An update on prevention and management of preterm birth

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Abstract

Preterm birth is a pregnancy complication that is associated with neonatal adverse outcomes. It is considered an obstetric syndrome and several factors contribute to its pathogenesis, both of maternal and fetal origin. The knowledge of the pathogenetic mechanisms leading to preterm birth is very important in order to recognize women at risk and to perform the strategies for reducing the morbidity and mortality. Nowadays, the interventions to prevent preterm birth are represented by the administration of tocolytic and steroids drugs to mother and fetus, respectively. The development of new and safe drugs decreasing uterine contractility and infection will improve the prognosis of preterm birth.

Key words: **Preterm birth, stress, inflammation, CRH, prevention, risk factors, tocolytics.**

1. Inflammation and stress: impact on preterm birth

Preterm birth (PTB) is defined as birth before 37 weeks gestational age, occurs with an incidence of 7-11% and represents one of the most important causes of perinatal mortality and morbidity (Lockwood, 2002).

PTB may be considered a clinical syndrome that arises from different pathological processes that activate before 37 weeks of gestation one or more of the components of the pathway of parturition: cervix, fetus, fetal membranes, placenta and myometrium. This premature activation may be caused by multiple conditions, as inflammation/infection, uteroplacental ischaemia or haemorrhage, uteroplacental insufficiency (hypertension, insulin-dependent diabetes, drug abuse, smoking, alcohol consumption), uterine overdistension, cervical disease, stress and endocrine disorders, and/or other immunologically mediated processes (Romero et al., 2006) (Fig. 1).

Among all causes of PTB, inflammation, with or without infection, is a common condition leading to PTB and its pathogenetic mechanisms are related to the activation of the innate immune system (Romero et al., 2006; Romero et al., 2007; Challis et al., 2009). In this context, placenta, fetal membranes and the other key tissues activate the inflammatory pathway leading to PTB throughout the up-regulation of several molecules such as proinflammatory interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) and interleukin-8 (IL-8), chemokines and prostaglandins (PG) (Romero et al., 2002).

Therefore, the various causes of PTB act through some common mechanisms (Fig. 2):

a) ripening of the cervix: cytokines increases the production of matrix metalloproteinases (MMP-8, MMP-9), cyclooxygenase (COX)-2, PGE2, which are involved in the softening and dilation of the cervix (Sennström et al., 2000).
b) rupture of the membranes: proinflammatory cytokines increase MMP-9, collagenases and PG and decrease levels of tissue inhibitor of MMP-2, resulting in the rupture of the membranes (Xu et al., 2002).
c) myometrial contractility: TNF-α and IL-1β increase uterine contractility, the local expression

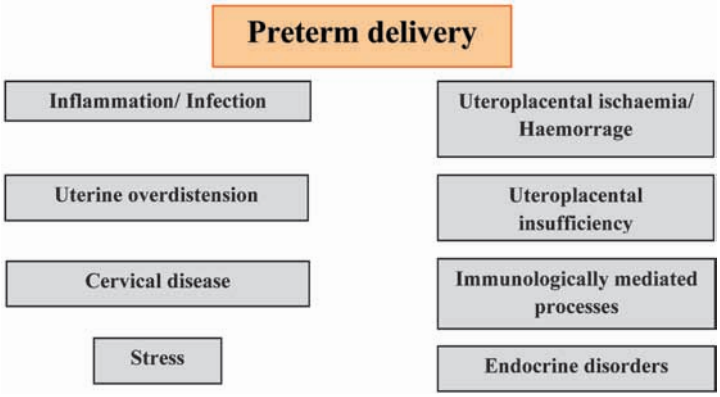

Fig. 1. — Pathogenetic mechanisms of preterm delivery

of COX-2 and the production of PGE2 (Slater et al., 1999). IL-6 up-regulates the expression of oxytocin receptors on myometrial cells (Rauk et al., 2001).

Beside inflammation, stress represent another key event for PTB (Copper et al., 1996), involving both neuroendocrine and immune functions. In this context, an increased secretion of several neuropeptides, such as corticotropin releasing hormone (CRH), occurs. It represents a key pivotal brain factor activated by all stressful conditions and modulating the endocrine (ACTH release from pituitary), the metabolic (adrenaline release from the adrenal medulla), the immune (cortisol release from the adrenal cortex) and the behavioural responses.

During pregnancy, CRH is produced by placenta and gestational tissues (Petraglia et al, 1987) and it is involved in different processes of pregnancy, as uteroplacental blood flow regulation, myometrial contractility, regulation of maternal-fetal HPA axis and feto-placental inflammatory/immune response (Petraglia et al., 2010). Concerning PTB, serum concentration and placental mRNA expression of CRH are higher than in control group (Wolfe et al., 1988; Torricelli et al, 2007) and in particular when associated with vaginal infection (Petraglia et al., 1995). Indeed, microbial invasion of the amniotic cavity represent a stress condition associated with significant CRH elevation in placenta extracts, both in maternal plasma and in amniotic fluid (Petraglia et al., 1995). To corroborate the important role of CRH in inflammatory events occurring in a recent study it was demonstrated that the expression of CRH mRNA was higher in placental tissues collected from women delivered preterm with histological chorioamnionitis (Torricelli et al., 2011). A feed-forward loop between proinflammatory cytokines and CRH exists: CRH enhances the LPS induced IL-1β secretion, and in turn IL-1β increases CRH production from cultured human placental cells (Petraglia et al., 1990). All together, this findings suggest that

