Conclusion:

Cocaine use is an important modifiable determinant for adverse pregnancy outcomes. Cocaine affects the fetus by various mechanisms resulting in impaired growth or initiation of labor. Nutritional deficiency secondary to compromised uteroplacental blood flow is the major mechanism involved in LBW. Cocaine is associated with reductions in birth weight and probably gestational age. Stopping cocaine use during the first trimester is associated with a non-significant impact on birth weight. However, further research is necessary. More research is required regarding effective interventions to stop cocaine use and relapse prevention in pregnant women.

e. Marijuana use:

Marijuana use has been observed more frequently among populations from larger metropolitan cities in North America.¹⁹⁸

Biological plausibility:

The exact mechanisms of action and the effects on the fetus are not well understood. In the Ontario Prenatal Prospective Study (OPPS) it was observed that mothers who used marijuana on a regular basis had a higher frequency of precipitous labor.²⁰⁵ This indicates that marijuana has some effect on uterine contractions.

Epidemiological association:

The studies reporting the association between gestational length and the use of marijuana are conflicting.

Fried et al²⁰⁶ in a review of perinatal marijuana use and effects on the fetus and the infant identified two studies that found an association between marijuana use and preterm birth. Three other studies have not found a significant effect on gestational age. Two prospective studies assessing fetal and neonatal impacts of marijuana use found no difference in preterm births.

Cornelius et al²⁰⁷ studied adolescents living in Pittsburgh, US. The exposure to marijuana was ascertained by interview. First trimester use was associated with a reduction in gestational age by 9 days. Second trimester marijuana use was associated with an increased risk for SGA (OR 3.8, 95% CI 1.2, 14).

In-utero exposure to marijuana has toxic effects resulting in adverse long-term development. Fried et al²⁰⁶ in their review indicated a probable negative impact on certain aspects of “executive function” – attention behavior, visual analysis and hypothesis testing in toddlers exposed to marijuana use during pregnancy.

Intervention:

There is no intervention study on restricting marijuana use in pregnancy.

Local perspectives:

There are no data regarding the frequency of marijuana use during pregnancy in Canada. Data reported in the section on cocaine use includes the use of all known illicit drugs.

Conclusion:

The biological mechanisms of the effects of marijuana on either birth weight or duration of gestation are not clear. The epidemiological evidence of the effect of marijuana on the incidence of preterm/LBW births is conflicting. However, there is evidence of its effect on the neurological functions in childhood. Though 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. Further research is required regarding effective intervention strategies.

f. Alternative medicine:

No study was found which assessed the safety or benefit of alternative medicine on preterm/LBW births.

g. Herbal medicine:

No properly controlled study or review was identified regarding the safety of herbal medicines in pregnancy. Gallo et al²⁰⁸ reviewed herbal products and concluded that no product has been studied adequately for safety.

h. Exercise**Biological plausibility:**

Suggested mechanisms for the benefits of exercise during pregnancy are as follows:

- Exercise improves muscle tone and helps during labor.²⁰⁹
- Exercise may improve the immunological defense mechanisms and prevent urinary tract infection, which may be a triggering factor for preterm labor.²⁰⁹
- Exercise may increase fetal weight probably by improving blood flow.²¹⁰

The suggested mechanism for the disadvantage of exercise during pregnancy is as follows:

- Heavy exercise can be stressful and may provoke labor. The biological mechanism is unknown. It is suggested that norepinephrine and prostaglandins are released after exercise, which may cause uterine contractility and trigger the onset of labor.²⁰⁹

Epidemiological association:

Kramer et al²¹¹ appraised 5 controlled studies evaluating the effect of aerobic exercise on pregnancy outcomes for the Cochrane Collaboration. The studies were of small sample size and not of high quality. The results showed an improvement in maternal fitness. There was no difference in birth weight (WMD

6g, 95% CI – 99, 111g) or gestational age (WMD 0.02 week, 95% CI – 0.4, 0.4 week). There was an increased risk of preterm birth (RR 2.47, 95% CI 1.05, 5.81) in the control group in one study. There was no difference in the duration of the gestation.

Dye et al²¹² reviewed 8 prospective observational studies reporting the effects of exercise on pregnancy outcomes from 1990-96. Only one of the eight studies reported an increase in the risk of preterm labor (OR 1.69 – 1.75) in women engaged in heavy exercise in the US Army. Of the remaining seven studies, two studies showed significant decrease in birth weight and one study reported an increase in birth weight. Only one study reported results of preterm labor and there was no difference between the two groups. Several methodological flaws were identified in the study designs.

Lokey et al²¹³ performed a review of observational studies published until 1991. There was no difference in the birth weight ($p = 0.20$) or length of gestation ($p = 0.67$) between infants born to women performing various exercises. Exercise for an average of 43 minutes/day, three times a week leading to an increase in the average heart rate to 144/minute, had no influence on the pregnancy outcomes.

