

## 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 al<sup>23</sup> 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,<sup>29</sup> 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,<sup>30</sup> 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,<sup>31</sup> 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 al<sup>32</sup> 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.<sup>33</sup>

- Short interpregnancy interval may result in inadequate replenishment of maternal nutrient stores and reduced fetal growth.<sup>34</sup>
- Short interpregnancy interval can lead to increased stress and preterm/LBW births.<sup>34</sup>
- 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.<sup>33;35</sup>
- 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.<sup>34</sup>
- 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.<sup>34</sup>

### 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 al<sup>33</sup> 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 al<sup>34</sup> 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 al<sup>35</sup> 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 al<sup>36</sup> 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  $\geq$  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  $\geq$  3 months,  $p < 0.001$ ).

Ekwo et al<sup>37</sup> 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 al<sup>38</sup> 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 al<sup>39</sup> 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 al<sup>40</sup> 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 al<sup>41</sup> 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 al<sup>42</sup> 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 al<sup>30</sup> 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 al<sup>31</sup> 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.<sup>43;44</sup> 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.<sup>43</sup> 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.<sup>45</sup>
- Geronimus<sup>46</sup> 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, US<sup>47</sup> 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 al<sup>48</sup> 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 al<sup>49</sup> 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 al<sup>50</sup> 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).<sup>51</sup>

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 al<sup>30</sup> 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.<sup>52</sup> 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)<sup>18</sup> 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.

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

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.<sup>43</sup> 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.<sup>43</sup> 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.<sup>43</sup> 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.<sup>53</sup>
- Poor blood supply to the genital tract leads to an increased incidence of infections, which may act as a trigger for preterm birth.<sup>54</sup>
- 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.<sup>54</sup>
- 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.<sup>53</sup>
- 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.<sup>53</sup>

Roth et al<sup>53</sup> 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.<sup>55</sup>

##### **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 al<sup>56</sup> 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 al<sup>57</sup> 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.

Slap<sup>58</sup> 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  $\leq 5$  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  $\geq 40$  years old).<sup>9</sup>

### **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 al<sup>59</sup> 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.<sup>26</sup>

<b>Table 2. Toronto Residents - Live Births 1997</b>						
	<b>Age of Mother</b>					
	<b>15-19</b>	<b>20-24</b>	<b>25-29</b>	<b>30-34</b>	<b>35-39</b>	<b>40-44</b>
<b>Total Live Births</b>	970	3,895	8,670	11,014	5,725	1,032
<b>Population Estimate</b>	66,810	85,520	115,335	121,277	111,014	97,644
<b>Age Specific Fertility Rate/1000</b>	14.5	45.5	75.2	90.8	51.6	10.6
<b>Singleton Births</b>	952	3,826	8,499	10,733	5,562	1,018
<b>With Known Weight</b>	952	3,824	8,497	10,731	5,562	1,017
<b>Singleton LBW</b>	70	237	478	516	320	72
<b>% LBW</b>	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.<sup>53</sup>

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.<sup>53</sup> The social, economic and educational challenges resulting from adolescent pregnancy are associated with intergenerational disadvantages for both the mother and the child.<sup>4</sup>

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 al<sup>23</sup> 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 al<sup>60</sup> 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 al<sup>61</sup> 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 al<sup>32</sup> 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 al<sup>31</sup> 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.<sup>62</sup> 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.<sup>4;63</sup>

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.<sup>64</sup>

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 al<sup>62</sup> 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.<sup>62</sup> Uncontrolled experiments of infusion of glucose and amino acids into the amniotic fluid surrounding human fetuses have shown benefit.<sup>65</sup> This method has not been tested in other studies.

Uncontrolled experiment<sup>65</sup> 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 al<sup>66</sup> 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 al<sup>67</sup> 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:**

Kramer<sup>68</sup> 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:**

Kramer<sup>69</sup> 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.<sup>62</sup>

**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.<sup>63</sup>

Kramer<sup>70</sup> 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 al<sup>71</sup> 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 al<sup>72</sup> 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.<sup>73</sup> Several mechanisms for the association of iron deficiency and adverse pregnancy outcomes have been proposed.