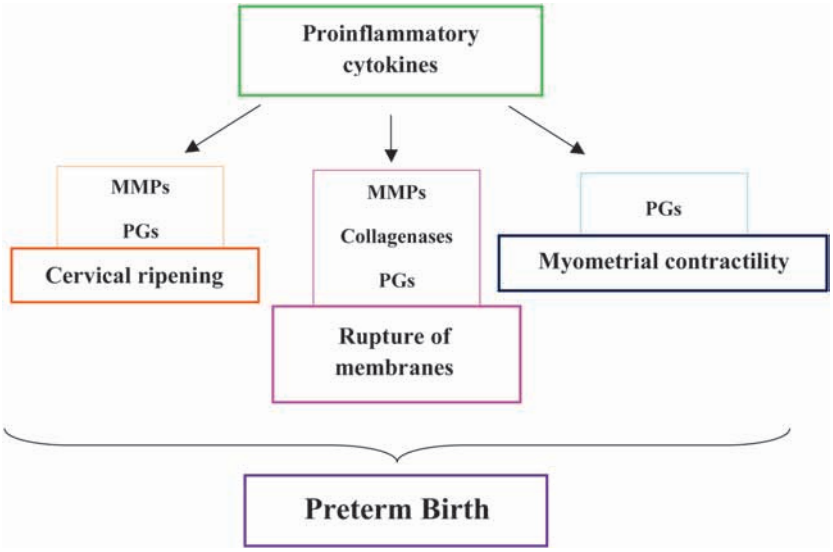

Fig. 2. — Common mechanisms leading to preterm birth

when an inflammatory process occurs, a placental expression of stress-related pathways is activated. Several evidences indicate that during pregnancy the secretion of CRH from intrauterine sources may be influenced by maternal and/or fetal physiological and pathological stress conditions (Pike, 2005). In fact, a relationship exists between stressful life events or poor social circumstances, psychological aspects, environment (eg, poverty, minority or unmarried status, and loss of employment, housing, or partner) and PTB, suggesting that external environmental events are responsible of this syndrome (Petraglia et al, 2001). Psychosocial stress may initiate preterm labor modulating placental products, such as ACTH, cortisol and prostaglandins (Challis et al., 2000; Petraglia et al., 2010). In fact, prematurity seems to be more common among mothers reporting increased stress and anxiety (Lockwood, 1999a) because of maternal stress is associated with PTB, the aberrant regulation of CRH and consequently the production of inflammatory cytokines could represent the pathophysiologic basis of this association. Maternal stress may act via different pathways: (a) a neuroendocrine pathway resulting in the activation of maternal-placental-fetal endocrine systems promoting parturition; (b) an immune/inflammatory pathway wherein maternal stress may modulate placental-decidual immunity thus increasing susceptibility to intrauterine and fetal inflammatory processes. In conclusion, the resultant increase in CRH production may represent a critical factor that could contribute to the early initiation and activation of uterine contractility and PTB (Wadhwa et al., 2001).

2. Identify women at risk

The prediction of spontaneous PTD represents a topic goal with the aim to reduce fetal and neonatal morbidity and mortality. To identify women at risk is a fundamental part of strategies to reduce the PTB in the general population (Goldenberg et al., 2005a). The major objectives to prevent PTB are represented by: (1) better understand the pathways leading to PTB; (2) identify a high risk population that could benefits from particular treatment and identify a low risk population to avoid unnecessary and costly interventions (Behrman et al., 2007) and (3) to initiate risk specific treatment.

Once the pathogenesis is addressed, interventions may be directed to prevent and reduce, before or during pregnancy, both the risk, morbidity and mortality related to PTB (Iams et al., 2008; Petraglia and Visser, 2009).

Many maternal or fetal characteristics have been considered as associated risk factors with PTB (Goldenberg et al, 2005a), and they were classified as periconceptiona, obstetric history or pregnancy associated risk factors (Fig. 3).

a) *Periconceptional risk factors*

- *Socioeconomic characteristics:* Black women are three times more likely to have a PTB than women from other racial (Goldenberg et al., 1996). Low socioeconomic status, low and high maternal ages, and single marital status are associated with PTB (Smith et al., 2007).
- *Nutritional status:* A low BMI, low serum concentrations of iron, folate or zinc are associated with high risk of spontaneous PTB (Bloomfield, 2011).
- *Stress:* Mothers experiencing psychological stress are at increased risk of PTB(Copper et al, 1996), and a role of CRH is proposed (Challis et al., 2000).
- *Systemic diseases:* Thyroid diseases, asthma, diabetes, and hypertension, are associated with increased rates of PTB (Goldenberg et al., 2005b).

b) *Obstetric history*

- *Previous PTB:* The recurrence risk in women with a previous PTB ranges between 15%-50%, depending on number and gestational age of previous deliveries and the risk is inversely related to the gestational age of previous PTB (Goldenberg et al., 2006).
- *Interval between pregnancies:* An interpregnancy interval of less than 6 months confers a increased risk of PTB (Smith et al., 2003a).
- *Previous uterine surgery:* History of myomectomy, cervical cone biopsy or loop electrocautery excision procedures have been associated with an increase in spontaneous PTB (Jakobsson et al., 2007).
- *Smoke:* Tobacco use increases the risk of PTB. Both nicotine and carbon monoxide are powerful vasoconstrictors, and are associated with placental damage and decreased uteroplacental blood flow, leading to fetal growth restriction and PTB (Ebrahim et al., 2000; Aliyu et al., 2010).

c) *Pregnancy associated risk factors*

- *Local or systemic infections:* Infections, such as pyelonephritis and asymptomatic bacteriuria are associated with PTB (Goldenberg et al., 2005). Peridontal disease has received widespread scrutiny suggesting an increased risk independent of other factors (Offenbacher et al., 2006).
- *Intrauterine infection:* Intrauterine infection is an important mechanism leading to PTB and related

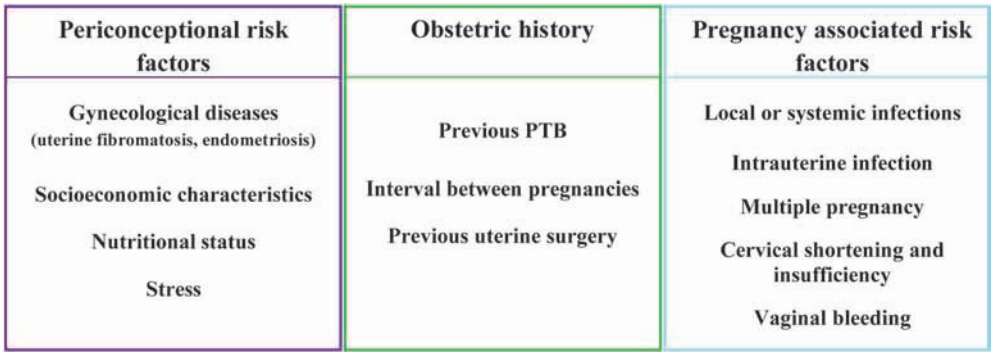

Fig. 3. — Risk factors of preterm delivery

to activation of the innate immune system. The microorganisms most commonly reported are genital Mycoplasma (Larsen and Hwang, 2010). The mechanism by which bacterial vaginosis is associated with PTB is unknown, but microorganisms probably ascend into the uterus before or early during pregnancy (Hillier et al., 1994).

