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Prevention of preterm delivery in twin pregnancy

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The incidence of twin gestation has increased markedly over the past decades, mostly because of increased use of assisted reproductive technologies. Twin pregnancies are at increased risk of preterm delivery (i.e. birth before 37 weeks of gestation). Multiple gestations therefore account for 2–3% of all pregnancies but constitute at least 10% of cases of preterm delivery. Complications from preterm birth are not limited to the neonatal period, such as in retinopathy of prematurity, intraventricular haemorrhage, necrotising enterocolitis, respiratory disorder and sepsis; they can also constitute sequelae such as abnormal neurophysiological development in early childhood and underachievement in school. Several treatment modalities have been proposed in singleton high-risk pregnancies. The mechanism of initiating labour may, however, be different in singleton and twin gestations. Therefore, it is mandatory to evaluate the proposed treatments in randomised trials of multiple gestations. In this chapter, we describe the results of trials to prevent preterm delivery in twin pregnancies.

Prevention of preterm delivery in twin pregnancies

The diversity in the causes of preterm delivery is reflected in the many different treatments that have been investigated and used for the prevention of preterm delivery in high-risk pregnancies. Some treatments have been directed towards reducing myometrial activity or inflammation, and others have used more mechanical approaches to prevent cervical shortening and contractions.

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For many years, bed rest has been widely used in the prevention of preterm delivery based on results from observational studies suggesting an association between hard physical activity and risk of preterm delivery. Bed rest, however, has been shown to entail potentially severe psychological and physiological maternal adverse effects [1]. A large meta-analysis investigating the effect in singleton pregnancies found no evidence of effect of bed rest, and concluded that bed rest should not be used routinely in the prevention of preterm delivery in singleton pregnancies [2]. Bed rest for multiple gestations may improve fetal growth, but a recent meta-analysis concurrently found that risk of preterm delivery may be increased in women with uncomplicated twin pregnancies [3].

A frequent cause of preterm delivery is intrauterine infections, which may in part be caused by bacterial stimulation of the biosynthesis of prostaglandins [4,5]. It has been shown that the lower the gestational age at delivery, the higher the rate of intrauterine infection [6]. Little information is available for twin cohorts. In singleton pregnancies, antibiotics have been used to treat bacterial vaginosis during pregnancy, for prevention of preterm delivery in women with preterm labour and intact membranes, or for the prevention of preterm delivery in women with preterm rupture of membranes [7]. Treatment with antibiotics may eradicate bacterial vaginosis. A recent review, however, concluded that, at present, little evidence is available of a preventive effect on preterm delivery by screening and treating women with asymptomatic bacterial vaginosis [8]. Similar results have been found for the treatment of women with preterm labour without membrane rupture. In these women, treatment with antibiotics may significantly reduce the risk of maternal infections, such as chorioamnionitis and endometritis. Meta-analyses have not found any statistically significant differences in other maternal and neonatal outcomes, including mean gestational age at delivery and rate of preterm delivery [9]. In women presenting with membrane rupture, infection seems to be either a cause or a consequence of preterm rupture of membranes. Some bacteria may produce proteases, which weaken the membranes leading to preterm rupture of membranes. In addition, infection may be secondary to rupture of membranes. Treatment with antibiotics for women with preterm rupture of membranes seems to improve short-term outcome by reducing the risk of delivery within 7 days of membrane rupture and risk of chorioamnionitis. Concurrently, risk of neonatal infection is decreased [5]. A follow-up study of children after the ORACLE trial, however, suggested that, among women with prelabour rupture of membranes, the prescription of antibiotics had little effect on health and educational achievement of children at age 7 years; in fact, prescription of the examined antibiotics (i.e. erythromycin and co-amoxiclav) for women with spontaneous preterm labour was associated with increased risk of cerebral palsy [10,11]. In conclusion, antibiotics may, therefore, be effective once membrane rupture has occurred, but evidence of a preventive effect of antibiotics in asymptomatic women is lacking.

Progesterone

Progesterone is vital for early pregnancy, and it also plays an important but not fully elucidated role later in pregnancy. Progesterone treatment in early pregnancy is used for luteal phase support after assisted reproduction technology to supplement a corpus luteum that may be functioning suboptimally owing to either ovulation induction or oocyte retrieval [12]. Progesterone may be administered vaginally as gel or pessaries containing micronised progesterone, which is progesterone identical to the form produced by the placenta and, therefore, is often referred to as natural progesterone. The synthetic compound 17-alpha-hydroxyprogesterone caproate (17-OHPC) is administered intramuscularly. Micronised progesterone may also be administered as oral treatment, but owing to a first-pass hepatic metabolism if administered orally, parenteral progesterone treatments are more effective[13]. Vaginal progesterone treatment is often considered more convenient for the patient and easier to use than intramuscular treatment. In addition, uterine first-pass may increase availability of progesterone to the myometrium. The most common side-effects to vaginal progesterone treatment are local irritation and vaginal discharge, whereas intramuscular treatment has side-effects such as injection site pain, itching, and swelling [13,14].

Accumulating evidence has shown that progesterone supplementation in the second and third trimester of pregnancy significantly reduces risk of preterm delivery in high-risk singleton pregnancies. As early as the 1950s, Arpad Csapo [15] suggested that progesterone supplementation could