Conclusion:

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

3. Environmental toxins:

a. Passive smoking or environmental tobacco smoke exposure:

In addition to active smoking, passive smoking or environmental exposure to tobacco smoke is an important determinant of LBW/preterm births.

Biological plausibility:

The mechanisms illustrated in the section on active smoking are operative for passive smoking. However, the amount of exposure is smaller compared to active smoking and thus the magnitude of the adverse consequences may be less.²¹⁴

Epidemiological association:

Misra et al²¹⁴ reviewed 11 observational studies relating environmental tobacco smoke exposure and adverse pregnancy outcomes. The reduction in mean birth weight between the exposed and non-exposed groups in various studies was between 25 to 125g. The studies adjusting for gestational age found a difference of 25 to 87g in birth weight. The major problem with these studies was the ascertainment of exposure. Various methods were employed to quantify the level of exposure. Three studies that used biomarkers confirmed a significant association between passive smoking and LBW. Three studies that examined the exposure in the first trimester of pregnancy and one study that measured cotinine

level in the second trimester of pregnancy noted a significant association with LBW. Overall there was a statistically significant reduction in the birth weight in the cohort (WMD for mean birth weight -24g , 95% CI -9g , -39g), but the clinical significance of this finding was less obvious. The difference in the incidence of LBW/SGA was significant. It was hypothesized that the effects of passive smoking “operate at the lower end of the birth weight distribution” implying that fetuses near the cut-off level of 2,500g were more affected than heavier fetuses.

Windham et al²¹⁵ performed a review of 29 studies of environmental tobacco smoke exposure. Studies with the highest quality reported a decrease in birth weight by 15-60g. The methodological problems in the studies were different methods of assessing exposure and not accounting for other biases. The pooled estimate from 22 studies revealed a difference in birth weight of 25g (95% CI 34, 16g). There was no difference in the results when only studies adjusting for other factors were combined. A pooled estimate from 16 studies reporting on risk of LBW resulted in an 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. All the results were confirmed by influential analysis (removing one study at a time and calculating the risk again).

In a study to assess the impact of double exposure Dejin-Karlsson et al²¹⁶ examined a prospective cohort over 1 year in Sweden. The risk of SGA was increased in mothers exposed to passive smoking either at home or in the workplace (OR 2.3, 95% CI 1.1, 4.6). No relationship to preterm births was found. Mothers who were exposed to active and passive smoking were at higher risk of SGA (OR 3.6, 95% CI 1.5, 8.6) reflecting double-dose effect.

Ahluwalia et al¹⁵⁰ studied the effects of passive smoking in older mothers (> 30 years of age). The risks for LBW (OR 2.42, 95% CI 1.51, 3.87) and preterm births (OR 1.88, 95% CI 1.22, 2.88) were higher for older mothers. This has important implications because of the shift in the age distribution of the first pregnancy in Canada and the US.

Intervention:

There has been no specific intervention study concerning passive smoking. The results of interventional studies of active smoking can possibly be extrapolated to passive smoking.

Conclusion:

The biological mechanisms of passive smoking or environmental tobacco smoke exposure are similar to that of active tobacco use. Epidemiological results indicate a small but significant negative effect on birth weight and an increased risk of LBW. Measures employed for reduction in active smoking will decrease the exposure of the fetus to passive smoking or environmental tobacco smoke. In addition, strategies to reduce pregnant women’s exposure to environmental tobacco smoke exposure in the work place need to be explored.

b. Environmental pollutants:

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

Biological plausibility:

There are several different pollutants in the air. In addition, air pollution varies from area to area. It is highest in the industrial areas of the world. Sulphur dioxide and total suspended particles are the major particles implicated in air pollution.²¹⁷ The biological mechanisms possibly affecting fetal growth due to outdoor air pollution are complex and currently not well understood.

The following theories have been proposed.

- Exposure to pollutants leads to increased incidence of maternal infection and illness. This may lead to increased incidence of preterm births.¹³⁵
- It has also been observed that pollution exposure leads to increase in blood viscosity. Blood viscosity is an important factor influencing placental flow and perfusion. Increased blood viscosity leads to a reduction of blood flow to the placenta, which may have consequences for the fetus.^{76;218}
- Air pollution has been shown to affect DNA transcription. DNA adducts (altered DNA) were observed in mothers exposed to high levels of air pollution. Fetal growth and birth weight are affected by DNA adducts.^{219;220}

Epidemiological association:

No review was identified. The following represent recent reports of the effects of environmental exposure on preterm/LBW births. Studies conducted through out the world have reported different results. Bobak et al²¹⁷ studied the effect of environmental air pollution in the Czech Republic in 67 different districts. The exposure was measured by calculating the mean level of pollutants every day. A dose response effect was observed [adjusted OR for LBW (1.2, 95% CI 1.11, 1.30 and 1.15, 95% CI 1.07, 1.24 for 50 microgram per m³ increase in sulphur dioxide and total suspended particles respectively) and adjusted OR for preterm (1.27, 95% CI 1.16, 1.39 and 1.18, 95% CI 1.05, 1.31 for 50 microgram per m³ increase in sulphur dioxide and total suspended particles respectively)].