- *Multiple pregnancy:* Multiple gestations carry a risk of PTB, and result in 15-20% of all PTB. Uterine overdistension, resulting in contractions and P-PROM, is the causative mechanism for the rate of increased risk (Stock and Norman, 2010).
- *Cervical shortening and insufficiency:* Cervical shortening is a risk factor for PTB. So, the shorter cervix, the greater the risk of preterm delivery (Di Renzo, 2009).
- *Vaginal bleeding:* Vaginal bleeding caused by placental abruption or placenta praevia is associated with a very high risk of PTB (Krupa et al., 2006).

Clinical assessment of risk

To support clinical practice, several biophysical and biochemical markers have been proposed in addition to the evaluation of the obstetric history and maternal risk factors, to identify patients at risk of spontaneous PTB (Lamont, 2006). Patients with a short cervix could have a higher rate of PTB and they may benefit from targeted interventions (Di Renzo, 2009). Therefore, accurate prediction of the risk of PTB among asymptomatic pregnant women and those symptomatic with threatened preterm labor may offer the opportunity to target care at those most likely to benefit.

Vaginal digital examination to assess the cervix in pregnancy is simple to do but suffers from large variation among examiners (Holcomb and Smeltzer, 1991). Therefore, an useful tool in detecting patients at risk of PTB is the measurement of cervical length (CL) by transvaginal ultrasonography, a reproducible method of examination during pregnancy (Sonek et al., 1990). The assessment of CL has been well standardized (Sonek and Shellhaas, 1998) and it is reproducible among different examinators (Burger et al, 1997). The length of the cervix is directly related to the duration of pregnancy: the shorter the cervix, the greater the likelihood of PTB (Iams et al., 1996; Severi et al., 2003).

In the highest risk women, a CL of 25 mm has a positive predictive value of 70% for PTB < 35 weeks when detected at 14-18 weeks, and of 40% when detected at 18-22 weeks of pregnancy (Mella and Berghella, 2009).

In clinical practice in addition to the use of digital examination and CL evaluation, the identification of other possible biophysical markers should be considered: membrane thickness (Severi et al., 2008) and estimated fetal weight (EFW) (Severi et al., 2012).

It was demonstrated, a positive correlation between membrane thickness and the time of delivery. Indeed, in women at risk for PTB, when this parameter is above the cut-off value of 1.2 mm, the probability to delivery preterm is higher (likelihood ratios of 3.3), with a sensitivity and specificity of 100% (95% CI, 80.3-100) and 69.5% (95% CI, 61.2-77.0) respectively (Severi et al., 2008).

Moreover, a relationship between ultrasound EFW at third trimester and the risk of PTB after premature onset of labor exists. In asymptomatic women between 28 and 36 weeks gestation, EFW lower than 0.90 MoM increases 4.6 times the risk of spontaneous PTB (Severi et al., 2012).

Regarding biomarkers in a biologic fluids a clinical usefulness to predict PTB (Menon et al., 2011) has been shown:

i) Fetal fibronectin (fFN): a glycoprotein found in the extracellular substance of the decidua basalis next to the intervillous space (Kiefer and Vintzileos 2008; Lookwood et al., 1999b). A positive fFN test in vaginal fluids is the most accurate investigation in predicting spontaneous PTB within 710 days after testing among women with symptoms of threatened

PTB (Honest et al., 2002) and improves the predictive value of cervical ultrasonography to identify patients at risk (Honest et al., 2009). A fFN positive test represents a powerful marker of PTB when measured at or after 22-24 weeks of gestation in asymptomatic high risk women (Kurtzman, 2009; Berghella et al., 2008).

ii) CRH and its binding protein (CRH-BP): maternal plasma CRH in the second trimester might be of use in identifying women at high risk of PTB before 34 weeks, detecting about 40% of women who will deliver preterm (McLean and Smith, 2001). Recently, it is found that maternal serum CRH beyond 28 weeks, in presence of intact membranes, is the most accurate biomarkers in predicting preterm birth within 48 hours (Hill et al., 2008). Maternal serum CRH-BP in asymptomatic women at high risk for PTB decreases as parturition approaches, suggesting that CRH bioavailability increases at delivery (Berkowitz et al., 1996).

iii) Ratio of E3/E2: An increase of estriol production is related to the timing of the onset of labor, however, a pivotal event of parturition is represented by a change in the ratio of the E2 and E3 as labor approaches, leading to a more than 10-fold excess of E3. Since E3/E2 increased in the month before delivery, creating an estrogenic environment at the onset of labor, the E3 increase and the altered E3/E2 ratios may be clinically useful in predicting PTB (Smith et al., 2009).

iv) Salivary estriol: hight salivary estriol concentrations from 24 to 34 weeks may be clinically helpful in the identification women with singleton pregnancies at risk of PTB who delivering preterm. An increase in salivary estriol concentrations occurs about 3-4 weeks before the onset of labor in women delivering preterm, with a sensitivity of 71% and specificity of 77% when exceeding a 2.3 ng/ml (McGregor et al., 1995).

Nevertheless, current knowledge of risk factors and biomarkers in predicting the PTB has not been successful in reducing the rate of PTB which continues to rise in the last decades.

3. Management of women at risk of preterm birth

a) *Periconceptional interventions*

- **Periconceptional interventions for women without risk factors**

As many as 50% of PTB occur in women who do not have known risk factors (Mercer et al., 2005). Smoking cessation, optimal nutrition, and periodontal care are commonly recommended. Interventions targeted to reproductive-age women include improved public awareness of the lifetime consequences of PTB (Masset et al., 2003) and the increased risk of PTB that accompanies pregnancies conceived after assisted reproductive technology (ACOG, 2005). Women programming a pregnancy are routinely advised to initiate prenatal vitamins prior to conception and to avoid known risk factors such as cigarette smoking (ACOG, 2005). A reduction in maternal smoking may reduce the rate of PTB (Burguet et al., 2004). The risk attributable to cigarette smoking is greater than 25% for PTB (Shah and Bracken, 2000) and it is about 5% for infant mortality (Salihu et al., 2003). A review of prior pregnancies could be useful to identify opportunities to reduce risks, including periconceptional intervention such as correction of Mullerian anomalies (Patton et al., 2004).

