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Review Article

Anaesthesiological considerations on tocolytic and uterotonic therapy in obstetrics

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Aim: Significant side effects of tocolytic and uterotonic substances may be of concern to the anaesthesiologist. Recently, new drugs have been introduced having less side effects for both the mother and the neonate.
Methods: A literature search was undertaken mainly focusing on meta-analyses, to review the possible side effects that might affect the course of anaesthesia and to suggest which precautions should be considered to prevent the occurrence of significant interactions with anaesthetic manipulations and drugs.
Results: Magnesium sulphate has a proven benefit in lowering systolic blood pressure and preventing the occurrence of eclampsia, but not as a tocolytic. β-adrenergic agonists are being abandoned due to the availability of tocolytic agents causing less side effects. Calcium channel blockers (CCB) are frequently used but can cause major maternal cardiovascular complications. Nitroglycerin seems to be appreciated as an acute tocolytic rather than a routine substance during pre-term labour. Cyclo-oxygenase-2 inhibitors are still under investigation but their tocolytic benefit is questionable mainly due to foetal side effects. Atosiban is considered the first-choice tocolytic. With respect to oxytocic drugs, oxytocine, prostaglandines and methylergometrine may all cause serious side effects especially when combined. The cardiovascular side effects of prostaglandins and methylergometrine can be life-threatening. Both oxytocin and carbetocin have a rather low risk for maternal complications.
Conclusion: Atosiban and CCB are at least as effective tocolytic agents as β-mimetics but have significantly less side effects. Magnesium sulphate can cause neuromuscular blockade, especially when combined with CCB. Concerning oxytocic agents, short-acting oxyctocin and long-acting carbetocin have the least side effects as compared with prostaglandins and methylergometrine.

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Tocolytic and uterotonic drugs are administered to influence the contractility of the uterus. For this effect the most important factor is the amount of intracellular calcium that can be changed by influx from the extracellular compartment or release/reuptake from the sarcoplasmatic reticulum (Fig. 1). Another way to block uterine contraction is through a direct effect on the enzyme that interferes with phosphorylation of myosin.

The present overview highlights the different medications in use and their reported interaction with anaesthetic procedures.

Tocolytic substances

These are given to prevent pre-term delivery or to enable some manipulations. Pre-term birth rates are not declining but are in fact slowly increasing.[1] Pre-term birth is a major contributor to perinatal mortality and morbidity.[2]

On the other hand, it may be questioned whether it is wise to keep the foetus in a possibly hostile intrauterine environment with the risk of infection and hypoxic stress. Most authors agree that only with intact membranes and with a gestational age of <34 weeks, the foetus may benefit from short-term tocolysis, allowing the administration of corticosteroids for lung maturation and/or transportation to a neonatal care centre.[3] Administration of corticosteroids and better neonatal care are associated with improved neonatal outcome. To date, tocolysis has not been convincingly shown to improve neonatal outcome above that achieved with the administration of corticosteroids alone.[4]

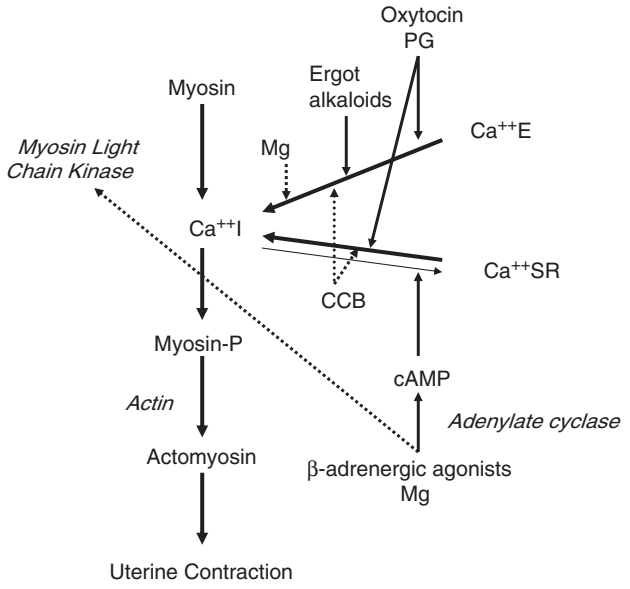

Fig. 1. A schematic overview of uterine contraction. Calcium, Ca^{2+}; I, intracellular; E, extracellular; SR, sarcoplasmatic reticulum; Mg, magnesium; CCB, calcium channel blockers; PG, prostaglandins; cAMP, cyclic adenosin monophosphate. The dotted lines represent an inhibitory effect. Enzymes are printed in italic.