Makowiec et al²²¹ performed a case controlled study based on a questionnaire in Poland assessing the effects of physical (noise, vibration, hot environment and cold environment) and chemical (anesthetic gases, lead, solvents, pigments, mercury, and pesticides) factors on pregnancy outcomes. Among the physical factors vibration during first trimester was significantly associated with LBW (9.61% vs 5.78% in the control group). Combined exposure to physical and chemical agents was associated with an increased risk of preterm birth (OR 1.82, 95% CI 1.00, 3.29). There was a tendency to report exposure to physical agents more readily than chemical agents because they were easier to appreciate.

Lin et al²²² performed a survey in 2 cities in Taiwan, one of which had a petrochemical factory. The exposure level was measured from the reports of a government agency. An increased risk of LBW was observed in term infants in the city with the factory (OR 1.767, 95% CI 1.002, 3.116).

Seidler et al²²³ performed a prospective study of 3,946 women in Germany. The level of exposure to chemicals at work was measured using a validated Job Matrix Exposure scale. The exposure to chlorophenols ($p=0.02$) and aromatic amines ($p=0.05$) involved in leather work was associated with increased risk of SGA.

Other toxins implicated in preterm labor are aldrin, dieldrin, hexachlorocyclohexane, lead and polychlorinated biphenyls. The chemicals implicated for LBW are benzene, cadmium, lead and polychlorinated biphenyls.⁹

The reports both from exposure in the environment and at work place are indicative of associated adverse perinatal outcomes.

Intervention:

No intervention studies were identified.

Local perspectives:

There are no data available on the status of exposure to pollutants among pregnant women in Canada.

Conclusion:

Exposure to environmental toxins can result in preterm/LBW births. The biological mechanisms are poorly understood for most environmental toxins. Epidemiological data are supportive of a trend towards an increase in preterm/LBW births following exposure. Additional research is needed from a local perspective. The Canadian Institute of Child Health¹⁸² suggests that the “Precautionary Principle” should be applied to reduce the impact of environmental deterioration on the health of children and youth. The “Precautionary Principle” suggests that “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”. Recommendations are needed to enforce a safe work place for pregnant women and to limit the exposure to toxins during the prenatal period.

c. Noise:

Biological plausibility:

Noise is an excessive sound, which can result in adverse effects on the cochlear system. The mechanism of noise-induced effect on preterm/LBW births is not known.

Epidemiological association:

Nurminen et al²²⁴ 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 birth (RR 1.6, 95% CI 0.9, 2.9) and the other reported no association (adjusted OR 0.7, 95% CI 0.1, 3.5). Four studies that reported on the risk of LBW found that the RR/OR ranged from 1.2 – 2.5 in the exposed group. One study found an insignificant reduction in birth weight

(WMD - 228g, 95% CI – 471, +15g). It was not possible to assess the cut off values for a noise level resulting in preterm/LBW births. All four studies that reported the effect on birth weight reported a reduction in birth weight in the exposed group. Noise exposure above 85 – 90 decibels was suggested as a probable cut off in one study.

The Committee on Environmental Health, American Academy of Pediatrics²²⁵ reviewed the effect of noise on the developing fetus. High frequency hearing loss and minor congenital malformations were reported in human and animal studies. Eight studies were reviewed. Four studies reviewed found a reduction, two studies found no effect on gestational length and two studies were inconclusive. Four studies of effect of noise on birth weight were reviewed. Three studies showed a reduction in the birth weight in the noise-exposed group. One retrospective study reported higher incidence of a birth weight <3,000g (23.8% compared to 18.1%) for women residing in an area where the noise level exceeded 60 – 65 decibels.

Conclusion:

There is lack of well-controlled observational and/or randomized studies. Available studies have suggested a possible role of noise and adverse pregnancy outcomes. It is possible that the effect of noise is a marker for other risk factors such as other environmental exposures, pattern of work or stress or duration of work. Further research controlling for other variables is needed. Strategies to decrease women's exposure to excessive noise may be beneficial in reducing adverse pregnancy outcomes. More research is needed.

4. Occupational hazards:

Duration of work, type of work and workplace activities are important factors related to pregnancy. 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. The following theories have been proposed.

- Prolonged standing reduces venous return.²²⁶ 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 and subsequent adverse outcomes.²²⁷
- Mothers who work in a standing position and who work late into gestation have an increased incidence of large uteroplacental infarcts, leading to reduced perfusion to the uterus and the placenta.²²⁸
- The development of hyperthermia following excessive activity may have an effect on the fetus.²²⁷
- Some women continue to hide their pregnancy due to 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 labor.²²⁷

Epidemiological association:

Mozurkewich et al²²⁹ reviewed 29 studies assessing the impact of work on the risk of preterm/SGA births. Case control, cross-sectional and prospective cohort studies were included. Methodological assessment of the studies was performed. Physically demanding work (defined as heavy and/or repetitive lifting or load carrying, manual labor or significant physical exertion) was statistically significantly associated with SGA (OR 1.37, 95% CI 1.30, 1.44) and preterm births (OR 1.22, 95% CI 1.16, 1.29). The association was almost similar among cross sectional and prospective cohort studies. Prolonged standing (defined as greater than 3 hours per day or 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 increased risk of preterm birth (OR 1.24, 95% CI 1.06, 1.46). The authors estimated that one preterm birth may be prevented for each 27 – 80 women who discontinue prolonged standing, for each 23 – 171 women who discontinue shift or night work and each 36 – 65 women who discontinue physically demanding work.