- **Periconceptional interventions for women who have a prior preterm birth**

Women with a prior PTB have an increased risk of recurrence of PTB (Iams and Berghella, 2010). Women with increased medical risks for PTB might benefit from periconceptional interventions such as control of medical disorders (eg, diabetes, seizures, asthma, or hypertension) or interventions that influence prenatal care such as prophylactic progesterone or cerclage before the cervix has dilated (cervical cerclage helps to prevent second trimester loss or PTB in women with at least three previous second trimester losses or PTB (with history indicated cerclage placed at 12 to 14 weeks) (Berghella and Seibel-Seamon, 2007).

b) *Postconceptional interventions*

- **Prenatal care and social support**

The rate of PTB is high in women who do not receive prenatal care. Although perhaps beneficial in adolescents (Quinlivan and Evans, 2004), enhanced prenatal care including social support, home visits, and PTB education have not reduced PTB (Klerman et al., 2001).

- **Modification of maternal activity**

Bed rest is frequently recommended for women whose pregnancies are at risk for PTB, but there is no evidence that it is beneficial (Sosa et al., 2004). Limitation of work and sexual activity is commonly recommended despite a lack of supporting evidence (Yost et al., 2006).

- **Nutritional supplements**

Dietary supplementation of omega-3 polyunsaturated fatty acids is associated with reduced production of inflammatory mediators, and omega-3 supplementation in women at risk for PTB decreases rate of preterm (Barger, 2010).

- **Periodontal care**

The risk of PTB rises with increased severity of periodontal disease and when periodontal disease progresses in pregnancy (Offenbacher et al., 2006). Although postulated to arise from hematogenous transmission of oral microbial pathogens to the genital tract, it is more likely the result of variations in the inflammatory response to resident microflora (Stamilio et al., 2007).

- **Antibiotic treatment**

Treatment of asymptomatic bacteriuria reduces the rate of PTB (Smaill, 2007). The current consensus is that symptomatic vaginal infections with bacterial vaginosis should be treated but screening and prophylaxis are not recommended (ACOG, 2001).

- **Progesterone supplementation**

Progesterone supplementation for women at risk for PTB has been investigated on the basis of several mechanisms of action, including reduced gap junction formation and oxytocin antagonism leading to relaxation of smooth muscle, maintenance of cervical integrity, and anti-inflammatory effects (Dodd et al., 2006; Romero et al., 2011).

- **Cervical cerclage**

The cervix normally stays tightly closed during pregnancy. Since cervical incompetence is considered one of the causes of the PTB, the evaluation of cervical characteristics may provide informations and allows action on a one cause of the syndrome (Mancuso and Owen, 2009). Cervical cerclage (Bergella et al., 2005) is a frequent intervention proposed to prevent PTB once the short CL has been detected or in women with prior spontaneous PTB (Eskandar et al., 2007). Placement of a therapeutic cerclage may reduce the incidence of PTB at <34 weeks' gestation among high-risk patients. A cervical cerclage may be inserted prophylactically before pregnancy or during the first trimester **in women at high risk** or it may be placed therapeutically after detection of cervical changes (Althuisius et al, 2000). It is a surgical treatment to insert a suture to keep the cervix closed. There are a number of proposed treatments (Shirodkar and McDonald techniques) (Shirodkar, 1995; McDonald, 1957) designed to keep the cervix closed until the expected time of birth.

Elective cervical cerclage carries risks for the pregnancy: surgical manipulation of the cervix can cause uterine contractions, bleeding, infection with pyrexia which may lead to miscarriage or preterm labor (Drassinower et al., 2011).

In the last few years the use of cervical pessary (a silicone ring to close the cervix) was introduced in clinical practice. Cervical pessary is a simple and non-invasive alternative that might replace the cervical stitch operation and it could be removed at around 37 weeks. Arabin pessary is a flexible, ring-like silicone pessary available in different sizes (Arabin et al., 2003), relatively non-invasive. It is easy to use, operator independent, it do not require anaesthesia, and it is easily removed when necessary. A possible complication with the use of pessary is represented by changes in vaginal flora during pregnancy (Arabin et al., 2003). However, there is evidence from non-randomised trials concerning some benefit with the use of cervical pessary in preventing PTB (Abdel-Aleem et al., 2010).

4. Management of preterm birth

Prevention and treatment of PTB are crucial interventions to improve fetal/neonatal outcome. In many cases, it may not be appropriate to consider interventions as tocolysis, such as in advanced labor or in case of intrauterine infection or placental abruption (RCOG, 2011). It remains plausible that, for selected women, such as those who require transfer for neonatal care or time to complete a course of corticosteroids, there may be benefit associated with tocolysis (RCOG, 2011).

Thus, management of PTB is oriented to the stabilization both of the mother and the fetus and to the transport of the fetus in uterus to allow delivery in hospitals with resources to properly support preterm infants; it consist in:

- monitoring fetal heart and uterine contractions;
- considering antenatal transfer of the mother and fetus to equipped hospital to care preterm infants;
- administering antibiotics in case of PPROM;
- administering corticosteroid;
- if < 32 weeks, consider tocolysis.

Antibiotics and Preterm Premature Rupture of Fetal Membranes

Preterm premature rupture of membranes (PPROM) complicates 2% of pregnancies but is associated with 40% of PTB and can result in neonatal morbidity and mortality (Merenstein and Weisman, 1996), due to prematurity, sepsis and pulmonary hypoplasia (RCOG, 2006) and in maternal infection and consequently increased risk of chorioamnionitis. Maternal infections are reduced in women exposed to antibiotics (King and Flenady, 2002) and antibiotic treatment is associated with a significant reduction in maternal infections and chorioamnionitis (Kenyon et al., 2003), and with improved neonatal outcome (Mercer et al., 2003) without side effect on childhood outcomes and children health at 7 years of age (Kenyon et al., 2008a). Unlike pPROM, antibiotic therapy is not recommended in cases of intact membranes, as associated with an increase in functional impairment among children at 7 years follow-up

(Kenyon et al., 2008b). Erythromycin or penicillin are the antibiotic of choice, since are associated with a reduction in the numbers of babies born within 48 hours and who had positive blood cultures. Delivery should be considered at 34 weeks of gestation; the expectant management requires an assessment of the risks related to the development of intrauterine infection (RCOG, 2006).

Antenatal Corticosteroids

Antenatal steroids are associated with a significant reduction in rates of neonatal death within the first 24 hours, respiratory distress syndrome (RDS), intraventricular haemorrhage, necrotising enterocolitis, and patent ductus arteriosus (Roberts and Dalziel, 2006), and are safe for the mother. In the lung, corticosteroids promote surfactant synthesis, increase lung compliance, reduce vascular permeability, and generate a greater response to postnatal surfactant treatment. Antenatal corticosteroids have maximal effectiveness in preventing neonatal complications of prematurity when delivery is within 2-7 days after administration (Crowley, 2000).

