

Guidelines for the management of spontaneous preterm labour

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Introduction

Preterm birth is defined as delivery at < 37 completed weeks of pregnancy (World Health Organization). Spontaneous preterm birth (SPB) includes preterm labor, preterm spontaneous rupture of membranes, preterm premature rupture of membranes (PPROM) and cervical weakness; it does not include indicated preterm delivery for maternal or fetal conditions. Early SPB (< 32 weeks' gestation) is associated with an increased higher perinatal mortality rate, inversely proportional to gestational age. The pathophysiologic events that trigger SPB are largely unknown but include decidual hemorrhage (abruption), mechanical factors (uterine overdistention or cervical incompetence), and hormonal changes (perhaps mediated by fetal or maternal stress). In addition, several cervicovaginal infections have been associated with preterm labor. SPB is also the leading cause of long-term morbidity, including neurodevelopmental handicap, cerebral palsy, seizure disorders, blindness, deafness and non-neurological disorders, such as bronchopulmonary dysplasia and retinopathy of prematurity. Delaying delivery may reduce the rate of long-term morbidity by facilitating the maturation of developing organs and systems. The benefits of administration of antepartum glucocorticosteroids to reduce the incidence and severity of respiratory distress syndrome may be exploited by delay. Delay may also permit transfer of the fetus *in utero* to a center with neonatal intensive care unit facilities.

There is considerable variation in the way that spontaneous preterm labor (SPTL) is diagnosed, managed and treated internationally.

The development of clinical guidelines requires an evidence-based approach to improve outcome and allow more efficient use of resources. With recent advances in our understanding of the etiology and mechanisms of SPTL and the availability of safer, more specific tocolytics, it was felt that guidelines should be developed to achieve, if possible, an European consensus in patient diagnosis, management and treatment.

Myths to dispel

It may be worth pointing out that the incidence of SPB has not changed because we are now including more babies

born at very early gestational age, at extremely low birth weight, and at the limits of viability, who were never included in our previous statistics. There is also an increasing trend towards elective preterm delivery as neonatal intensive care has improved, and finally, that term delivery per se is not a good indicator of outcome bearing in mind that each day of delay between 22 and 28 weeks gestation increases survival by 3% without the need to get to full term. In addition, the myth that tocolytics only work for 48 hours arose from the inaccurate interpretation of the meta-analysis of beta-agonists which found that 48 hours was the only consistent finding among the 16 papers analyzed to allow comparison, but many tocolytics have been shown to work beyond 48 hours. With respect to the claim that no tocolytic has been shown to reduce the incidence of perinatal mortality and morbidity, it should be noted that no study on tocolytics has ever been carried out with a sufficient statistical power to show such a benefit.

The diagnosis of spontaneous preterm labor

On admission with suspected SPTL, the accuracy of the expected date of confinement should be re-checked scrupulously because the best estimate will influence whether or not intervention should take place.

The diagnosis of SPTL on clinical grounds should include the following:

- 1) Contractions that are painful, palpable, last longer than 30 seconds and occur at least four times per 20 minutes;
- 2) Evidence of a change in the position, consistency, length and/or dilatation of the cervix.

When compared with digital examination and transabdominal scanning, transvaginal ultrasound has a higher sensitivity for the detection of cervical shortening and the risk of SPB. Oncofetal fibronectin (fFN) may be considered to complement the clinical assessment. The availability of fFN testing was associated with a reduction in hospital admissions, length of hospital stay, and overall hospital costs in the management of SPTL.

fFN testing supplemented by ultrasonography to determine cervical length, may be useful in defining women at high risk for preterm labor.

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Table 1. Tocolytics for preterm labour