Simpson²²⁷ in 1993 reviewed the literature regarding physical activity and employment during pregnancy. Ten studies were identified which demonstrated the deleterious effect of work on preterm/LBW births, while six studies observed no effect of physical exertion on pregnancy outcomes. The discrepancy in the results was described as due to the following reasons. 1) The effects of confounding factors for preterm/LBW births were not assessed in detail in all studies. 2) The reason some women work late into gestation could be poor socio-economic status, the impact of which can not be separated out. 3) Simultaneous assessments of effects of occupational hazards were not considered in most studies. The reason some studies showed a positive correlation could be because of the toxin exposure rather than the duration of work. 4) Most investigators have failed to identify the importance of stress in the causation of adverse pregnancy outcomes. 5) The results may have been affected by memory and recall biases. The author concluded that the studies showing negative impact (increase in the incidence of preterm/LBW births) of work had more power than studies demonstrating no effect. However, the author cautioned against complete employment leave during pregnancy to all women. A suggestion was made to encourage women to take voluntary leave if they were experiencing occupational fatigue.

Fortier et al²²⁶ interviewed women in Quebec City, Canada in 1989 who gave birth to a singleton liveborn neonate. They found that the risk of an IUGR infant was increased for women who worked 6 hours a day in a standing position. The adjusted ORs were 1.13 (95% CI 0.83, 1.55) and 1.42 (95% CI 1.02, 1.95) for women working in a standing position for 3 - 5 hours and ≥ 6 hours respectively compared to women who were employed for < 3 hours suggesting a dose response. The risk of an IUGR birth increased for women who worked until 24 weeks of gestation (OR 1.91, 95% CI 1.12, 3.25). The rate of preterm births

was not increased in this study even for women employed in a job involving prolonged standing, shift work or lifting heavy objects. There was a higher incidence of preterm births for women who stopped work between 24 - 31 weeks of gestation compared to women who were still working at 32 weeks. This may reflect what has been described as a “healthy worker effect”; ie women working late in pregnancy are women who are at lower risk of adverse pregnancy outcomes.

Hanke et al⁶¹ interviewed a group of women during the postnatal period in Poland and found that 25% of all pregnant women remained in their employment for more than 6 months during pregnancy. There was no increase in the risk for SGA births for women who worked for < 3 months or > 6 months compared to women who worked 3 – 6 months. Among mothers of SGA infants the rate of heavy physical work was higher (OR 3.51, 95% CI 1.32, 9.14).

Wergeland et al²³⁰ studied the impact of work pace control and pregnancy outcomes. In this questionnaire based study authors attempted to evaluate the impact of power to control work pace by a pregnant women, measured by self-reported influence on breaks and work pace without the impact of external influences. The crude OR for no control versus high control was 2.7 (95% CI 1.1, 6.9) for LBW in nulliparous women. Women in paid work with better power to control their own work pace had a low risk of LBW.

Nurminen et al²²⁴ reviewed 3 studies reporting the effects of shift work on pregnancy outcomes. One study from China reported increased risk (adjusted OR 2.0, 95% CI 1.1, 3.4) for preterm birth, one study from Montreal, Canada reported elevated observed/expected rate of preterm birth rate (1.6, nonsignificant difference) and one study from France reported no statistically significant difference in the preterm birth rate (3.9% vs 4.8%) with shift work. The study from China also reported an increased risk of LBW with shift work (adjusted OR 2.1, 95% CI 1.1, 4.1). Overall rotating shifts and night shifts were indicative of increased risk of preterm/LBW births.

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.

Manshande et al²³¹ 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 to women who continued heavy physical activity. All infants were born full-term. The duration of rest had a strong influence on birth weight of the infant. There was a net increase of 334 grams in female infants but no difference in the birth weight of male infants.

Local perspectives:

As the number of employed women is increasing in developed nations it would not be erroneous to assume that in Canada the number of employed women is high. We do not have actual data for the percentage of pregnant women employed at the national, provincial or local level to extrapolate these

findings. However, the problem is recognized as a public health issue. Current legislation allows pregnant women to take 17 weeks of pregnancy leave and 35 weeks of parental leave during each pregnancy.

