Tocolytic treatment for the management of preterm labour: a systematic review

Tan T C, Devendra K, Tan L K, Tan H K

ABSTRACT

Spontaneous preterm labour and delivery accounts for approximately one-third of preterm births, which is the predominant cause of perinatal mortality and morbidity. This review aims to evaluate the evidence on the benefits and harms of five classes of tocolytic therapy, namely: betamimetics, calcium channel blockers, magnesium, non-steroidal anti-inflammatory agents, and atosiban. We performed a systematic review of the effectiveness of tocolytics to stop uterine contractions (first-line therapy). Reports of randomised controlled trials from searches of MEDLINE, bibliographies of review articles, Cochrane Collaboration and its Pregnancy and Childbirth Review Group between 1966 and 2003 were identified, using the search terms "randomised controlled trial" (RCT), "preterm labor", "tocolysis", "betamimetics", "ritodrine", "prostaglandin synthetase inhibitors", "indomethacin", "calcium channel blockers", "nifedipine", "oxytocin receptor blockers", "atosiban", and "magnesium sulphate". Studies on women with preterm labour comparing the effects of a tocolytic with a placebo or no treatment that met our inclusion criteria, were included. To our knowledge, the trials were conducted mainly before 1999 and there were no placebo-controlled trials after that. Of the 86 articles identified and evaluated, 14 first-line studies met more stringent requirements for meta-analyses. Tocolytics were associated with significant decreases in the odds of delivery within 24 hours (odds-ratio [OR] 0.54, 95 percent confidence interval [CI] 0.32-0.91) and 48 hours (OR 0.47, 95 percent CI 0.30-0.75). These effects were significant for beta-agonists, atosiban and indomethacin, but not magnesium sulphate. Maternal side-effects significantly associated with betamimetics were pulmonary oedema, cardiac arrhthymias and hypokalaemia. Although calcium antagonists have not been evaluated against placebo, comparative trials with beta-agonists have shown more favourable neonatal outcomes and better prolongation of gestation. In conclusion, the management of threatened preterm labour with first-line tocolytic therapy can prolong gestation. However, the time gained in-utero need to be optimised. There is no clear first-line tocolytic agent. The use of tocolytic agents should be individualised and based on maternal condition, potential side-effects and gestational age.

Keywords: gestation, preterm labour, systematic review, tocolytic treatment

Singapore Med J 2006; 47(5):361-366

INTRODUCTION

In 1907, Simpson referred to a birth on December 25, 1642 when a widow gave birth prematurely to a male child who was "so small that he could have been put into a quart mug". The infant survived and grew up to be Sir Isaac Newton, who subsequently described gravity. Indeed, this is one of the earliest descriptions of preterm labour[1]. However, a significant proportion of preterm births do not survive, let alone grow to become Newtons, and prematurity still remains a major contributor of neonatal morbidity and mortality today.

In 1959, the tocolytic properties of magnesium sulphate were described by Hall et al who observed the prolongation of labour in patients treated with it[2]. In 1961, isoxuprine, a beta-agonist, was the first drug to be published as a tocolytic agent to stop uterine contractions[3]. Since then, the armamentarium of tocolytics has expanded to include agents such as betamimetics, magnesium sulphate, non-steroidal anti-inflammatory drugs, calcium-channel blockers and oxytocin receptor antagonists, which have been used as tocolytic agents. The wide range of tocolytic

Department of General Obstetrics and Gynaecology
KK Women's and Children's Hospital
100 Bukit Timah Road
Singapore 229899

Tan TC, MBBS, MMed
Medical Officer

Maternal-Foetal Medicine Section
Department of Obstetrics and Gynaecology
Singapore General Hospital

Devendra K, MBBS, MRCOG
Consultant

Tan LK, MRCOG, FAMS
Consultant

Tan HK, MRCOG, MMed
Senior Consultant

Correspondence to:
Dr Tan Thiam-Chye
Tel: (65) 6394 1019
Fax: (65) 6298 6343
Email: dr.tctan@pacific.net.sg

agents in use is testament to the fact that we still do not have an ideal drug available. We undertook a systematic review of the literature regarding the effectiveness of tocolytics to stop uterine contractions (first-line therapy). The tocolytics used in clinical practice can be grouped into five classes, namely: betamimetics, calcium channel blockers, magnesium sulphate, non-steroidal anti-inflammatory agents, and atosiban (oxytocin receptor antagonist).

