Preterm Labour Management - an Evidence - Update

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Preterm birth is the leading cause of perinatal mortality and morbidity. Biologic markers, fetal fibronectin and transvaginal ultrasound scanning, have been introduced to identify the risk of preterm birth. The aim of management of preterm labour is to reduce neonatal complications. Various groups of tocolytic agents have been used, including beta-adrenergic agonists, calcium channel blockers, magnesium sulphate, prostaglandin synthetase inhibitors and oxytocin receptor antagonists. Beta-adrenergic agonists, the most widely used tocolytic agent, seem to show significant serious side effects. Calcium channel blockers and oxytocin receptor antagonists provide comparable efficacy to beta-adrenergic agonists, while giving fewer adverse effects. However, calcium channel blockers are cheaper and more convenient to administer. During 28-34 weeks of gestation, it is recommended to use tocolytics just for the first 24-48 hours waiting for fetal lung maturity after corticosteroid treatment or in utero transfer. Maintenance therapy of tocolytics is not useful in prolongation of pregnancy and does not improve perinatal outcomes. After 34 weeks of gestation there is no benefit of prolongation of the pregnancy. A single course of corticosteroid treatment is effective in preventing respiratory distress syndrome during 28-34 weeks of gestation. However, repeated treatment as a weekly course seems to do more harm than good.

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Definition

Preterm birth is the leading cause of neonatal mortality and morbidity. The definition of preterm birth is delivery before 37 completed weeks of pregnancy or 259 days from last menstrual period. However, most adverse outcome is encountered by infants born before 34 weeks, while neonatal outcome and management of preterm labour during 34-37 weeks are not different from those at term. Therefore, the diagnosis of preterm birth at 34-37 weeks is becoming less helpful. It may soon be time to adjust the clinical definition of preterm birth.

Diagnosis

Identifying threatened preterm labour is sometimes problematic. Clinical diagnosis of labour is made by observing regular uterine contraction together with cervical progression. False labour, or Braxton-Hicks contraction, may cause pain and mislead as true labour, consequently, leads to unnecessary treatment in up to 80% of cases[1]. There are several risk factors of preterm birth including low socioeconomic status, previous preterm delivery, cigarette smoking, cervical infection, urinary tract infection, intrauterine infection, multiple pregnancy, polyhydramnios, cervical incompetence, uterine anomalies and fetal anomalies. However, about half of preterm births are believed to be idiopathic and risk scoring systems provided low positive predictive value[2]. Many markers for preterm delivery have been proposed for guiding appropriate management of preterm labour, those with documented beneficial clinical use include cervical length measurement and biochemical markers of infection.

By definition, preterm labour arises with the change of the cervix, in term of softening and shortening, which can be identified by digital vaginal examination or ultrasound scanning. However, transvaginal ultrasonography appears to possess the highest sensitivity as a marker for preterm birth[3]. The risk of preterm birth increases if the cervical length is shorter than 15-20 mm at 23-24 weeks of gestation. Cervicovaginal fetal fibronectin, an extracellular ma-

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trix glycoprotein, is one of the most effective predictors of preterm delivery providing a high negative predictive value but a low positive predictive value[4]. Therefore, fetal fibronectin is helpful in avoiding unnecessary tocolytic treatment. Other predictors being studied include interleukin-6, interleukin-8, salivary estriol and serum corticotropin-releasing hormone.

Management

Some cases of preterm birth are believed to cause from cervical incompetence, which can be prevented by a cervical cerclage. Cervical cerclage is associated with a small decrease in births before 33 weeks of gestation and mild pyrexia in one largest trial[5]. However, more studies are needed before the clear benefit of cervical cerclage can be concluded[6]. Infection, in particular bacterial vaginosis and asymptomatic bacteriuria, is one of the major risk factors of preterm labour. Identifying and treatment of asymptomatic bacterial vaginosis with antibiotics is helpful in reducing preterm delivery in high risk women[7]. Asymptomatic bacteriuria appears in about 10% of pregnant women and can lead to preterm birth. Treatment of asymptomatic bacteriuria decreases the risk of preterm delivery and low birthweight[8]. Moreover, treatment with single dose antibiotics provides the same effectiveness as long course therapy[9].

In general, the aim of treatment of preterm labour is trying to extend the gestational age until the stage of neonatal survival, although in some cases no such benefit is obtained despite the success in pregnancy prolongation. There is evidence that maternal infection is associated with cerebral palsy. Therefore, in case of maternal infection, prompt delivery may lead to a better fetal outcome.