Hydration

Although not considered as medication, hydration of the patient has been suggested to decrease uterine activity. This should be done very carefully because it may increase the risk of pulmonary oedema associated with the use of other tocolytic agents. Meta-analysis has shown that hydration is no better than placebo.[5]

β-adrenergic drugs

The use of β-mimetics as tocolytic agents is declining for several reasons. They have the most important list of side effects, as up to 25 fatal cases have been described following pulmonary oedema. Also, the lack of evidence of improved neonatal outcomes and the availability of at least as effective other tocolytics with less side effects have resulted in the suggestion to abandon the β-agonists.[6,7]

The most widely used β-mimetics are fenoterol and ritodrine. Ritodrine is a rapid-acting substance with a rather short half-life but tachyphylaxis may occur after prolonged use whereas fenoterol, which is somewhat more β-2 selective, has a longer duration of action. Only limited experience exists with salbutamol and terbutaline.[7]

Maternal haemodynamic side effects consist of tachycardia (β-1), arrhythmia (supraventricular tachycardia, atrial flutter and ventricular extrasystoles), hypotension (vasodilation and decreased diastolic blood pressure), myocardial ischaemia and pulmonary oedema (risk 1/1000). The latter complication may occur more than 24 h after the start of treatment and rarely earlier than that while the risk of pulmonary oedema may remain up to 24 h after discontinuation of the tocolytic agent. The risk of pulmonary oedema is enhanced in case of intravenous therapy, polyhydramnios, multiple gestations, excessive fluid therapy (to treat hypotension), corticosteroid therapy, anaemia and hypertension. Other contributing factors are fluid retention (due to ADH and aldosterone secretion), decrease of colloid oncotic pressure, infection (endotoxin release), disturbed oxygen delivery balance and pregnancy itself due to the increase of intravascular volume.[8]

Pulmonary oedema may be avoided by careful fluid therapy, not combining tocolytics and maintaining the maternal heart rate below 120 b.p.m. β-mimetics should not be given to patients with pre-existing cardiac disease such as arrythmias and poorly controlled thyroid hyperactivity.[9]

Other side effects described with β-mimetics are tremor, palpitations, restlessness, nervousness, anxiety, nausea/vomiting, fever, hallucinations and probably, more importantly, some metabolic effects.

β-mimetics increase the secretion of glucagon in the pancreas. This leads to glucogenolysis and gluconeogenesis and finally hyperglycaemia stimulating the production of insulin. As a consequence, hypokalaemia, even after cessation of therapy, may also occur, causing cardiac arrhythmias. Potassium administration is rarely required because total potassium will not change. On the other hand, rebound hyperkalaemia has been reported after abrupt discontinuation of β-mimetic therapy.[10]

β-mimetics should be avoided in diabetic patients, severe pre-eclampsia, cardiac disease, hypovolaemia and thyroid disease.[7]

As β-mimetics cross the placenta, this may affect the neonatal outcome. Besides an increase in the foetal heart rate, the neonate may suffer mostly from the metabolic side effects. Hyperinsulinism may cause neonatal hypoglycaemia. Also, increased neonatal intraventricular haemorrhage has been reported while, due to surfactant release, the risk of developing hyaline membrane disease may be decreased.[11]

With all the side effects in mind, it is not surprising that therapy with β-mimetics may

have significant anaesthetic implications. There are no prospective, randomized-controlled trials of anaesthesia after β-mimetic administration. As the mean disposition half-life of ritodrine has been reported to be 156 ± 51 min[12], it may be prudent to delay the induction of general anaesthesia at least 60 min after discontinuation of the tocolytic. This is in accordance with a recent case report of six patients who underwent an emergency Caesarean section 45–75 min after cessation of ritodrine treatment. A rebound hyperkalaemia with peak levels from 6.8 to 7.9 mmol/l was noted in each case 60–150 min after cessation of ritodrine.[13] However, women with failed tocolysis often need emergency administration of anaesthesia. In such cases regional anaesthesia may be preferable. Regional anaesthesia may enhance the hypotensive effect, which makes some anaesthetists prefer epidural rather than spinal anaesthesia. When hypotension occurs, it is recommended to be careful with fluids and rather select a vasopressor drug. Phenylephrine may be more beneficial than ephedrine as the latter further increases the heart rate.