- Godfrey et al<sup>74</sup> 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.<sup>75</sup>
- Chronic hypoxia resulting from anemia itself can cause release of stress hormones including CRH.<sup>75</sup>
- Iron deficiency anemia per se predisposes women to increased risk of infection.<sup>75</sup>
- High hemoglobin leads to increased viscosity and sluggishness of circulation and reduced uteroplacental blood flow. This can lead to IUGR births.<sup>76</sup>

**Epidemiological association:**

Rasmussen<sup>73</sup> 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).

Mahomed<sup>77</sup> 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 al<sup>78</sup> 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 al<sup>79</sup> 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 al<sup>80</sup> 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 al<sup>81</sup> reported megaloblastic anemia in 3.4% and folate deficiency in one third of pregnant women.

**Epidemiological association:**

Mahomed<sup>82</sup> 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.

Ramkrishnan<sup>79</sup> 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 al<sup>80</sup> 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.<sup>83</sup>

**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 al<sup>84</sup> 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 al<sup>80</sup> 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.<sup>79</sup>

#### **Epidemiological association:**

Makrides et al<sup>85</sup> 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 al<sup>86</sup> 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 al<sup>80</sup> and Ramkrishnan et al<sup>79</sup> 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.<sup>79</sup> The biological mechanism is not clear.

**Epidemiological association:**

Mahomed et al<sup>87</sup> 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 al<sup>79</sup> and Ramkrishnan et al<sup>80</sup> from their reviews.

Osendarp et al<sup>88</sup> 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 al<sup>79</sup> 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 al<sup>89</sup> 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 al<sup>90</sup> 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 al<sup>79</sup> 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 B<sub>6</sub>:**

Vitamin B<sub>6</sub> is an important co-enzyme for protein metabolism. Ramkrishnan et al<sup>79</sup> reviewed one randomized controlled study of 50 mothers who received 7.5 mg of Vitamin B<sub>6</sub> or placebo. There was no difference in the birth weight of these infants. The study lacked power. Further research in women deficient in B<sub>6</sub> is needed.

**(xiii). Vitamin B<sub>12</sub>:**

Vitamin B<sub>12</sub> is involved in metabolic functions and DNA synthesis. Ramkrishnan et al<sup>79</sup> reviewed 2 observational studies of Vitamin B<sub>12</sub> status and risk of preterm labor. Both studies revealed an association of low Vitamin B<sub>12</sub> 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 al<sup>79</sup> 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 al<sup>79</sup> 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 al<sup>79</sup> 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 al<sup>79</sup> 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.<sup>91</sup>
- 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 (PGE<sub>2</sub> and PGF<sub>2α</sub>) involved in the triggering of parturition.<sup>91</sup>
- Long chain n-3 fatty acids increase the formation of PGI<sub>2</sub> and PGI<sub>3</sub> leading to relaxation of myometrium and prolongation of the gestation.<sup>91</sup>
- Long chain n-3 fatty acids lower the thromboxane/prostacyclin ratio and blood viscosity leading to improved placental blood flow and subsequently fetal growth.<sup>91</sup>
- N-3 fatty acids are believed to protect against preeclampsia and pregnancy induced hypertension.<sup>91</sup>

**Epidemiological association:**

de Onis et al<sup>80</sup> 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 al<sup>91</sup> 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 al<sup>92</sup> 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 al<sup>79</sup> 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.<sup>93</sup> The review of Canadian Prenatal Nutrition Programs by Health Canada<sup>94</sup> 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.<sup>95</sup>

### **Local perspectives:**

The “Toronto Healthiest Babies Possible Program (HBP)” was launched in Toronto in 1979 and is still ongoing.<sup>96:97</sup> 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.<sup>95</sup> 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.<sup>95</sup> From an epidemiological standpoint the results reported so far lack methodological rigor.<sup>95</sup> 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 al<sup>64</sup> 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).<sup>98</sup>

##### **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.<sup>99</sup>
- 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.<sup>99</sup>
- Early nutritional insult can result in poor plasma volume expansion and insufficient development of maternal tissues for support of the fetus.<sup>99</sup>
- 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 al<sup>99</sup> 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 al<sup>64</sup> 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.<sup>64</sup>