The most extensively studied and used regimens of corticosteroid treatment for the prevention of RDS is represented by two doses of betamethasone 12 mg given intramuscularly 24 hours apart or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart (RCOG, 2010).

Tocolysis

In some cases tocolytics are administered to the mother to temporarily (48 h) delay threatened spontaneous PTB, facilitating the maternal antenatal corticosteroid administration and the transfer to a specialist unit (Greenfield and Lamont, 2000). The use of tocolytic drugs is associated with a prolongation of pregnancy for up to 7 days and is not associated with a reduction in perinatal or neonatal morbidity (Petraglia and Visser, 2009).

There are a variety of tocolytic agents in use. The most common are oxytocin-receptor antagonists, betamimetics, magnesium sulphate, cyclo-oxygenase inhibitors and calcium channel blockers (Table I). In the absence of any clear evidence that one tocolytic is more efficacious than another, relative safety (Table II) is the main reason for choosing one over the other.

4.1. *Oxytocin-receptor antagonists*

Oxytocin receptor antagonists block oxytocin receptors in the myometrium, preventing a rise in intracellular calcium and thereby relaxing the myometrium. Atosiban is an oxytocin receptor antagonist specifically developed for the treatment of preterm labor (Usta et al., 2011). Potential maternal side-effects are relatively moderate: adverse injection side reaction, nausea, vomiting, headache, chest pain and hypotension (Moutquin et al., 2000).

4.2. *β-adrenergic-receptor agonists*

β-adrenergic-receptor agonists have been the most widely used agents to treat threatened preterm labor (Anotayanonth et al., 2004). The β-adrenergic-receptor agonists cause myometrial relaxation by binding to β2-adrenergic receptors and subsequently increasing the levels of intracellular cyclic AMP. An increase in intracellular cyclic AMP activates protein

Table I. — Tocolytic Agents.

Class of tocolytics	Types	Mechanism(s) of action
Oxytocin-receptor antagonists	Atosiban	Inhibits myometrial contractions and induces uterine quiescence
β-adrenergic-receptor agonists	Ritodrine, Salbutamol, Terbutaline	Bind to β-adrenergic-receptors increasing intracellular levels of cAMP; increase in cAMP initiate reduction in intracellular calcium, in turn inhibiting muscle contraction
Magnesium sulphate		At high levels displaces calcium fromsarcoplasmic reticulum, thereby increasing repolarization time between contractions and decreasing force of contractions
Cyclo-oxygenase inhibitors	Indomethacin	Inhibits production of prostaglandins
Calcium-channel antagonists	Nicardipine, Nifedipine	Prevent entry of calcium in smooth muscle cells by blocking calcium channels and suppressing release of intracellular calcium stores

Table II. — Side-Effect Profiles of Tocolytic Agents.

Class of tocolytics	Maternal side effects	Fetal side effects	Controindications
Oxytocin-receptor antagonists	Hypersensitivity, injection-site reactions	Increased rate of fetal or infant death	None
β-adrenergic-receptor agonists	Tachycardia and hypotension, Tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, hyperglycemia	Tachycardia	Tachycardia-sensitive maternal cardiac disease, poorly controlled diabetes mellitus
Magnesium sulphate	Flushing, diaphoresis, nausea, loss of deep-tendon reflexes, respiratory paralysis, cardiac arrest, suppression of heart rate, contractility, and left ventricular systolic pressure, and neuromuscular blockade	Conficting data	Myasthenia gravis
Cyclo-oxygenase inhibitors	Nausea, esophageal reflux, gastritis and emesis, platelet dysfunction	In utero closure of ductus arteriosus, oligohydramnios, patent ductus arteriosus in neonate (conflicting data)	Platelet dysfunction or bleeding disorder, hepatic or renal dysfunction, gastrointestinal or ulcerative disease, asthma
Calcium-channel antagonists	Dizziness, flushing, hypotension, suppression of heart rate, contractility, and left ventricular systolic pressure, neuromuscular blockade, elevation of hepatic aminotransferase levels		Hypotension, preloaddependent cardiac lesions

kinase, which inactivates myosin light-chain kinase, thus diminishing myometrial contractility (Caritis et al, 1991). The most common β-adrenergic-receptor agonists employed in clinical practice is ritodrine (CPIG, 1992). b2-Agonists lack uterine selectivity and can cause metabolic and cardiovascular side-effects. Most serious maternal side-effects are pulmonary edema, myocardial ischemia and heart failure (Smith, 2003b).

4.3. *Magnesium sulphate*

Magnesium sulphate is commonly used to treat pregnancy-induced hypertension and though unlicensed, is widely used for tocolysis in the USA (Greenfield and Lamont, 2000). It decreases uterine activity; one possible mechanism of action is represented by its competition with calcium for entry into the myometrial cells through voltage-gated channels (Mercer and Merlino, 2009).

4.4. *Cyclo-oxygenase (COX) inhibitors*

COX enzymes are fundamental to the production of PGs and inhibitors reduce uterine contractions (Loudon et al, 2003). COX inhibitors are easily administered with few maternal side-effects. COX inhibitors, however, freely cross the placenta and can interfere with prostaglandin homeostasis in the fetus (Moise et al., 1988). The administration of indomenthacin (the most commonly used COX inhibitor) causes any adverse effects in the fetus during tocolysis (Cordero et al., 2007), that include oligohydramnios, renal failure, premature closure of the ductus arteriosus with consequent pulmonary hypertension, persistent patent ductus arteriosus, necrotising enterocolitis, and intraventricular haemorrhage (Vermillion et al., 1997). In fact, they can be administered before 32 weeks and for a maximum of 72 hours.

4.5. *Calcium-channel antagonists*

Calcium-channel antagonists act inhibiting calcium ions influx across the cell membrane, thereby decreasing the tone in the smooth muscle vasculature (Sanborn, 1995). Nifedipine is the most commonly used to inhibit labor; although has been shown to have a more favourable neonatal outcome and better prolongation of gestation, it is not licensed for tocolysis (Blea et al., 1997).

5. Delivery of preterm infants

Routine caesarean delivery of preterm or very-low birthweight infants is controversial, but most evidence does not support the practice (Deulofeut et al., 2005; Riskin et al., 2004). Neonatal intracranial haemorrhage seems to arise commonly before, after and during labor and delivery. For infants in breech presentation, caesarean delivery might avoid trapping of the aftercoming head and other manipulations that could lead to trauma or hypoxia. Optimum delivery of very-low birthweight babies might nevertheless appropriately lead to a caesarean section without labor because of complications associated with growth restriction, ruptured membranes, cord prolapse, bleeding, or expected difficulty with vaginal breech delivery (Grant et al., 1996).