Magnesium sulphate

Although rarely used in Europe, in the United States, it is still popular as a tocolytic despite several studies demonstrating no tocolytic activity.[14] The main reason for this is the lack of evidence that magnesium sulphate really has benefit over controls (placebo and other tocolytics) while it may induce a higher risk of neonatal death.[14,15] Recently, but this needs confirmation in prospective trials, it has been used for neuroprotection for very pre-term birth, i.e. <30 weeks. The effectiveness may also depend on the stage of labour.[16] Magnesium sulphate should be administered in every case of severe pre-eclampsia for the prevention of eclamptic seizures.[17]

When compared with other tocolytics, magnesium sulphate is relatively well tolerated. Especially haemodynamically magnesium sulphate is quite safe but with this drug pulmonary oedema may also occur. Respiratory difficulty and cardiac arrest may theoretically occur but at extremely high plasma concentrations. Other well-known side effects are mostly lethargy, flushing, headache, muscle weakness, diplopia, dryness of the mouth, nausea/vomiting and shortness of breath. Some authors found that magnesium, especially after prolonged cumulative administration, may increase maternal morbidity following intake for 48 h or more as compared with intake for shorter periods.[18]

It may be contraindicated in patients with myasthenia gravis, evidence of marginal cardiac compensation and renal disease. Calcium gluconate can be administered to reverse untoward effects. Magnesium crosses the placenta and neonatal side effects may be: lethargy, hypotonia, respiratory depression and bone demineralization.[18] In a comparative study with nifedipine, it was found that magnesium sulphate caused neonates to spend longer times in the neonatal intensive care unit.[19]

For the anaesthetist the interaction between magnesium sulphate and muscle relaxants may be of additional importance. This increased sensitivity may cause overdose, faster onset and prolonged duration of action of neuromuscular blocking agents. In pre-eclamptic patients, the association between a low platelet count and the weak tocolytic effect of magnesium given for its anticonvulsive properties may cause major bleeding in case of uterine atony.

CCB

These substances have been known to have tocolytic properties for a long time even if they have never been compared with placebo. CCB inhibit the transmembrane influx of calcium ions into smooth muscle cell by producing an interference with slow voltage-dependent calcium channels. When compared with β-mimetics, it was shown that nifedipine caused more frequent successful prolongation of pregnancy in case of pre-term labour, with fewer neonatal problems.[20,21] The most well-known substances are nifedipine (orally) and nicardipine (intravenously). Vasodilatation and hypotension are usually mild. Despite the low incidence of side effects, serious complications may occur such as pulmonary oedema (more risk with nicardipine) and neuromuscular blockade (after combination with magnesium sulphate). The combination of these two synergistic myocardial depressants has been reported to induce symptomatic hypocalcaemia.[21] Also, the combination with β-mimetics should be avoided.[22]

Combined use of CCB with potent inhalation anaesthetics may lead to vasodilatation, hypotension, myocardial depression and conduction defects. They should be given with caution to mothers with already existing hypotension and multiple gestation.[22] Especially, the short-acting form of

nifedipine seems to result in increased cardiovascular mortality.[23] Several cases of acute pulmonary oedema during tocolytic therapy with nifedipine[24,25] and nicardipine[26,27] have been reported especially in multiple pregnancy. The pathophysiology of pulmonary oedema has been postulated to be an acute diastolic dysfunction resulting from reflex tachycardia. Vasodilatation caused by nifedipine may be more pronounced in pre-capillary than post-capillary vessels, with an increase in hydrostatic pressure as a result. Further exaggerating factors may be increased extracellular volume due to corticosteroid administration and infusion of fluids. Other minor side effects are flushing, headache, dizziness and nausea.

Prostaglandin synthesis inhibitors

Prostaglandins are mediators of uterine contraction. They block cyclo-oxygenase (COX) 1 and 2 and decrease the levels of potent myometrial constrictors, prostaglandins $F_{2\alpha}$ and $E_{2\alpha}$. Indomethacin is known to have tocolytic properties since more than three decades. The most important concern is their effect on platelet function and premature closure of the ductus arteriosus but the latter does not seem to be a major problem when gestational age is <32 weeks. Also, ketorolac may be used for tocolysis but cannot be administered orally.

The discovery of two types of more or less specific COX inhibitors has led to focus of attention and hope on the COX-2-specific inhibitors causing less side effects. Rofecoxib has been compared with magnesium sulphate and no difference was found but the former was better tolerated. In the light of overall evidence indicating that magnesium is ineffective, this does not necessarily represent an argument in favour of rofecoxib. Limited experience also exists with celecoxib and nimesulide.[28–30]

The side effects of COX inhibitors are well known. Especially when COX-1 inhibitors are used, care should be taken with patients having ulcer disease, NSAID-sensitive asthma, renal or hepatic impairment, coagulation disorders and thrombocytopenia. Also in case of oligo-hydramnios their use should be weighed against the risk of renal impairment. The antipyretic effect may mask fever.

Recently, attention has been focused on cardiovascular side effects especially with the use of some COX-2 inhibitors.