Conclusion:

The evidence from epidemiological studies on work, type of work, shift work and control at workplace indicates that physically demanding work increases the risk of SGA/LBW/preterm births. The biological mechanisms underlying the effect of work on pregnancy are unclear. Several mechanisms are probably working simultaneously. Further research is needed to ascertain biological mechanisms, the amount of work exposure, the timing of the exposure and the effects of work control during pregnancy. Current information on the magnitude of the problem from a local perspective is needed. Though the evidence for efficacy is poor, it seems logical to avoid prolonged work related exertion by pregnant women.

5. Violence/abuse:

Violence or abuse during pregnancy poses threats both to the mother and the fetus.

Biological plausibility:

The mechanism by which violence may lead to adverse pregnancy outcomes could be either a direct or indirect influence.

- Direct influences include trauma to the abdomen leading to release of arachidonic acid initiating contractions and preterm labor,²³² rupture of fetal membranes, placental abruption or rarely rupture of the uterus.²³³ All these conditions lead to preterm births.
- Indirect influences include resultant ongoing psychological stress from violence. This may lead to depression and adoption of risky or dangerous behaviors such as use of tobacco, alcohol or illicit drugs or inadequate utilization of health services. All these behaviors are associated with preterm/LBW births.²³⁴
- The pathway of stress leading to the onset of labor has been theorized as due to changes in the hormonal homeostasis. (please refer to section on psychosocial factors).

Epidemiological association:

The reported incidence of violence in published studies probably does not reflect the actual incidence.

Murphy et al²³³ performed a systematic review of the studies reporting violence during the prenatal period. The review included 6 cohort studies and 2 case controlled studies with marked heterogeneity among the populations included in the studies. The rate of violence varied from 5.6% to 16.6%. The definition of violence differed among the studies and there were differences in the time at which the mothers were assessed. Most studies used interview based standardized questionnaires or assessment tools. In six studies the mothers

were interviewed during the prenatal period while in 2 studies data were collected postnatally. The results of the individual studies showed a tendency towards an increased risk of LBW but this finding was statistically significant in only one study. The combined results showed a statistically significant increased risk of LBW (OR 1.36, 95% CI 1.06, 1.75) for women exposed to violence/abuse. The reduction in birth weight ranged from 19 to 133g in five studies that reported the difference in birth weights.

Gazmararian et al²³⁵ reviewed the method of assessing or ascertaining the incidence of abuse across various studies. The incidence of abuse during pregnancy varied between 0.9 - 20.1% among the studies. There were differences between studies in terms of how violence was measured, the population studied and the methods of assessment. The prevalence was higher in the studies in which violence/abuse was assessed more than once during pregnancy or when ascertained later in the pregnancy (7.4 - 20.1%). The incidence was lower among the mothers attending private clinics and when personnel other than a health care provider asked the questions.

Covington et al²³⁴ performed a prospective cohort study between 1994-96. Pregnant women were administered a validated questionnaire 3 times during pregnancy. The incidence of reported violence was 16.1% among adolescents compared to 11.6% in adults. The rate of severe violence was 9.4% among adolescents. Adolescents reported a higher rate of abdominal trauma compared to adults (56% vs 22%). The risk of preterm labor was statistically significantly increased among adolescents (OR 3.5, 95% CI 1.1, 10.8). The risk for adult women did not reach statistical significance. In addition, severe violence increased the risk of preterm/LBW births compared to no violence or non-severe violence (OR 3.0, 95%CI 1.1, 8.1). All 4 adolescents who reported trauma to the abdomen delivered preterm. The authors hypothesized several reasons for increased violence and why the abdomen was a target among adolescents. Firstly, adolescent fathers in the denial phase disagreed about their role in causing the pregnancy due to lack of understanding. Secondly, protrusion of the abdomen was the most obvious visible sign of pregnancy. Thirdly, adolescent fathers had not come to terms with the responsibilities of their role as a father. Lastly, adolescent fathers may have suspicions of the female partner regarding paternity.

National perspectives:

There are no data available for the entire Canadian population. Individual Canadian studies have reported the incidence of violence in pregnancy as 5.5 - 6.6%.^{236;237} The reported incidences probably under-represent the magnitude of the problem.

Intervention:

Further research is needed regarding effective strategies to identify and respond to violence/abuse in pregnancy.

Conclusion:

Reported prevalence of violence/abuse during pregnancy varies. Violence/abuse are important factors in the causation of adverse pregnancy outcomes. Direct effects of trauma and indirect influences such as stress and risk-taking behaviors following abuse are possible biological mechanisms. The epidemiological evidence is suggestive of violence/abuse as one of the factors in the causation of preterm/LBW births. It is important to investigate the possibility of violence during the prenatal period with all pregnant women. There is a need to develop and implement a comprehensive assessment tool to identify violence/abuse during pregnancy. The Society of Obstetricians and Gynecologists of Canada²³⁸ recommends prenatal screening and identification of women who are victims of violence/abuse. The Antenatal Psychosocial Health Assessment (ALPHA) form can help health care providers in assessing the risk factors.²³⁹ Vigilant assessment and recognition of signs of violence/abuse during antenatal contacts may reduce adverse perinatal outcomes including preterm/LBW births.