Tocolytic agent	Dosage and administration	Contraindications	Maternal side effects	Fetal and neonatal side effects
Beta-mimetics	Terbutaline, 0.25 mg subcutaneously every 20 min. to 3 hr (hold for pulse > beats per minute)	Cardiac arrhythmias, poorly controlled thyroid disease, poorly controlled diabetes mellitus	Cardiac or pulmonary arrhythmias, pulmonary edema, myocardial ischemia, hypotension, tachycardia, shortness of breath, hyperglycemia, hyperinsulinemia, antidiuresis, altered thyroid function, hyperkalemia, tremor, nervousness, nausea or vomiting, hypokalemia	Tachycardia, hyperinsulinemia, fetal hyperglycemia
	Ritodrine initial dose of 50-100 µg/min i.v., increase 50 µg/min every 10 min until contractions cease or side effects develop, maximum dose = 350 µg/min		Severe hallucinations	
Calcium channel blockers: nifedipine	30 mg loading dose, then 10-20 mg every 4-6 hr	Cardiac disease, use caution with renal disease, maternal hypotension (< 90/50 mm Hg), avoid concomitant use with magnesium sulphate	Flushing, headache, dizziness, nausea, transient hypotension, transient tachycardia, palpitations	Sudden fetal death. Fetal distress
Prostaglandin synthetase inhibitors: indomethacin	Indomethacin loading dose of 50 mg rectally or 50-100 mg orally, then 25-50 mg orally every 6 hr × 48 hr.	Significant renal or hepatic impairment	Nausea, heartburn gastritis, nausea, proctitis with hematochezia, impairment of renal function, increased postpartum hemorrhage, heartburn, headache, dizziness, depression	Constriction of ductus arteriosus, pulmonary hypertension, reversible decrease in renal function with oligohydramnios, intraventricular hemorrhage, hyperbilirubinemia, necrotizing enterocolitis
	Ketorolag loading dose of 60 mg intramuscularly, then 30 mg intramuscularly every 6 hr × 48 hr	Active peptic ulcer disease	-	-
	Sulindac, 200 mg orally every 12 h × 48 hr	Coagulation disorders or thrombocytopenia, NSAID-sensitive asthma, other sensitivity to NSAID	-	-
Nitric oxide donors	Glyceriltrinitrate	Headache	Headache, hypotension	Neonatal hypotension
	10 mg patch for every 12 hr continuing until contraction cease, up to 48 hours			
Oxytocin antagonists	Atosiban initial bolus dose: 6.75 mg over one minute, followed by an infusion of 18 mg/hour for three hours and then 6 mg/hour for up to 45 hours	None	Nausea (short duration), allergic reaction, headache (short duration)	None noted as yet

However, their clinical usefulness may rest primarily with their negative predictive value given the lack of proven treatment options to prevent SPB. Bearing in mind the excellent negative predictive value of such tests (when fibronectin is negative and cervical length by transvaginal ultrasound is > 2.5 cm) we recommend that tocolytic therapy should be withheld if fetal fibronectin or transvaginal ultrasound scan indicate a low risk of SPB. Perceptions of uterine contractions have always been interpreted by pregnant women as evidence for impending SPTL. The majority of these women will present to their local hospitals for assessment of labor, resulting in over half being admitted, treated and released without delivering after a few days. With the use of biochemical markers and sonographic evaluation of the cervix, it is possible to identify the majority of women who are not in preterm labor.

Standardization of assessment and disposition of patients presenting with the signs and symptoms of SPTL will:

- 1) allow for timely interventions for preterm labor;
- 2) maintain maternal-fetal safety;
- 3) minimize the need for hospitalization only for those patients at greater risk of preterm delivery; and
- 4) promote effective transport of preterm labor patients to higher, more appropriate levels of care.

An example of a clinical methodology that was developed to determine the optimal disposition of women who present with signs and symptoms of PTL can be found in the March of Dimes Preterm Labor Assessment Toolkit, endorsed by the American Society of Maternal Fetal Medicine in 2005. This toolkit was developed with the dual aim of 1) the recommendations being evidence based and 2) the information can be utilized effectively at all levels of facilities receiving PTL patients. As such, the toolkit contains two algorithms. One algorithm uses fFN in addition to clinical assessment. A second algorithm is for the subset of facilities which have regular access to reliable transvaginal ultrasound. Both algorithms provide the same outcome: determination of the optimum disposition of women who present with signs and symptoms of preterm labor. This document can be retrieved at www.marchofdimes.com.

A wide variety of agents have been advocated as suppressing uterine contractions. Those in current use include beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donors, and oxytocin receptor antagonists. There is little reliable information about current clinical practice but it is likely that ritodrine hydrochloride, a beta-agonist, remains the most widely used in Europe.

The primary aims of tocolytic therapy are to delay delivery to allow the administration of a complete course of antepartum glucocorticosteroids in order to primarily reduce the incidence and severity of idiopathic respiratory distress syndrome and to arrange *in utero* transfer to a center with neonatal intensive care unit facilities.

The secondary aim of tocolytic therapy is to delay delivery to reduce the perinatal mortality and morbidity associated with severe prematurity. A full comparison of costs has not been

reported but this should also take into account the costs of administering each drug against any benefits or adverse effects, primarily the costs of SPB itself, savings on midwifery care and the comparison of obstetric and tocolytic budgets to other hospital budgets.