Luke et al<sup>64</sup> 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 al<sup>100</sup> 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 al<sup>101</sup> 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 al<sup>102</sup> 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.<sup>1;7;15;103-105</sup>

Chronic maternal hypertension resulting either from renal parenchymal diseases or essential hypertension can reduce fetal growth by a factor of 2 - 3.<sup>103</sup> This may be due to a reduction in blood flow or an increased risk of developing preeclampsia. The mechanism is unclear.<sup>103</sup> 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.<sup>103</sup>

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.<sup>1;7;15;103-105</sup>

### **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.<sup>106</sup>

Misra et al<sup>107</sup> 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.<sup>108</sup>

Maternal infection with rubella, cytomegalovirus, malaria, syphilis, varicella, herpes, *Listeria*, Epstein-Barr virus and Chagas disease can cause fetal growth restriction.<sup>1;15;103-105</sup> 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.<sup>104</sup>

### 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*.<sup>109</sup> Estrogen affects the distribution of these organisms through out the life of a woman.<sup>110</sup>

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.<sup>111</sup> The evidence supporting<sup>112-115</sup> the trigger for the onset of labor from biochemical studies is as follows:

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

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.<sup>121</sup>

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 al<sup>121</sup> 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.<sup>110;114</sup> Gardnerella vaginalis, Bacteroides, Peptostreptococcus, Ureaplasma or Mycoplasma species replace the normal flora.<sup>109;110;113;114</sup> The incidence of BV among pregnant women in general is reported to be 10 - 41% and more than 50% in high-risk populations.<sup>109</sup> The method of ascertainment of BV is important in detecting the prevalence of BV. Krohn et al<sup>122</sup> 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 al<sup>123</sup> 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 al<sup>109</sup> 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 al<sup>110</sup> reviewed studies of vaginal infection and obstetric outcomes. They concluded that these infections were linked to preterm/LBW births.

Yost et al<sup>114</sup> 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 al<sup>115</sup> 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 al<sup>124</sup> 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 al<sup>125</sup> 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 al<sup>109</sup> 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 al<sup>124</sup> 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 al<sup>126</sup> 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 al<sup>127</sup> 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 ( $38.5 \pm 1.5$  weeks in the treatment group vs.  $39.8 \pm 1.3$  weeks in the control group).

Klebanoff et al<sup>128</sup> 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.<sup>129</sup>

### Intervention:

Brocklehurst et al<sup>129</sup> 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.<sup>130</sup> Fiumara et al<sup>131</sup> 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 al<sup>130</sup> 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.<sup>132</sup> Women harboring bacteria in the urinary tract are symptomatic or asymptomatic. Asymptomatic bacteriuria results in pyelonephritis in approximately 30% of untreated women.<sup>133</sup>

**Intervention:**

Vazquez et al<sup>134</sup> 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 al<sup>133</sup> 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.<sup>121</sup>
- 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.<sup>135</sup>

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.<sup>112</sup> 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 al<sup>112</sup> 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 al<sup>136</sup> 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 al<sup>137</sup> 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 al<sup>138</sup> 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 al<sup>139</sup> 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 al<sup>140</sup> 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.<sup>141</sup> No review addressing the outcomes of interest was identified.

**Epidemiological association:**

Offenbacher et al<sup>141</sup> 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.<sup>142</sup> 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.<sup>143;144</sup> Psychosocial factors are interrelated. Economic potential, occupation and educational achievement are commonly used measures of the socioeconomic status of an individual.<sup>145</sup> Disadvantaged people are exposed to long standing psychological stress and economic constraints<sup>146</sup> 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.<sup>44</sup> 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.<sup>147</sup> 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.<sup>44</sup> 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.<sup>147</sup>

#### **2. Immunological/ infection induced changes:**

Animal experiments have indicated that stress hormones released due to chronic stress lead to immunosuppression<sup>44</sup> and alteration of both cellular and humoral immunity. The altered immune responses make the host susceptible to