References

Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. Cochrane Database Syst Rev. 2010 Sep 8;(9):CD007873. Review.

ACOG Practice Bulletin number 31. Assessment of risk factors for preterm birth. Obstet Gynecol. 2001;98:709-16.

ACOG Committee Opinion 313. The importance of preconception care in the continuum of women's health care. Obstet Gynecol. 2005;106:665-6.

ACOG Committee Opinion 324. Perinatal risks associated with assisted reproductive technology. Obstet Gynecol. 2005;106:1143-6.

Aliyu MH, Lynch O, Saidu R et al. Intrauterine exposure to tobacco and risk of medically indicated and spontaneous preterm birth. Am J Perinatol.. 2010;27:405-10.

Althuisius SM, Dekker GA, van Geijn HP et al. Cervical Incompetence Prevention Randomized Cerclage Trial (CIPRACT): Study design and preliminary results. Am J Obstet Gynecol. 2000;183:823-9.

Anotayanonth S, Subhedar NV, Garner P et al. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD004352. Review.

Arabin B, Halbesma JR, Vork F et al. Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix? J Perinat Med. 2003;31:122-33.

Barger MK. Maternal nutrition and perinatal outcomes. J Midwifery Womens Health. 2010;55:502-11.

Behrman RE, Butler AS (Editors). Preterm Birth: Causes, Consequences, and Prevention. Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes Washington (DC): National Academies Press (US); 2007.

Berghella V, Odibo AO, To MS et al. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. Obstet Gynecol. 2005;106:181-9.

Berghella V, Hayes E, Visintine J et al. Fetal fibronectin testing for reducing the risk of preterm birth. Cochrane Database Syst Rev. 2008;8:CD006843. Review.

Berghella V, Seibel-Seamon J. Contemporary use of cervical cerclage. Clin Obstet Gynecol. 2007;50:468-77.

Berkowitz GS, Lapinski RH, Lockwood CJ et al. Corticotropin-releasing factor and its binding protein: maternal serum levels in term and preterm deliveries. Am J Obstet Gynecol. 1996;174:1477-83.

Blea CW, Barnard JM, Magness RR et al. Effect of nifedipine on fetal and maternal hemodynamics and blood gases in the pregnant ewe. Am J Obstet Gynecol. 1997;176:922-30.

Bloomfield FH. How is maternal nutrition related to preterm birth? Annu Rev Nutr. 2011;31:235-61.

Burger M, Weber-Rossler T, Willmann M: Measurement of the pregnant cervix by transvaginal sonography: an interobserver study and new standards to improve the interobserver variability. Ultrasound Obstet Gynecol. 1997;9:188-93.

Burguet A, Kaminski M, Abraham-Lerat L et al. The complex relationship between smoking in pregnancy and very preterm delivery: results of the Epipage study. BJOG. 2004; 111: 258-65.

Canadian Preterm Labor Investigators Group (CPIG). Treatment of preterm labor with the beta-adrenergic agonist ritodrine. N Engl J Med. 1992;327:308-12.

Caritis SN, Chiao JP, Kridgen P. Comparison of pulsatile and continuous ritodrine administration: effects on uterine contractility and beta-adrenergic receptor cascade. Am J Obstet Gynecol. 1991;164:1005-11.

Challis JRG, Matthews SG, Gibb W et al. Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev. 2000;21:514-50.

Challis JRG, Lockwood CJ, Myatt L et al. Inflammation and pregnancy. Reprod Sci. 2009;16:206-15. Review.

Copper RL, Goldenberg RL, Das A et al. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than 35 weeks' gestation. Am J Obstet Gynecol. 1996;175:1286-92.

Cordero L, Nankervis CA, Gardner D et al. The effects of indomethacin tocolysis on the postnatal response of the ductus arteriosus to indomethacin in extremely low birth weight infants. J Perinatol. 2007;27:22-7.

Crowley P. Prophylactic corticosteroids for preterm birth. Cochrane Database Syst Rev. 2000;(2):CD000065. Review.

Deulofeut R, Sola A, Lee B et al. The impact of vaginal delivery in premature infants weighing less than 1251 grams. Obstet Gynecol. 2005;105:525-31.

Di Renzo GC. The great obstetrical syndromes. J Matern Fetal Neonatal Med. 2009;22:633-5.

Dodd JM, Flenady V, Cincotta R et al. Prenatal administration of progesterone for preventing preterm birth. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004947. Review.

Drassinower D, Poggi SH, Landy HJ et al. Perioperative complications of history-indicated and ultrasound-indicated cervical cerclage. Am J Obstet Gynecol. 2011;205:53.

Ebrahim SH, Floyd RL, Merritt RK et al. Trends in pregnancy related smoking rates in the United States, 1987-1996. JAMA. 2000; 283:361-6.

Eskandar M, Shafiq H, Almushait MA et al. Cervical cerclage for prevention of preterm birth in women with twin pregnancy. Int J Gynecol Obstet. 2007;99:110-2.

Goldenberg RL, Cliver SP, Mulvihill FX et al. Medical, psychosocial, and behavioural risk factors do not explain the increased risk for low birth weight among blackwomen. Am J Obstet Gynecol. 1996;175:1317-24.

Goldenberg RL, Culhane JF. Pregnancy health status and the risk of preterm delivery. Arch Pediatr Adolesc Med. 2005; 159:89-90.

Goldenberg RL, Goepfert AR, Ramsey PS. Biochemical markers for the prediction of preterm birth. Am J Obstet Gynecol. 2005a;192:36-46.

Goldenberg RL, Culhane JF, Johnson DC. Maternal infection and adverse fetal and neonatal outcomes. Clin Perinatol. 2005b; 32:523-59.

Goldenberg RL, Andrews WW, Faye- O et al. The Alabama preterm birth project: placental histology in recurrent spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2006;195:792-6.

Grant A, Penn ZJ, Steer PJ. Elective or selective caesarean delivery of the small baby? A systematic review of the controlled trials. Br J Obstet Gynaecol. 1996;103:1197-200.

Greenfield PJ, Lamont RF. The contemporary use of tocolytics. Current Obstet Gynaecol. 2000;10:218-24.