6. Antenatal care:

Throughout the world antenatal care is provided to pregnant women. The emotional component attached with the provision of antenatal care prevented researchers for years from testing its efficacy. The primary aim of providing such a wide scale health service is to reduce adverse consequences for the mother and the fetus. The psychosocial component of antenatal care is covered in the section on psychosocial factors. This section represents the evaluation of the medical component of antenatal care.

Biological plausibility:

There is no known direct biological mechanism by which antenatal care directly influence pregnancy outcomes.²⁴⁰ Screening of mothers, identification of maternal or fetal problems, appropriate nutritional advice, counseling against substance use, psychosocial support and early intervention are the key components of antenatal care. The biological plausibility related to certain specific components is addressed in the relevant sections of the report.

Epidemiological association:

Blondel et al¹⁵⁴ reviewed the efficacy of antenatal programs. A total of 11 randomized controlled trials were identified. Three trials were excluded (one because of methodological issues, one where antenatal care provision was a part of a larger intervention program and one due to unusable outcomes of interest for the review). Of the eight studies only 3 studies provided medical care during antenatal visits while the remaining 5 provided social support (reviewed in psychosocial/stress/socioeconomic factors). The programs included home visits by community midwives at frequent intervals to provide medical care to high-risk women such as those with complicated pregnancy, threatened preterm labor and gestational age between 20-36 weeks. These studies did not show any difference in the risk of preterm birth (OR 1.0, 95% CI 0.8, 1.1). The absence of a beneficial effect was perceived to be due to problems in the study methods.

Women who consented to participate could have been more health conscious or women with the knowledge of being in the control group might have adopted different behaviors.

Carroli et al²⁴¹ reviewed randomized controlled trials of routine antenatal care. Seven studies were identified. There was no difference in the risk of LBW (OR 1.04, 95% CI 0.93, 1.17) between a “model with reduced number of prenatal visits” and a traditional model. Two studies had high attrition rates. A sensitivity analysis was performed to assess estimates excluding these two trials. The sensitivity analysis did not change the results. There was no difference in perinatal mortality (OR 1.06, 95% CI 0.82, 1.36). The studies included were of high quality however there was mild to moderate degree of bias. This included unmasked ascertainment of outcomes, co-intervention, protocol deviation and unclear intention to treat analysis in some studies.

Villar et al²⁴² performed a multicenter randomized controlled trial in 4 countries assigning mothers to either standard prenatal care or a “new model” with reduced number of prenatal visits based on risk assessment. More than 20,000 women participated in this quantitative and qualitative research. No statistically significant difference in the rate of LBW (adjusted OR 1.06, 95% CI 0.97, 1.15) was found. A significant reduction in the number of prenatal visits in the “new model” was observed compared to the traditional model without any significant difference in maternal satisfaction.

Orvos et al²⁴³ compared the outcomes of pregnancies of women delivered following prenatal care and those who delivered after no prenatal care. Between 1996 and 1998 at the University of Szeged, Hungary, 54 (1%) of the total 5,262 deliveries had no prenatal care. A case controlled comparison (control n=108) was performed. There was higher incidence of preterm births (OR 3.1, 95% CI 1.4, 6.8) and lower mean birth weights ($p < 0.001$) in women without any prenatal care.

Hodnett et al²⁴⁴ reviewed the effect of continuity of care during pregnancy and childbirth and the puerperium for the Cochrane Collaboration. Two studies including a total of 1815 women were reviewed. The trials were of good quality. 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 to 0.97), and an increase in the attendance in educational programs (OR 0.58, 95% CI 0.41 to 0.81) in the continuity of care group. There was no reduction in the risk for preterm birth (RR 0.97, 95% CI 0.68, 1.39). There was increased satisfaction with care among mothers in the continuity of care group.

Local perspectives:

The provision of antenatal care in Canada is similar to that in other developed countries. In addition, there is the advantage of free access of medical care. Data regarding the percentage of women not utilizing antenatal care in Canada are not available.

Conclusion:

Prenatal care is the entry point for pregnant women to the health care system. The medical component has the capability to identify at risk pregnancies. Prenatal visits provide a platform to assess risk factors associated with pregnancy, counseling and further management. Case controlled study has provided some insight in the effectiveness of prenatal care in reducing preterm/LBW births. It is not ethical to perform a randomized controlled study. The randomized controlled trials have compared a reduced visit model to a standard care model and showed no difference in terms of fetal growth or preterm births. However, provision of prenatal care has advantages at an individual level. 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 to care provided by several different health professionals.

C. Uterine factors:

Structural abnormalities in the uterus are associated with a higher incidence of preterm birth. Uterine anomalies can account for 3 -16% of preterm births. Unicornuate, bicornuate and didelphic uterus can result in preterm labor in 18 - 80% of women with such abnormalities. Uterine leiomyomas have been associated with preterm labor due to bleeding or preterm prelabor rupture of the membranes.²⁴⁵

Cervical incompetence due to several reasons can result in preterm labor. In-utero exposure of Diethyl Stilbestrol (DES) can cause structural abnormalities in the uterus and cervical incompetence. This has led to numerous abortions and preterm births. This was observed over a 30 year period (1940 - 1971), and the drug is no longer used. Trauma following obstetric or gynecological procedures may lead to cervical incompetence.²⁴⁵

Uterine factors as a cause of growth restriction are mainly secondary to vascular phenomena and will be considered in the section regarding placental factors.

