

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.