Hill JL, Campbell MK, Zou GY et al. Prediction of preterm birth in symptomatic women using decision tree modeling for biomarkers. Am J Obstet Gynecol. 2008;198:468.e1-7.
Hillier SL, Krohn MA, Cassen E et al. The role of bacterial vaginosis and vaginal bacteria in amniotic fluid infection in women in preterm labor with intact fetal membranes. Clin Infect Dis. 1994;20:276-8.
Holcom WL Jr, Smeltzer JS. Cervical effacement: variation in belief among clinicians. Obstet Gynecol. 1991;78:43-5.
Honest H, Bachmann LM, Gupta JK et al. Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: systematic review. BMJ. 2002;325:301. Review.
Honest H, Forbes CA, Durée KH et al. Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modeling. Health Technol Assess. 2009;13:1-627. Review.
Iams JD, Goldenberg RL, Meis PJ et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med. 1996;334:567-72.
Iams JD, Romero R, Culhane JF et al. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet. 2008;371:164-75.
Iams JD, Berghella V. Care for women with prior preterm birth. Am J Obstet Gynecol. 2010;203:89-100.
Jakobsson M, Gissler M, Sainio S et al. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. Obstet Gynecol. 2007;109:309-13.
Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of membranes. The Cochrane Database Syst Rev. 2003;(2):CD001058. Review.
Kenyon S, Pike K, Jones DR et al. Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. Lancet. 2008a;372:1310-8.
Kenyon S, Pike K, Jones DR et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet. 2008b;372:1319-27.
Kiefer DG, Vintzileos AM. The utility of fetal fibronectin in the prediction and prevention of spontaneous preterm birth. Rev Obstet Gynecol. 2008;1:106-12.
King J, Flenady V. Antibiotics for inhibiting preterm labour with intact membranes. The Cochrane Database Syst Rev. 2002; (3):CD001807. Review.
Klerman LV, Ramey SL, Goldenberg RL et al. A randomized trial of augmented prenatal care for multiple-risk, Medicaid-eligible African American women. Am J Public Health. 2001; 91:105-11.
Krupa FG, Faltin D, Cecatti JG, et al. Predictors of preterm birth. Int J Gynaecol Obstet. 2006;94:5-11.
Kurtzman J, Chandiramani M, Briley A et al. Quantitative fetal fibronectin screening in asymptomatic high-risk patients and the spectrum of risk for recurrent preterm delivery. Am J Obstet Gynecol. 2009;200:263.e1-6.
Lamont RF. Setting up a preterm prevention clinic: a practical guide. BJOG. 2006;113:86-92. Review.
Larsen B, Hwang J. Mycoplasma, Ureaplasma, and adverse pregnancy outcomes: a fresh look. Infect Dis Obstet Gynecol. 2010; pii: 521921.
Lockwood CJ. Stress-associated preterm delivery: The role of corticotropinreleasing hormone. Am J Obstet Gynecol. 1999a;180:264-6.
Lockwood CJ, Senyei AE, Dische MR et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. N Engl J Med. 1999b;325:669-74.
Lockwood CJ. Predicting premature delivery-no easy task. N Engl J Med. 2002;346: 282-4.
Loudon JA, Groom KM, Bennett PR. Prostaglandin inhibitors in preterm labour. Best Pract Res Clin Obstet Gynaecol. 2003;17:731-44.
Mancuso MS and Owen J. Prevention of Preterm Birth Based on a Short Cervix: Cerclage. Semin Perinatol. 2009;33:325-33.
Massett HA, Greenup M, Ryan CE et al. Public perceptions about prematurity: a national survey. Am J Prev Med. 2003;24:120-7.
McDonald IA. Suture of the cervix for inevitable miscarriage. J Obstet Gynaecol Br Emp. 1957;146:346-50.
McGregor JA, Jackson GM, Lachelin GC et al. Salivary estriol as risk assessment for preterm labor: a prospective trial. Am J Obstet Gynecol. 1995;173:1337-42.
McLean M and Smith R. Corticotrophin-releasing hormone and human parturition. Reproduction. 2001;121:493-501. Review.
Mercer BM, Goldenberg RL, Das AF et al. What we have learned regarding antibiotic therapy for the reduction of infant morbidity after preterm premature rupture of the membranes. Semin Perinatol. 2003;27:217-30.
Mercer B, Milluzzi C, Collin M. Periviable birth at 20 to 26 weeks of gestation: proximate causes, previous obstetric history and recurrence risk. Am J Obstet Gynecol. 2005; 193:1175-80.
Mercer BM, Merlino AA. Magnesium sulfate for preterm labor and preterm birth. Obstet Gynecol. 2009;114:650-68.
Merenstein GB,Weisman LE. Premature rupture of the membranes: neonatal consequences. Semin Perinatol. 1996; 20:375-80.
Mella MT, Berghella V. Prediction of preterm birth: cervical sonography. Semin Perinatol 2009;33:317-24. Review.
Menon R, Torloni MR, Voltolini C et al. Biomarkers of spontaneous preterm birth: an overview of the literature in the last four decades. Reprod Sci. 2011;18:1046-70.
Moise KJ, Huhta JC, Sharif DS et al. Indomethacin in the treatment of premature labor. Effects on the fetal ductus arteriosus. N Engl J Med. 1988;319:327-31.
Moutquin JM, Sherman D, Cohen H et al. Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. Am J Obstet Gynecol. 2000;182:1191-9.
Offenbacher S, Boggess KA, Murtha AP et al. Progressive periodontal disease and risk of very preterm delivery. Obstet Gynecol. 2006;107:29-36.
Patton PE, Novy MJ, Lee OM et al. The diagnosis and reproductive outcome after surgical treatment of the complete septate uterus, duplicated cervix and vaginal septum. Am J Obstet Gynecol. 2004;190:1669-75.
Petraglia F, Sawchenko PE, Rivier J et al. Evidence for local stimulation of ACTH secretion by corticotropin-releasing factor in human placenta. Nature. 1987;328:717-9.
Petraglia F, Garuti GC, De Ramundo B et al. Mechanism of action of interleukin-1 beta in increasing corticotropin-releasing factor and adrenocorticotropin hormone release from cultured human placental cells. Am J Obstet Gynecol. 1990;163:1307-12.
Petraglia F, Aguzzoli L, Florio P et al. Maternal plasma and placental immunoreactive corticotrophin-releasing factor concentrations in infection associated term and pre-term delivery. Placenta. 1995;16:157-64.
Petraglia F, Hatch MC, Lapinski R et al. Lack of effect of psychosocial stress on maternal corticotropin-releasing factor and catecholamine levels at 28 weeks' gestation. J Soc Gynecol Investig. 2001;8:83-8.
Petraglia F, Visser GH. Prevention and management of preterm labour. J Matern Fetal Neonatal Med. 2009;22:24-30.
Petraglia F, Imperatore A, Challis JR. Neuroendocrine mechanisms in pregnancy and parturition. Endocr Rev. 2010; 31:783-816. Review.
Pike IL. Maternal stress and fetal responses: evolutionary perspectives on preterm delivery. Am J Hum Biol. 2005;17: 55-65.
Quinlivan JA, Evans SF. Teenage antenatal clinics may reduce the rate of preterm birth: a prospective study. BJOG. 2004;111:571-8.