D. Placental factors:

The placenta functions as a nutrient supplier and gas exchanger. Both of these functions are necessary for maintaining proper fetal growth. Birth weight has been shown to demonstrate a relation with the 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 gonadotrophins from the placenta, which is responsible for mobilization of the maternal stores. Further in the process, thickening of the vascular membranes of the placenta causes reduction in the blood flow. The placental causes of IUGR are listed in appendix 5.^{1;15;245}

E. Pharmacological factors:

The most common manifestation of drug administration to mothers is teratogenicity. Many of the malformation syndromes are associated with IUGR.

The effect of pharmacological factors on birth weight may represent a part of a larger spectrum. The drugs associated with IUGR are listed in appendix 6.

Toxic effects of the drugs can be due to their appetite suppressant effects, direct effects on cell replication (heroin, methadone, alcohol, antimetabolites) or interference with the transport of aminoacids (cocaine, alcohol).²⁴⁵

F. Paternal factors:

Biological plausibility:

LBW and preterm births tend to occur again in the same family. Genetic factors play a significant role in the recurrence. The mechanism regarding the role of paternal factors is not clear. Paternal factors are important in certain genetic conditions that may result in LBW.

Epidemiological association:

No review was identified. The following represents details from individual studies on the subject.

Basso et al²⁴⁶ studied the effects of paternal factors in a fertility database in Denmark. Fathers who had an index LBW/preterm child were followed. The birth weight of the next child was not affected whether they remained with the same female partner or changed partner. There was no impact of the father's occupational status, residence or social status with LBW.

Klebanoff et al²⁴⁷ studied a cohort of mothers and ascertained the father's birth weight and adult BMI. Fathers who weighed less than 3 kg at birth had an infant that was 176g lighter and fathers who weighed 3 - 3.9 kg had an infant that was 109g lighter than a father who weighed > 4 kg at birth. Fathers who had a BMI of < 20.08 kg/m² had infants who were 105g lighter compared to fathers with a BMI > 23.05 kg/m². Paternal birth weight, adult height and adult weight explained 3% of variance in the birth weight of the offspring.

Father's occupation has been shown to play a role in the risk of preterm labor. Fathers employed in glass, clay, textile and mining occupations have a higher risk of preterm births. Fathers working in art and textile occupations have a higher risk of SGA births.²⁴⁸

Conclusion:

Paternal genetic factors may play a role in the constitution of an infant. The evidence is currently insufficient and further research is needed. Paternal occupations involving handling of chemical hazardous substances require further research to identify the role in preterm/LBW/SGA births.

G. Fetal factors:

1. Sex:

Biological plausibility:

The biological mechanisms of influence of sex of the fetus on pregnancy outcomes are not clear. On average, the weight of a male fetus is 150g higher than that of a female fetus. The difference in fetal weight starts to appear at 28 weeks gestation. It 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.¹⁰⁴

Epidemiological association:

Male infants are known to have higher incidences of adverse outcomes in follow up studies of preterm and LBW infants. No reviews examining the effect of sex on preterm/LBW births were identified. The following represents information from individual studies.

Kesmodel et al³¹ in a cohort study of the effect of alcohol on preterm delivery reported that the risk for preterm birth was 4.3% in males compared to 4.0% for females (RR 0.92, 95% CI 0.80, 1.06). Frisbie et al³² found no significant difference in the risk for male infants compared to female infants for IUGR (OR 1.0, 95% CI 0.8, 1.1) or for preterm birth (OR 1.5, 95% CI 0.9, 2.5).

Chen et al²⁴⁹ in a study of twin pairs found that female twin pairs had longer gestation (29.2 ± 2.5 weeks) compared to either male twin pairs (27.4 ± 2.0 weeks) or male-female twin pairs (27.0 ± 3.0 weeks).

Conclusion:

Based on these studies there is no conclusive evidence of difference in the risk of IUGR/preterm births in relation to sex of the infant. Male newborns are of higher weight compared to female newborns, which may have some effect at the lower end of the spectrum of the definition of LBW.

2. Genetic factors:

Biological plausibility:

There is variation in the normal birth weight in different populations. The variability is commonly due to maternal environmental and hereditary factors and a small proportion is due to fetal genotype. The difference in the birth weight of male and female neonates may be related to the genetic material carried on the “Y” chromosome. Among the chromosomally abnormal infants 22 - 38% are IUGR.^{1;105;245;250} The alteration in fetal growth may be due to the effects on cell division. Autosomal dominant, recessive or polygenetic inheritance can affect fetal growth. A list of some of the syndromes associated with a reduction in fetal growth is included in appendix 7.