Atosiban represents an advance in currently available tocolytics, and should be considered a first-line tocolytic for the management of SPTL.

Atosiban is licensed in Europe for treatment of SPTL. The recommended dosage and administration schedule for atosiban is a three-step procedure (see Table 1). Duration of treatment should not exceed 48 hours and the total dose given during a full course should preferably not exceed 330 mg of atosiban. In the early gestational age with or without PPROM, the use of atosiban can be prolonged for further few days without any significant side effects.

Table 2. The recommended guidelines for monitoring i.v. administration with β -agonists

Monitoring
• Maternal pulse and BP should be monitored every 15 minutes
• Chest auscultation should be performed every 4 hours
• Strict input/output charts should be measured for fluid balance
• Urea, electrolytes, and hematocrit should be measured every 24 hours
• Maternal blood glucose should be measured 4-hourly

(From reference: Royal College of Obstetricians and Gynecologists. Clinical Green Top Guidelines. Tocolytic Drugs for Women in Preterm Labour (IB) – Oct. 2002. <http://www.rcog.org.uk/guidelines/tocolytics.html>).

The risk of adverse events associated with β -agonists in the management of SPTL requires close monitoring of the mother in a high dependency unit (Table 2). Common adverse effects, when beta-agonists are compared to no treatment or placebo, include palpitation (68% with beta-agonists vs. 5% with controls), tremor (39% vs. 4%), nausea (20% vs. 12%), headache (23% vs. 6%) and chest pain (10% vs. 1%). Rare, but serious and potentially life threatening adverse effects have been reported following beta-agonists use and a few maternal deaths associated with use of these drugs were reported. Pulmonary edema is a well-documented complication, usually associated with aggressive intravenous hydration. A systematic review reported one case of pulmonary edema among 850 women (1/425 with beta-agonists vs. 0/427 with placebo). For the other tocolytic drugs (magnesium sulphate, indomethacin and atosiban), fewer types of adverse effects were reported and these occurred less frequently. For atosiban, the only documented adverse effect is nausea (11% with atosiban vs. 5% with placebo) but this is only of short duration and only in

association with about the minute during which the bolus dose is administered. The same study reported no increase in vomiting (3% with atosiban vs. 4% with placebo), headache (5% vs. 7%), chest pain (1% vs. 4%), or dyspnea (0.4% vs. 3%). Among unlicensed tocolytic therapy, *calcium channel blockers*, such as nifedipine and nicardipine, inhibit the influx of calcium ions into myometrial cells, and the decreased intracellular calcium results in decreased myometrial activity. Recent reviews of the evidence pertaining to the use of nicardipine or nifedipine suggest that the safety profiles of these drugs are incomplete and should lead to careful consideration before use. Particularly, a number of studies have been published documenting serious maternal cardiovascular and pulmonary adverse events.

Key guidelines

- Administration of one single-course of antenatal glucocorticosteroids is the most important treatment to prevent brain injury and increase survival that can be provided by the obstetrician to patients at risk of preterm delivery at 24-34 weeks of gestation
- Based on observational clinical and animal studies, betamethasone is preferable to dexamethasone
- Multiple courses of corticosteroids should be avoided
- There is no direct evidence that tocolytic treatment *per se* might affect the risk of perinatal brain injury or adverse neurological outcome

It has been recommended that nicardipine should only be used in a clinical trial setting. Documented maternal side effects include: dizziness, lightheadedness, headache, flushing, nausea, and transient hypotension. The combination of magnesium sulphate and nifedipine should be avoided because of reported cases of symptomatic hypocalcemia, neuromuscular blockade, and cardiac toxicity, including maternal death. There is an increasing number of case reports of adverse fetal-maternal events with the use of nifedipine, particularly in twin pregnancies. In addition, there is a case report of a myocardial infarction in a 29-years old woman who received nifedipine immediately after intravenous ritodrine therapy. The evidence pertaining to nifedipine for the treatment of SPTL is based largely upon a small number of poor quality investigator-led studies of small sample size.

A systematic review has identified serious concerns with respect to the topic and method-specific conduct and, hence, because of the quality of such studies they should not be used to guide practice. *Magnesium sulphate* is ineffective at delaying birth or preventing SPB after preterm labor, and its use is associated with an increased infant mortality. Magnesium sulphate is popular for tocolysis in the USA and some other parts of the world, but is rarely used for this indication in Europe and it is not recommended for tocolysis.