Neonatal effects are constriction and premature closure of the ductus arteriosus, pulmonary hypertension, decrease in renal function, intraventricular haemorrhage and necrotizing enterocolitis but most of them only occur after a long treatment, use of large doses and after 32 weeks of gestation.[30]

Nitroglycerin

Nitroglycerin has been used for relaxation of the uterus, removal of a retained placenta, facilitation of foetal extraction during a Caesarean section, twin manipulation and correction of uterine inversion. It acts by direct vasodilatation and the production of nitric oxide. It may be administered as a patch, sublingually or intravenously. Patches have been studied in one randomized-controlled trial (RCT) and nitroglycerin has been compared with β-mimetics, demonstrating a decrease of the risk of birth before 28 weeks of pregnancy.[31] In one trial comparing nitroglycerin with β-mimetics, the latter were found to be more effective.[32]

Nitroglycerin can also be used to ameliorate foeto-placental blood flow in case of intrauterine growth restriction, but no good prospective trials on this are available.[33] Hypotension may occur and require discontinuation with subsequent failure of tocolysis. In addition, a meta-analysis of studies comparing nitroglycerin with magnesium sulphate or ritodrine did not find the former to be superior despite more effectiveness vs. placebo.[34]

In anaesthetic literature, its use has been suggested for acute tocolysis when foetal bradycardia occurs following uterine hypertonicity as described after CSE analgesia (although not all authors agree with a possibly higher incidence than with epidural analgesia).[35] The recommended single intravenous dose is 100 μg.

Oxytocin antagonists

Although the exact mechanism of the initiation of pre-term labour remains unknown, one pathway concerns oxytocin. As a consequence, it seems logical that oxytocin receptor antagonists might be effective tocolytic agents. Although several agents have been studied, atosiban has been tested most completely including randomized-controlled clinical trials comparing atosiban with β-mimetics but no direct comparative studies between atosiban and nifedipine exist.[36–38] When compared with ritodrine, the previous gold standard, atosiban is associated with a higher gestational age at delivery, a lower incidence of maternal side effects and improved neonatal outcome while infants being

followed for several years did not experience long-term effects.[39] A recent prospective, open-label, randomized study comparing atosiban with usual care of threatened pre-term labour (β-mimetics, CCBs, magnesium sulphate or any other tocolytic, alone or in combination) suggested that the use of atosiban resulted in more women remaining undelivered not requiring an alternative tocolytic agent after 48 h and was associated with fewer maternal and foetal adverse events.[40] In general, atosiban is now considered to be the drug of first choice mainly because it has less side effects than β-mimetics.[41] It is the only tocolytic that has shown the benefit of long-term (>48 h) tocolysis in an RCT.

Atosiban lacks cardiovascular, pulmonary or central nervous system activity. Minor side effects are the classical atypical complaints such as nausea, vomiting and headache, rarely necessitating discontinuation. Effects on maternal or neonatal diuresis have not been observed.

A disadvantage of atosiban is its complicated intravenous administration (bolus and different infusion rates) as compared with other orally and rectally administered drugs. It is also more expensive than the CCBs. It is now licensed by the FDA while other intravenous and oral oxytocin receptor antagonists are in development. No interaction with anaesthetics has been reported to date.

Progesterone

Progesterone has been reported in double-blind, placebo-controlled randomized clinical trials to be effective in decreasing the risk of pre-term birth both when administered in an intramuscular way as when given vaginally.[42] Progesterone should only be considered as a preventive agent whereas it is not used for tocolysis once pre-term labour has developed. No major interactions of anaesthetic importance have been reported but progesterone has a known sedative effect and might decrease the need for anaesthetic medication.[43]

Uterotonic substances

Uterotonic or oxytocic drugs are used to induce or augment labour but they may be life-saving in the prevention or the treatment of post-partum bleeding.[44] Like with the tocolytics, calcium plays a predominant role. They all increase intracellular calcium, thus stimulating myosin phosphorylation. Three categories are actually administered: oxytocin, prostaglandins and ergot alkaloids, all having their specific receptors. Ergot alkaloids are not used for labour induction. Some prostaglandins are effective for labour induction and cervical ripening, and others for treating and preventing post-partum haemorrhage (PPH).

The risk of serious side effects is enhanced when combining them as reported in a case study of pulmonary oedema following the combined use of oxytocin, prostaglandin $F_{2-\alpha}$ and methylergometrine.[45]

Oxytocin

Oxytocin is used for labour induction and during the third stage of labour. It is the drug of choice for preventing and treating bleeding during vaginal or operative delivery. Routine administration of oxytocin has been demonstrated to reduce the incidence of PPH (>500 ml) by 40%.[46] It is given after a Caesarean section to promote uterine contraction either as an intravenous bolus or as an infusion. Effective uterine contraction can be achieved after an elective Caesarean section in non-labouring women at term by administering boluses of oxytocin no larger than 1 IU, the minimum effective intravenous bolus dose of oxytocin being 0.35 IU[47], while the necessary dose in labouring women at Caesarean delivery is about nine times higher.[48] The difference is believed to be due to the reduction of oxytocin-binding sites and desensitization of myometrial oxytocin receptors in active labour. Exogenous oxytocin is exactly similar to the natural hormone released by the posterior pituitary gland. The chemical structure of oxytocin resembles that of the antidiuretic hormone and antidiuresis with hyponatremia and water intoxication may occur after prolonged administration of high doses, especially when given with a dextrose solution instead of a salt solution.[49]

