

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

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

## **F. Paternal factors:**

### **Biological plausibility:**

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

### **Epidemiological association:**

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

Basso et al<sup>246</sup> studied the effects of paternal factors in a fertility database in Denmark. Fathers who had an index LBW/preterm child were followed. The birth weight of the next child was not affected whether they remained with the same female partner or changed partner. There was no impact of the father's occupational status, residence or social status with LBW.

Klebanoff et al<sup>247</sup> studied a cohort of mothers and ascertained the father's birth weight and adult BMI. Fathers who weighed less than 3 kg at birth had an infant that was 176g lighter and fathers who weighed 3 - 3.9 kg had an infant that was 109g lighter than a father who weighed > 4 kg at birth. Fathers who had a BMI of < 20.08 kg/m<sup>2</sup> had infants who were 105g lighter compared to fathers with a BMI > 23.05 kg/m<sup>2</sup>. Paternal birth weight, adult height and adult weight explained 3% of variance in the birth weight of the offspring.

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

### **Conclusion:**

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

## **G. Fetal factors:**

### **1. Sex:**

#### **Biological plausibility:**

The biological mechanisms of influence of sex of the fetus on pregnancy outcomes are not clear. On average, the weight of a male fetus is 150g higher than that of a female fetus. The difference in fetal weight starts to appear at 28 weeks gestation. It is believed to be due to the effects of androgen, maternal fetal antigen difference or genetic material on the “Y” chromosome carrying genetic material for growth.<sup>104</sup>

**Epidemiological association:**

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

Kesmodel et al<sup>31</sup> in a cohort study of the effect of alcohol on preterm delivery reported that the risk for preterm birth was 4.3% in males compared to 4.0% for females (RR 0.92, 95% CI 0.80, 1.06). Frisbie et al<sup>32</sup> found no significant difference in the risk for male infants compared to female infants for IUGR (OR 1.0, 95% CI 0.8, 1.1) or for preterm birth (OR 1.5, 95% CI 0.9, 2.5).

Chen et al<sup>249</sup> in a study of twin pairs found that female twin pairs had longer gestation ( $29.2 \pm 2.5$  weeks) compared to either male twin pairs ( $27.4 \pm 2.0$  weeks) or male-female twin pairs ( $27.0 \pm 3.0$  weeks).

**Conclusion:**

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

**2. Genetic factors:**

**Biological plausibility:**

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

**Epidemiological association:**

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

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

### **Interventions:**

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

### **Conclusion:**

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

## **H. Multiple births:**

### **Biological plausibility:**

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

### **Epidemiological association:**

A rise in the frequency of multiple birth and preterm births was noticed in Canada in the years 1992 - 94 compared to 1981 - 83.<sup>20</sup>

Since the birth of the first baby via invitro fertilization in 1978<sup>253</sup> there has been a steady increase in the number of infants born through assisted reproductive technologies. The success rate with these techniques has increased in the last decade.<sup>254</sup> A similar increase in the rates of multiple births has been observed in the US.<sup>255;256</sup>

Schieve et al<sup>257</sup> studied 42,463 infants born in the US between 1996 and 1997 by assisted reproductive technology compared to the remaining 3,389,098 infants born during that period. Among the singletons born after 37 weeks gestation there was an increased risk of LBW (risk ratio 2.6, 95% CI 2.4, 2.7). There was an increased risk of multiple gestation following the use of artificial reproductive technology but its use was not associated with further increase in the risk of LBW in multiple births. The total percentage of infants born with assisted reproductive technologies was 0.6%. This constituted 3.5% of LBW infants born to mothers > 20 years old in 1997.

Tough et al<sup>254</sup> reported on the in vitro fertilization (IVF) component of the rise in preterm births and LBW in Alberta, Canada. IVF accounted for 17.8% of the rise in LBW and 10.5% of the rise in preterm birth rates during the period 1994 - 96. There was an increased risk of LBW (RR 4.89, 95% CI 4.16, 5.74) and preterm birth (RR 5.36, 95% CI 4.64, 6.18) for IVF births compared to non-IVF births.