Epidemiological association:

Several associations suggest the role of genetic factors in preterm births. Higher risk of preterm birth in mothers with a history of a previous preterm birth, racial predispositions and implication of certain single gene disorders favor the possibility of a genetic predisposition.²⁵¹ Maternal hyperhomocystinemia

predisposes mothers to an increased risk of preeclampsia, recurrent miscarriage and placental abruption. This may lead to preterm labor. Mutations in the gene encoding methyltetrahydrofolate reductase causes elevated levels of homocystine in mothers.

Interventions:

Wang et al.²⁵² have proposed a study of 500 preterm infants, their parents and 500 control maternal age-matched term infants. The plan is to examine candidate genes responsible for decidual chorioamniotic inflammation, maternal and fetal stress, uteroplacental vascular lesions and susceptibility to environmental toxins.

Conclusion:

Genetic factors may be playing a role in preterm/LBW births. Further research is needed.

H. Multiple births:

Biological plausibility:

The biological mechanism of multiple births causing preterm labor is probably due to stretching of the myometrium leading to initiation of labor.

Epidemiological association:

A rise in the frequency of multiple birth and preterm births was noticed in Canada in the years 1992 - 94 compared to 1981 - 83.²⁰

Since the birth of the first baby via invitro fertilization in 1978²⁵³ there has been a steady increase in the number of infants born through assisted reproductive technologies. The success rate with these techniques has increased in the last decade.²⁵⁴ A similar increase in the rates of multiple births has been observed in the US.^{255;256}

Schieve et al²⁵⁷ studied 42,463 infants born in the US between 1996 and 1997 by assisted reproductive technology compared to the remaining 3,389,098 infants born during that period. Among the singletons born after 37 weeks gestation there was an increased risk of LBW (risk ratio 2.6, 95% CI 2.4, 2.7). There was an increased risk of multiple gestation following the use of artificial reproductive technology but its use was not associated with further increase in the risk of LBW in multiple births. The total percentage of infants born with assisted reproductive technologies was 0.6%. This constituted 3.5% of LBW infants born to mothers > 20 years old in 1997.

Tough et al²⁵⁴ reported on the in vitro fertilization (IVF) component of the rise in preterm births and LBW in Alberta, Canada. IVF accounted for 17.8% of the rise in LBW and 10.5% of the rise in preterm birth rates during the period 1994 - 96. There was an increased risk of LBW (RR 4.89, 95% CI 4.16, 5.74) and preterm birth (RR 5.36, 95% CI 4.64, 6.18) for IVF births compared to non-IVF births.

National perspectives:

Millar et al²⁵⁸ 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 904.5 to 1037.2 per 100,000 confinements in 1995) and triplet births and higher order births (from 8.3 to 21.7 per 100,000 confinements between 1974 and 1990). The increase was more pronounced in women over 30 years of age. The rate of preterm birth among multiple births has 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 2.5% in 1997 (excluding Newfoundland).²¹ Among multiple births the rates of preterm births are higher. In Canada (excluding Ontario) there were 4,953 twin births (2,556 preterm births: preterm birth rate 51.6/100 live births among twins) and 218 triplet or higher order multiple births (209 preterm births: preterm birth rate 95.9/100 live births among triplets) in 1997. The rise has been secondary to an increased use of fertility treatments.²¹

Conclusion:

The incidence of multiple births is increasing in Canada. In-vitro fertilization is contributing to this increase. Multiple birth puts a social and economic strain on families and society. The children are at increased risk of disabilities and birth defects.²⁵⁹ 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 Gynecologists, Canada²⁶⁰ has urged for national regulations regarding the maximum number of embryos that may be transferred in artificial reproductive treatment programs in Canada as well as the prescribing practices of the clinics and physicians in relation to ovulation inducing agents.

I. Miscellaneous factors**1. Electromagnetic beds:**

Bracken et al²⁶¹ performed a prospective study to assess the effects of electromagnetic field exposure particularly from electrically heated beds and waterbeds on fetal growth. Exposure to electromagnetic fields during pregnancy or before conception had no effect on LBW/IUGR births.

2. Licorice ingestion:

Glucocorticoids are thought to play a role in the initiation of labor. Licorice contains glycyrrhizin, which is an inhibitor of cortisol metabolism. Strandberg et al²⁶² studied 1049 women in Finland to assess the impact of licorice ingestion on preterm/LBW births. The glycyrrhizin content in licorice is approximately 0.2% in Finland. Common sweet sizes are 100 grams to 200 grams, so they contain 200 mg and 400 mg of glycyrrhizin acid, respectively. The risk of delivery before 38 weeks was increased in women consuming a high intake (≥ 500 mg/week) of glycyrrhizin (OR 2.5, 95% CI 1.1, 5.5) compared to women with a low intake (< 250 mg/week).

No other studies were identified. Further research on this possible association is needed before reaching any conclusions. Until such evidence is available, women should be informed of the potential risks of excessive ingestion of licorice.