Haemodynamic alterations will depend on the amount of vasopressin available, resulting in either hypertension or hypotension. Oxytocin given as a rapid intravenous bolus causes a dose-related hypotension, tachycardia and an increase in cardiac output in healthy women undergoing a Caesarean section under spinal anaesthesia.[50] Hypotension is most likely due to vasodilatation as receptors are also present in vascular smooth muscles and increases in heart rate and cardiac output are believed to be signs of compensatory mechanisms. Nevertheless, cardiovascular changes after boluses are usually mild (15–20%) and short lived and well tolerated by healthy women.

Several regimens for administration of oxytocin have been described. Two randomized trials suggest that in healthy women undergoing an elective Caesarean section under regional anaesthesia, there appears to be no benefit in giving more than 5 IU of oxytocin in terms of estimated blood loss, cardiovascular side effects and uterine tone.[50,51] Administration of 5 IU of oxytocin as a slow infusion over 5 min is associated with greater haemodynamic stability compared with a rapid bolus injection.[52]

Carbetocin

Carbetocin is a new synthetic oxytocin analogue for preventing PPH and uterine atony although it is not available throughout Europe. The onset time is very short, i.e. within 2 min while the plasma half-life is six to seven times longer than with oxytocin. It can be administered by the intravenous and intramuscular route although the nasal route may also be suitable. In a meta-analysis four studies were included, yielding a total of 1037 patients.[53] Three out of the four studies were performed in Caesarean section patients. As compared with oxytocin, 100 μg of intravenous carbetocin resulted in a similar incidence of PPH and blood loss. However, carbetocin required less uterine massage and additional therapeutic uterotonic agents, and also nausea was also less in the vaginal delivery study.

It is unclear why currently its use is mainly recommended following a Caesarean section while it is discouraged in pre-eclampsia, renal and liver disease.

Prostaglandins

Prostaglandins are used both to induce labour and to prevent or treat PPH.[54,55] The most frequently given prostaglandins are PGE_1 (misoprostol), PGE_2 (dinoprostone, prostin) and $PGF_{2-\alpha}$.[44] The initial parent compound $PGF_{2-\alpha}$ has been replaced by 15-methyl $PGF_{2-\alpha}$ (hemabate) in most cases. They may be administered by different routes: orally, rectally, vaginally and intravenously. The most currently used prostaglandin for uterine atony is misoprostol that is administered vaginally, rectally or sublingually.[54] It has a faster effect than PGE_2 and has limited side effects with respect to the cardiovascular system, both after vaginal delivery and after Caesarean section. The effect of oral, sublingual or rectal misoprostol is comparable to that of intravenous oxytocin for the prevention of PPH.[54] Most reported problems to date are hyperstimulation, foetal heart rate abnormalities, chorioamnionitis, neonatal infection, antibiotic need and ICU transfers. PGE_2 and $PGF_{2-\alpha}$ have opposite side effects. PGE_2 decreases systemic vascular resistance, thus tending to cause hypotension (and also arrhythmias). Therapy-resistant hypotension has been reported during epidural anaesthesia for Caesarean section in three females receiving dinoprostone.[56] $PGF_{2-\alpha}$ increases pulmonary vascular resistance causing pulmonary hypertension and induces bronchoconstriction. The administration of $PGF_{2-\alpha}$ has been reported to result in pulmonary oedema during a Caesarean section[57] and maternal arterial desaturation with an increase in intrapulmonary shunting in five women with severe uterine atony.[58] These case reports suggest a ventilation/perfusion mismatch causing serious hypoxia after $PGF_{2-\alpha}$ administration. An overdose of $PGF_{2-\alpha}$ has been reported to produce cardiovascular collapse[59] and severe bronchospasm and hypotension.[60] Overhydration should be avoided when administration of this substance is considered.

Stimulation of the smooth muscle within the gastro-intestinal tract may cause nausea, vomiting and diarrhoea. Shivering and elevation of body temperature are also possible. The intensity and frequency of side effects may depend on the route of administration. Local application surely causes less problems.