Tocolytics

Beta-adrenergic agonists, e.g. terbutaline (Bricanyl), ritodrine, salbutamol, has been used as tocolytics for almost half a century. Evidences show that beta-sympathomimetic agents are effective in postponing preterm birth during the first 24-48 hours[10]. However, maintenance use of beta-adrenergic agonists after 48 hours is not useful in reducing the risk or preterm birth and does not improve the perinatal outcome[11]. Moreover, a high incidence of adverse effects, which can be fatal, to both mother and fetus has been reported. Therefore, it is recommended to use beta-adrenergic agonists during 24-34 weeks of gestation as first-line therapy for postponing preterm birth for 1-2 days in order to wait for the maximum effect of corticosteroids on fetal lung maturity or transferring the woman to deliver at a more appropriate neonatal care centre. Maintenance long-term therapy is no longer recommended for routine practice because the risks outweigh the benefits[12].

Calcium channel antagonists, e.g. nifedipine and nicardipine, have been used as a tocolytic for more than 3 decades. Evidence-based review suggests that calcium channel blockers should be used as a first-line tocolytic because they are more effective than beta-adrenergic agonists and magnesium sulphate while causing fewer side effects[13]. Moreover, calcium channel blockers can also be used in the treatment of pregnancy-induced hypertension. Nifedipine (Adalat) can be administered 10 mg sublingually every 15 min during the first hours until contractions stopped, then 20-30 mg orally every 4 hours or 60-160 mg/day of slow release nifedipine depending on uterine contraction[14].

Magnesium sulphate has also been used as a tocolytic in the treatment of preterm labour for a long time. However, recent control studies demonstrated that magnesium sulphate is not only ineffective for delaying preterm birth, but also associated with an increased incidence of maternal side effects and perinatal mortality[15]. Therefore, some authors advise not to use magnesium sulphate as a tocolytic anymore.

Prostaglandin synthetase inhibitors can be used to inhibit cyclooxygenase (COX) enzyme and prevent uterine contractions, especially in the cases associated with polyhydramnios. The risk of premature closure of fetal ductus arteriosus is low when using before 32 weeks of pregnancy, however, there is an increased risk of necrotising enterocolitis, cerebral haemorrhage and renal failure when using before 30 weeks of pregnancy[16]. Sulindac (Clinoril) is a COX inhibitor that does not cross the placenta, consequently, causes less adverse fetal effects, in particular oligohydramnios and ductal flow velocities, than indomethacin. Nimesulide is a specific COX II inhibitor, which does not cause adverse effects on fetal ductal flow, but still results in ologohydramnios[17]. Therefore, prostaglandin synthetase inhibitors can be used as a second-line tocolytic cautiously before 32 weeks of gestation, especially in case that associated with polyhydramnios.

Atosiban (Tractocile) is a specific oxytocin antagonist which can be used as an effective tocolytic. Comparative studies exhibit that atosiban provided equal effectiveness as beta-adrenergic agonists, but

with significantly fewer side effects[18]. However, atosiban is still expensive and only provided in injection form. The development of oral oxytocin antagonists with a more specific property, i.e. not acting with vasopressin receptors, are on the way.

Prophylactic corticosteroids

The effect of corticosteroids therapy has been studied extensively. It has been established that steroids treatment reduces the incidence of respiratory distress syndrome, neonatal mortality and intraventricular haemorrhage[19]. Two doses of beta-methasone 12 mg or 6 mg of dexamethasone can be administered at 24 hours interval. The beneficial effect, particularly useful during 28-34 weeks of gestation, starts within 24 hours after administration and remains for at least 7 days[20]. Recent review supports previous reports, but suggests not to continue repeated administration of weekly course due to the increased risk of perinatal infection and neonatal death[19]. Performing amniocentesis for testing for fetal lung maturity in idiopathic preterm labour is not worthwhile anymore[21]. Administration of 10 mg of vitamin K in combination with corticosteroid may reduce the risk of cerebral haemorrhage in neonates, but the data was not supported in later review[22].

Antibiotic treatment

Antibiotic treatment in women with premature rupture of membranes results in a significant pregnancy prolongation and a reduced risk of chorioamnionitis and neonatal infection, however, the risk of necrotising enterocolitis and perinatal mortality are still the same[23]. The use of antibiotics in preterm labour with intact membranes is helpful in reducing the risk of maternal infection and necrotising enterocolitis, however, it does not reduce preterm births or prolong pregnancy[24]. More studies are needed in order to clarify the benefit of antibiotic treatment in preterm labour.

Conclusion

Preterm labour is an important and challenging obstetric problem. During 28-34 weeks of gestation tocolytic may be used for 24-48 hours to allow maximum effectiveness of steroids treatment or *in utero* transfer. Calcium channel blockers and oxytocin receptor antagonists appear to be superior as tocolytic agents to beta-agonists, with fewer side effects. At present calcium channel blockers are cheaper and more convenient to administer than oxytocin receptor antagonists. Prostaglandin synthetase inhibitors can also be used as a tocolytic. Maintenance tocolytic treatment is not recommended anymore. During 28-34 weeks of gestation administration of a single course of corticosteroid is effective in preventing respiratory distress syndrome. Repeated treatment as a weekly course is harmful and should not be given. There is no reason to prolong the pregnancy beyond 34 weeks of gestation

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