Rauk PN, Friebe-Hoffmann U, Winebrenner LD et al. Interleukin-6 up-regulates the oxytocin receptor in cultured uterine smooth muscle cells. Am J Reprod Immunol. 2001; 45:148-53.
RCOG. Preterm Prelabour Rupture of Membranes Green-top Guideline No. 44; 2006.
RCOG.Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality. Green-top Guideline No. 7; 2010.
RCOG. Tocolysis for Women in Preterm Labour. Green-top Guideline No.1b; 2011.
Riskin A, Riskin-Mashiah S, Lusky A et al. The relationship between delivery mode and mortality in very low birthweight singleton vertex-presenting infants. BJOG. 2004;111:1365-71.
Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD004454. Review.
Romero R, Espinoza J, Chaiworapongsa T et al. Infection and prematurity and the role of preventive strategies. Semin Neonatol. 2002; 7:259-274.
Romero R, Espinoza J, Kusanovic JP et al. The preterm parturition syndrome. BJOG. 2006;113:17-35.
Romero R, Espinoza J, Gonçalves LF et al. The role of inflammation and infection in preterm birth. Semin Reprod Med. 2007;25:21-39.
Romero R. Vaginal progesterone to reduce the rate of preterm birth and neonatal morbidity: a solution at last. Womens Health (Lond Engl). 2011;7:501-4.
Salihu HM, Pierre-Louis BJ, Alexander GR. Levels of excess infant deaths attributable to maternal smoking during pregnancy in the United States. Matern Child Health J. 2003; 7:219-27.
Sanborn BM. Ion channels and the control of myometrial electrical activity. Semin Perinatol. 1995;19:31-40.
Sennström MB, Ekman G, Westergren-Thorsson G et al. Human cervical ripening, an inflammatory process mediated by cytokines. Mol Hum Reprod. 2000;6:375-81.
Severi FM, Bocchi C, Florio P et al. Comparison of two-dimensional and three-dimensional ultrasound in the assessment of the cervix to predict preterm delivery. Ultrasound Med Biol. 2003;29:1261-5.
Severi FM, Bocchi C, Voltolini C et al. Thickness of fetal membranes: a possible ultrasound marker for preterm delivery. Ultrasound Obstet Gynecol. 2008;32:205-9.
Severi FM, Bocchi C, Imperatore A et al. Ultrasound estimated fetal weight slightly below the median is associated with increased risk of spontaneous preterm birth. Prenatal Diagnosis. 2012; 32:588-91.
Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies in the association between maternal cigarette smoking and preterm delivery. Am J Obstet Gynecol 2000; 182:465-72.
Shirodkar VN. A new method of operative treatment for habitual abortions in the second trimester of pregnancy. Antiseptic. 1955;52:299-300.
Slater DM, Dennes WJ, Campa JS et al. Expression of cyclooxygenase types-1 and -2 in human myometrium throughout pregnancy. Mol Hum Reprod. 1999;5:880-4.
Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev. 2007 Apr 18;(2): CD000490. Review.
Smith GC, Pell JP, Dobbie R. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study. BMJ. 2003a;327:313.
Smith GN. What are the realistic expectations of tocolytics? BJOG. 2003b;110:103-6.
Smith LK, Draper ES, Manktelow BN et al. Socioeconomic inequalities in very preterm birth rates. Arch Dis Child Fetal Neonatal Ed. 2007;92:11-4.
Smith R, Smith JI, Shen X et al. Patterns of plasma corticotropin-releasing hormone, progesterone, estradiol, and estriol change and the onset of human labor. J Clin Endocrinol Metab. 2009;94:2066-74.
Sonek JD, Iams JD, Blumenfeld M et al. Measurement of cervical length in pregnancy: comparison between vaginal ultrasonography and digital examination. Obstet Gynecol. 1990;76:172-5.
Sonek J, Shellhaas C: Cervical sonography: a review. Ultras Obstet Gynecol. 1998;11:71-78.
Sosa C, Althabe F, Belizan J et al. Bed rest in singleton pregnancies for preventing preterm birth. Cochrane Database Syst Rev. 2004;(1):CD003581. Review.
Stamilio OM, Chang JJ, Macones GA. Periodontal disease and preterm birth: do the data have enough teeth to recommend screening and preventative treatment? Am J Obstet Gynecol. 2007;196:93-4.
Stock S, Norman J. Preterm and term labour in multiple pregnancies. Semin Fetal Neonatal Med. 2010;15:336-41.
Torricelli M, Giovannelli A, Leucci E et al. Labor (term and preterm) is associated with changes in the placental mRNA expression of corticotrophin-releasing factor. Reprod Sci. 2007;14:241-5.
Torricelli M, Novembri R, Bloise E et al. Changes in placental CRH, urocortins, and CRH-receptor mRNA expression associated with preterm delivery and chorioamnionitis J Clin Endocrinol Metab. 2011;96:534-40.
Usta IM, Khalil A, Nassar AH. Oxytocin Antagonists for the Management of Preterm Birth: A Review. Am J Perinatol. 2011;28:449-60.
Vermillion ST, Scardo JA, Lashus AG et al. The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age. Am J Obstet Gynecol. 1997;177:256-9.
Wadhwa PD, Culhane JF, Rauh V et al. Stress, infection and preterm birth: a biobehavioural perspective. Paediatr Perinat Epidemiol. 2001;15:17-29.
Wolfe CD, Patel SP, Linton EA et al. Plasma corticotrophin-releasing factor (CRF) in abnormal pregnancy. Br J Obstet Gynaecol. 1988;95:1003-6.
Yost NP, Owen J, Berghella V et al. Effect of coitus on recurrent preterm birth. Obstet Gynecol. 2006;107:793-7.
Xu P, Alfaidy N, Challis JR. Expression of matrix metalloproteinase (MMP)-2 and MMP-9 in human placenta and fetal membranes in relation to preterm and term labor. J Clin Endocrinol Metab. 2002; 87:1353-61.