Ergot alkaloids

Methylergonovine or methylergometrine causes a tonic uterine contraction and has a long duration of action. They are mostly given intramuscularly and intravenously. When injected intravenously as an undiluted substance, more side effects may occur because these substances also constrict smooth muscles in other tissues, causing hypertension (pulmonary and systemic), coronary artery spasm and bronchospasm. Nausea, vomiting and enhanced pain are other frequently observed side effects. They should not be given in case of pre-existing hypertension, bronchial asthma and pre-eclampsia or with the concomitant use of other vasopressors. At least seven cases of myocardial infarction after post-partum administration of ergot alkaloids have been reported in the literature.[61,62] Methylergonovine has been reported to relieve postdural puncture headache in obstetric

patients but the place of this approach is not yet defined.[63]

Combinations

In some countries, a combination of oxytocin with methylergometrine exists under a commercialized formulation, i.e. Syntometrine®. In a comparative study, this combination failed to decrease the incidence of nausea and hypertension, which was less with carbocetin.[64]

Conclusions

β-mimetics cause the most side effects explaining, why they have increasingly fallen from favour, especially because other safer substances exist nowadays. Calcium entry blockers cause less haemodynamic problems. Magnesium sulphate is not a tocolytic but prevents eclamptic seizures, but interferes with neuromuscular transmission. Atosiban may be considered as the tocolytic of first choice, together with CCBs.

Of the oxytocics, oxytocin in a bolus should be injected slowly or diluted. Carbetocin has a longer half-life and less maternal side effects such as nausea with a similar effect on PPH. Prostaglandin E_2 given intravenously may cause severe hypotension while $PGF_{2-\alpha}$ can cause pulmonary hypertension and bronchospasm. Methylergometrine may cause hypertension, bronchospasm, nausea and vomiting.

References

1. Murphy DJ. Epidemiology and environmental factors in preterm labour. Best Pract Res Clin Obstet Gynaecol 2007; 21: 773–8.
2. Gibson AT. Outcome following preterm birth. Best Pract Res Clin Obstet Gynaecol 2007; 21: 773–8.
3. Giles W, Bisits A. The present and future of tocolysis. Best Pract Res Clin Obstet Gynaecol 2007; 21: 857–68.
4. Iams JD, Romero D, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008; 371: 164–75.
5. Stan C, Boulvain M, Hirsbrunner-Amagbaly P, Pfister R. Hydration for treatment of preterm labour. Cochrane Database Syst Rev 2002 (2): CD003096.
6. King JF. Tocolysis and preterm labour. Curr Opin Obstet Gynecol 2004; 16: 459–63.
7. Anotayanonth S, Subhedar NV, Garner P, Neilson JP, Harigopal S. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev 2004 (4): CD004352.
8. Yayu Y, Yakayama T. Effectiveness and safety of ritodrine hydrochloride for the treatment of preterm labour: a systematic review. Pharmacoepidemiol Drug Saf 2006; 15: 813–22.
9. Chandraharan E, Arulkumaran S. Acute tocolysis. Curr Opin Obstet Gynecol 2005; 17: 151–6.
10. Kuczkowski KM, Benumof JL. Rebound hyperkalemia after cessation of intravenous tocolytic therapy with terbutaline in the treatment of preterm labor: anesthetic implications. J Clin Anesth 2003; 15: 357–8.
11. Kast A, Hermes M. Beta-adrenoceptor tocolysis and affects on the heart of the fetus and neonate: a review. J Perinat Med 1993; 21: 97–106.
12. Caritis SN, Venkataramanam R, Darby MJ, Chiao JF, Krew M. Pharmacokinetcs of ritodrine administered intravenously: recommendations for changes in the current regime. Am J Obstet Gynecol 1990; 162: 429–37.
13. Kotani N, Kushikata T, Hashimoto H, Muraoka M, Tonusaki M, Matsuki A. Rebound perioperative hyperkalemia in six patients after cessation of ritodrine for premature labor. Anesth Analg 2001; 93: 709–11.
14. Grimes DA, Nanda K. Magnesium sulfate tocolysis: time to quit. Obstet Gynecol 2006; 108: 986–9.
15. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst Rev 2002; 4: CD001060.
16. Marret S, Marpeau L, Zupan-Simunek V, Eurin D, Leveque C, Hellot MFBenichou J. PREMAG trial group. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial. Br J Obstet Gynecol 2007; 114: 310–8.
17. Duley L, Gulmezoglu AM, Henderson-Smart DJ. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev 2003 (2): CD000025.
18. Nasser AH, Sakhel K, Maarouf H, Haassan GR, Usta IM. Adverse maternal and neonatal outcome of prolonged course of magnesium sulphate tocolysis. Acta Obstet Gynecol Scand 2006; 85: 1099–103.
19. Lyell DJ, Pullen K, Campbell L, Ching S, Druzin ML, Chitkara U, Burrs D, Caughey AB, El-Sayed YY. Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labor: a randomized controlled trial. Obstet Gynecol 2007; 110: 61–7.
20. Papatsonis DN, Lok CA, Bos JM, Geijn HP, Dekker GA. Calcium channel blockers in the management of preterm labor and hypertension in pregnancy. Eur J Obstet Gynecol Reprod Biol 2001; 97: 122–40.
21. King JF, Flenady VJ, Papatsonis DN, Dekker GA, Carbonne B. Calcium channel blockers for inhibiting preterm labour. Cochrane Database Syst Rev 2003 (1): CD002255.
22. Oei SG. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. Eur J Obstet Gynecol Reprod Biol 2006; 126: 137–45.
23. Davies WB, Wells SR, Kuller JA, Thorp JM. Analysis of the risks associated with calcium channel blockade: implications for the obstetrician-gynecologists. Obstet Gynecol Surv 1997; 52: 198–201.
24. Abbas OM, Nassar AH, Kani NA, Usta IM. Acute pulmonary edema during tocolytic therapy with nifedipine. Am J Obstet Gynecol 2006; 195: e3–4.
25. Gatault P, Genee O, Legras A, Garot D, Mercier E, Fichet J. Calcium-channel blockers: an increasing cause of pulmonary edema during tocolytic therapy. Int J Cardiol 2007; 130: e123–4.
26. Vaast P, Dubreucq-Fossaert J, Houffin-Debarge V, Provost-Helou N, Ducloy-Bouthors AS, Puech F, Subtil D. Acute pulmonary oedema during nicardipine therapy for premature labour. Report of five cases. Eur J Obstet Gynecol Reprod Biol 2004; 113: 98–9.