Indomethacin and other prostaglandin synthesis inhibitors are effective in delaying preterm labor and increases birth weight; result in shorter stays in neonatal intensive care units and shorter intervals of mechanical ventilation. However, contradictory evidence exists that indomethacin fails to prolong gestation and infants are delivered prematurely. Potential fetal adverse effects include premature closure of the ductus arteriosus, necrotizing enterocolitis, respiratory distress syndrome and bronchopulmonary dysplasia, but also a potential increased risk of development of periventricular leukomalacia (at a daily dose of 200 mg).

Nitric oxide donors (glyceryl trinitrate or isosorbide) have been shown to act as tocolytic agents. Major side effects are maternal headache and hypotension. Their use is still limited by low compliance of the patients.

If a tocolytic agent is used, ritodrine no longer seems the best choice. Alternatives such as atosiban appear to have comparable effectiveness in terms of delaying delivery for up to seven days and are associated with considerably fewer maternal and fetal adverse effects.

Maintenance treatment after threatened preterm labor

Maintenance tocolysis is not recommended for routine practice

Data from systematic reviews provide insufficient evidence to show whether or not oral beta-agonists, or any other maintenance therapy will prevent SPB and its consequences after SPTL. In addition, one trial has compared subcutaneous terbutaline with placebo: although the β -agonists delayed the next episode of threatened labor, there is insufficient evidence for firm conclusions about the effects on other more substantive outcomes. Therefore; there is insufficient evidence for any firm conclusions about whether or not maintenance tocolytic therapy following SPTL is worthwhile. Maintenance therapy cannot be recommended for routine practice.

The administration of antepartum glucocorticosteroids

Prolonging gestation with tocolytic therapy allows for the administration of antepartum glucocorticosteroids to reduce the incidence and severity of respiratory distress syndrome and hence to reduce neonatal morbidity and mortality.

A single course of antepartum glucocorticoids (GC) to pregnant women, at risk of preterm delivery within 7 days, should be administered between 24-34 weeks' gestation.

A meta-analysis of 18 randomized trials demonstrates that antenatal corticosteroids significantly reduce the occurrence of neonatal respiratory distress syndrome (OR 0.53, 95% CI 0.44-0.63) and neonatal death (OR 0.6, 95% CI 0.48-0.75). Furthermore, a significant reduction of intraventricular hemorrhage (IVH) diagnosed both at autopsy (OR 0.29, 95% CI 0.14-0.61) and by ultrasound (OR 0.48, 95% CI 0.32-0.72) was shown. One single course of antenatal GC may also reduce periventricular leukomalacia (PVL) and cerebral palsy.

Betamethasone and dexamethasone are the two most widely used GC for antenatal prophylaxis, but no randomized controlled studies exist comparing the efficacy of these agents. Even though betamethasone seems to affect fetal heart rate variation and fetal movements more than dexamethasone, it seems to offer several advantages. The treatment should consist of two doses of 12 mg betamethasone given intramuscularly 24 hours apart or four doses of 6 mg dexamethasone given intramuscularly 12 hours apart. It should be pointed out that the fetal biophysical variables recorded by cardiotocography or ultrasound may be significantly modified by the corticosteroid administration, particularly betamethasone, and mothers should be informed on reduction of fetal movements in the 48 hours subsequent to drug injection. In the case of impending SPTL, betamethasone was administered in 12 mg, 12 hours apart, showing the same beneficial effects.

The role of infection and use of antibiotics in preterm labor

The following investigations should be routine in most units:

- 1) Full blood count and group and save serum for further analysis;
- 2) Midstream specimen of urine examined for bacteriuria;
- 3) High vaginal swab for culture microscopy and sensitivities; and
- 4) Low vaginal swab and rectal swab to be cultured in Granada or selective broth medium for Group B streptococci screening.

In the presence of PPROM, the ORACLE study showed that prophylactic erythromycin was of benefit but not amoxicillin-clavulanic acid (co-amoxiclav). Apart from these two antibiotics no other antibiotics were tested in the ORACLE study. Erythromycin is not active against anaerobes, Group B streptococcus (SGB), or many of the organisms associated with bacterial vaginosis. Similarly co-amoxiclav, while is active against anaerobes and being broad spectrum, may not be active against the more fastidious organisms like *Mycoplasma hominis* associated with bacterial vaginosis. Intrapartum chemoprophylaxis for SGB should be by intravenous penicillin given intravenously 4 hourly and if the patient is allergic to penicillin, then a combination of erythromycin and claritromycin or clindamycin is recommended. Claritromycin and clindamycin were not assessed as part of the ORACLE study, however.