27. Bal L, Thierry S, Brocas E, Adam M, Van de Louw A, Tenaillon A. Pulmonary edema induced by calcium-channel blockade for tocolysis. Anesth Analg 2004; 99: 910–1.
28. Stika CS, Gross GA, Leguizamon G, Gerber S, Levy R, Mathur A, Bernhard LM, Nelson DM, Sadovsky Y. A prospective randomized safety trial of celecoxib for treatment of preterm labor. Am J Obstet Gynecol 2002; 187: 653–60.
29. Sawdy RJ, Groom KM, Bennett PR. Experience of the use of nimesulide, a cyclo-oxygenase-2 selective prostaglandin synthesis inhibitor, in the prevention of preterm labour in 44 high-risk cases. J Obstet Gynaecol 2004; 24: 226–9.
30. King J, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. Cochrane Database Syst Rev 2005 (2): CD001992.
31. Smith GN, Walker MC, Ohlsson A, O'Brien K, Windrim R. Canadian Preterm Labour Nitroglycerin Trial Group. Randomized double-blind placebo-controlled trial of transdermal nitroglycerin for preterm labor. Am J Obstet Gynecol 2007; 196: 37.e1–8.
32. Bisits A, Madsen G, Knox M, Gill A, Smith R, Yeo G, Kwek K, Daniel M, Leung TN, Cheung K, Chung T, Jones I, Toohill J, Tudehope D, Giles W. The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. Am J Obstet Gynecol 2004; 191: 683–90.
33. Oyelese KO, Black RS, Lees CC, Campbell S. A novel approach to the management of pregnancies complicated by uteroplacental insufficiency and previous stillbirth. Aust NZ J Obstet Gynaecol 1998; 38: 391–5.
34. Morgan PJ, Kung R, Tarshis J. Nitroglycerin as a uterine relaxant: a systematic review. J Obstet Gynaecol Can 2002; 24: 403–9.
35. Van de Velde M, Vercauteren M, Vandermeersch E. Fetal heart rate abnormalities after regional analgesia for labor pain: the effect of intrathecal opioids. Reg Anesth Pain Med 2001; 26: 257–62.
36. Coomarasamy A, Knox EM, Gee H, Song F, Khan KS. Effectiveness of nifedipine versus atosiban for tocolysis in preterm labour: a meta-analysis with an indirect comparison of randomised trials. Br J Obstet Gynecol 2003; 110: 1045–9.
37. Al-Omari WR, Al-Shammaa HB, Al-Tikriti EM, Ahmed KW. Atosiban and nifedipine in acute tocolysis: a comparative study. Eur J Obstet Gynecol Reprod Biol 2006; 128: 129–34.
38. Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database Syst Rev 2005 (3): CD004452.
39. Locci M, Nazzaro G, Merenda A, Pisaturo ML, Laviscio P, Poppiti R, Mioranda M, Stile A, De Placido G. Atosiban vs ritodrine used prophylactically with cerclage in ICSI pregnacies to prevent pre-term birth in women identified as being at high risk on the basis of transvaginal ultrasound scan. J Obstet Gynaecol 2006; 26: 396–401.
40. Husslein P, Cabero Roura L, Dudenhausen JW, Helmer H, Frydman R, Rizzo N, Schneider D. Atosiban versus usual care for the management of preterm labor. J Perinat Med 2007; 35: 305–13.
41. Duley LMM. Guidelines and Audit Committee of RCOG. Tocolytic drugs for women in preterm labour. London, UK: RCOG Clinical Guidelines 2002; 1: 1–7.
42. Mackenzie R, Walker M, Armson A, Hannah ME. Progesterone for the prevention of preterm birth among women at increased risk: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol 2006; 194: 1234–42.
43. Erden V, Yangin Z, Erkalp K, Delatioglu H, Bahceci F, Seyhan A. Increased progesterone production during the luteal phase of menstruation may decrease anesthetic requirement. Anesth Analg 2005; 101: 1007–11.