Topical vaginal chlorexidine (0.5%) in gel or vaginal douches have been proposed and found a valid alternative to parental antibiotics for SGB prophylaxis or treatment.

Among women with PPROM, the use of antibiotics was associated with a statistically significant intrapartum reduction of chorioamnionitis (OR 0.57, 95% CI 0.37-0.86). The numbers of babies born within 48 h (OR 0.71, 95% CI 0.58-0.87) and seven days of randomization (OR 0.80, 95% CI 0.71-0.90) were reduced, as were the following markers of neonatal morbidity: neonatal infection (OR 0.68, 95% CI 0.53-0.87), use of surfac-

tant (OR 0.83, 95% CI 0.72-0.96), oxygen therapy (OR 0.88, 95% CI 0.81-0.96), and abnormal cerebral ultrasound scan prior to discharge from the hospital (OR 0.82, 95% CI 0.68-0.98) (this meta-analysis included 12 trials and 6294 babies). The reduction of cerebral sonographic abnormalities indicates a protective effect. Antibiotic treatment following PPROM is recommended

Overall management

As soon as the diagnosis has been reached, it is recommended that neonatologists involved in management decisions are informed to ensure that a neonatal intensive care is available on site or that an *in utero* transfer to a center with intensive care unit facilities may be arranged.

In absence of clear evidence that tocolytic drugs improve outcome following preterm labor, it is reasonable not to use them. Women who are more likely to benefit from tocolysis are those at a still very preterm gestational age, those needing transfer to a hospital that can provide neonatal intensive care, or those who have not yet completed a full course of corticosteroids to promote fetal lung maturity. For these women, tocolytic drugs should be taken into account.

If time permits, an ultrasound scan should be arranged to check for fetal viability, fetal morphology, fetal number, fetal presentation, placental site, an estimate of fetal weight and amniotic fluid volume index, all of which might affect management. Appropriate analgesia following discussion with an anesthetist should be arranged and opiates should be avoided, if possible, to prevent central fetal and neonatal respiratory depression.

If intervention is contraindicated or unsuccessful, then the mode of delivery of a preterm infant should be individualized according to gestational age, fetal presentation, number of fetuses and the presence or absence of non-reassuring fetal heart tracing on cardiotocography.

Contraindicated intervention in the management of spontaneous preterm labor

When considering intervention to prolong gestation, certain absolute and relative contraindications should also be considered in order to minimize maternal and fetal morbidity and mortality. Absolute contraindications are those in which prolongation of pregnancy is contraindicated *per se*, e.g. clinically apparent intrauterine infection, known lethal fetal congenital malformation, fulminating proteinuric pre-eclampsia and any other urgent fetomaternal indication for delivery. Relative contraindications are those in which a debate exists about the risks and benefits of intervention such as antepartum hemorrhage, ruptured membranes, non-reassuring fetal heart rate pattern on cardiotocography, intrauterine growth restriction, insulin-dependent diabetes and multiple pregnancy.

Tocolytics should not be used if there is a significant antepartum hemorrhage, especially if there are signs and symptoms of abruptio placentae. Following a mild bleeding due to placenta previa, it is acceptable to use tocolytics because they

may help to stop uterine contractions and the stretch they induce, leading to further separation of the placenta and hemorrhage.

In the presence of ruptured membranes, tocolytics are rarely indicated after 36 weeks' gestation. At an earlier gestation, tocolytics may be administered when the risk-benefit balance is in favor of delaying delivery to allow a full course of glucocorticosteroids to be administered or arrangements to transfer the woman to a center with neonatal intensive care facilities.

Tocolytics to delay delivery of the preterm infant are contraindicated when non-reassuring fetal heart rate patterns on cardiotocography occur in association with a significant hemorrhage or with signs of fetomaternal infection.

Well-controlled insulin-dependent diabetic women with SPTL can safely be treated with atosiban. Close monitoring is required in the case other tocolytics are used because both glucocorticosteroids and tocolytics are likely to affect diabetic control.

Twins and higher-order multiple births are associated with a greater and expanded maternal plasma volume and secondary hyperaldosteronism when compared with singleton pregnancies. Beta-agonists are known to increase both aldosterone and renin levels in twin pregnancies, which may potentiate the risk of pulmonary edema. Beta-agonists are therefore contraindicated in multiple pregnancies, and alternative tocolytics should be used. Also, calcium channel blockers potentiate negative effects on maternal cardiovascular balance, especially in multiples, and therefore are contraindicated in these pregnancies.

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