44. Chong YS, Su LL, Arulkumaran S. Current strategies for the prevention of postpartum haemorrhage in the third stage of labour. Curr Opin Obstet Gynecol 2004; 16: 143–50.
45. Heytens L, Camu F. Pulmonary edema during cesarean section related to the use of oxytocic drugs. Acta Anaesthesiol Belg 1984; 35: 155–64.
46. Nordström L, Fogelstam K, Fridman G, Larsson A, Rydhström H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. Br J Obstet Gynaecol 1997; 104: 781–6.
47. Carvalho JCA, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective cesarean delivery: a dose-finding study. Obstet Gynaecol 2004; 104: 1005–10.
48. Balki M, Ronayne M, Davies S, Fallah S, Kingdom J, Windrim R, Carvalho JCA. Minimum oxytocin dose requirement after cesarean delivery for labor arrest. Obstet Gynecol 2006; 107: 45–50.
49. Ophir E, Solt I, Odek M, Bornstein J. Water intoxication: a dangerous condition in labour and delivery rooms. Obstet Gynecol Surv 2007; 62: 731–8.
50. Pinder AJ, Dresner M, Calow C, O'Riordan JO, Johnson R. Haemodynamic changes caused by oxytocin during caesarean section under spinal anaesthesia. Int J Obstet Anesth 2002; 11: 156–9.
51. Sarna MC, Soni AK, Gomez M, Oriol NE. Intravenous oxytocin in patients undergoing elective cesarean section. Anesth Analg 1997; 84: 753–6.
52. Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing Caesarean section. Br J Anaesth 2006; 98: 116–9.
53. Su L, Chong Y, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2007 (3): CD005457.
54. Gulmezoglu A, Forna F, Villar J, Hofmeyr G. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2007 (3): CD000494.
55. Kelly AJ, Kavanagh J, Thomas J. Vaginal prostaglandin (PGE_2 and $PGF_{2-alpha}$) for induction of labour at term. Cochrane Database Syst Rev 2003: CD003101.
56. Veeckman L, Müller E, Van Aken H. Epidural anesthesia and local administration of high-dose prostaglandin in obstetrics. A dangerous combination. Reg Anesth 1989; 12: 76–9.
57. Rodriguez de la Torre MR, Gallego Alonso JI, Gil Fernandez M. Pulmonary edema related to administration of 15-methyl-prostaglandin $F_{2-alpha}$ during cesarean section. Rev Esp Anestesiol Reanim 2004; 51: 104–7.
58. Hankins GDV, Berryman GK, Scott RT, Hood D. Maternal arterial desaturation with 15-methyl prostaglandin F_2 alpha for uterine atony. Obstet Gynecol 1988; 72: 367–70.
59. Douglas MJ, Farquharson DF, Ross PL. Cardiovascular collapse following an overdose of prostaglandin F_2 alpha: a case report. Can J Anaesth 1989; 36: 466–9.
60. O'Leary AM. Severe bronchospasm and hypotension after 15-methyl prostaglandin $F_{2\alpha}$ in atonic post partum haemorrhage. Int J Obstet Anesth 1994; 3: 42–4.
61. Mousa HA, Mckinley CA, Thong J. Acute postpartum myocardial infarction after ergometrine administration in a woman with familial hypercholesterolaemia. Br J Obstet Gynaecol 2000; 107: 939–40.
62. Tsui BCH, Stewart B, Fitzmaurice A, Williams R. Cardiac arrest and myocardial infarction inbduced by postpartum

intravenous ergonovine administration. Anesthesiology 2001; 94: 363–4.
63. Alici HA, Cesur M, Erdem AF, Ingec M, Bebek Z. Is methergine alone sufficient in relieving postdural puncture headache? Acta Obstet Gynaecol Scand 2006; 85: 632–3.
64. Leung SW, Ng PS, Wong WY, Cheung TH. A randomised trial of carbocetin versus syntometrine in the management of the third stage of labour. Br J Obstet Gynaecol 2006; 113: 1459–64.

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