SYSTEMATIC REVIEW

Reports of randomised controlled trials from searches of MEDLINE, bibliographies of review articles, Cochrane Collaboration and its Pregnancy & Childbirth Review Group between 1966 and 2003 were identified, using the search terms "randomised controlled trial" (RCT), "preterm labor", "tocolysis", "betamimetics", "ritodrine", "prostaglandin synthetase inhibitors", "indomethacin", "sulindac", "calcium channel blockers", "nifedipine", "oxytocin receptor blockers", "atosiban", and "magnesium sulphate". To our knowledge, the trials were conducted mainly before 1999 and there were no placebo-controlled trials after that.

Our inclusion criteria were preterm labour of less than 37 weeks gestation, singleton pregnancy and studies that compared the effect of a tocolytic with a placebo or no treatment. The quality of the study was evaluated with Jadad scoring and only those studies with score of more than two were included. The data were analysed using the Review Manager 4.2 software. Heterogeneity among trials was assessed using simple χ^2 analysis. Meta-analyses of data for each outcome were done for all trials and for specific types of tocolytic therapy when possible. A random-effects model was used for the studies, which were heterogeneous. For each meta-analysis, the odds-ratio (OR) and 95% confidence interval (CI) were calculated.

THE EVIDENCE

The primary outcome was the prolongation of pregnancy for 24 hours, 48 hours and seven days; the secondary outcomes were the adverse neonatal outcomes, such as neonatal deaths, respiratory distress syndrome (RDS), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH) and maternal outcomes. We identified 86 trials that were potentially relevant; 25 RCTs satisfied our inclusion criteria, of which 15 RCTs had usable information by outcome. We then excluded one trial report of the same study. There were 14 RCTs included in our meta-analysis.

Tocolytics were associated with significant decreases in the odds of delivery within 24 hours (OR 0.54, 95% CI 0.32-0.91) and 48 hours (OR 0.47, 95% CI 0.30-0.75). There was a trend towards reduction in the odds of delivery within seven days (OR 0.34, 95% CI 0.34-1.10) (Figs. 1-3). For specific types of tocolytics, significant effects on prolongation of pregnancy were found with betamimetics, indomethacin and atosiban but not with magnesium sulphate (Table I). Indomethacin seems to be the most efficacious tocolytic agent in prolonging the pregnancy by 48 hours and seven days, although it should be noted that the studies were small and the results must be interpreted with caution.

Tocolytics were not associated with significantly reduced rates of perinatal death (OR 1.22, 95% CI 0.84-1.78), respiratory distress syndrome (RDS) (OR 0.82, 95% CI 0.64- 1.07), intraventricular haemorrhage (OR 0.73, 95% CI 0.46-1.15), and necrotising enterocolitis (OR 0.96, 95% CI 0.35-2.65) (Table III). Betamimetics increased the risk of pulmonary oedema (OR 7.47, 95% CI 0.15-37.7), cardiac arrthymias (OR 3.11, 95% CI 0.84-11.58) and hypokalaemia (OR 6.43, 95% CI 4.53-9.14). There were no maternal deaths reported in any study.

META-ANALYSIS LIMITATIONS

One of the key limitations of meta-analysis is possible publication bias. Studies that demonstrate effective treatments and positive outcomes are more likely to be published, resulting in spurious over-estimation of any benefits attributed to any one treatment. In addition, the studies had used different definitions of preterm labour and thus were heterogeneous. The use of beta-agonists, atosiban, and indomethacin, but not magnesium sulphate, was associated with significantly reduced odds of delivery within 24 hours, 48 hours and seven days. However, these apparent benefits did not translate into improvements in adverse neonatal outcomes.

We postulate the following reasons. Firstly, these studies were small and under-powered to study the rare adverse neonatal outcomes. Secondly, the time gained in delaying delivery was not exploited to optimise neonatal outcomes in these studies. Indeed, in the largest randomised tocolytic trial done by the Canadian Preterm Labour Investigators' Group, only 34.6% of women completed glucocorticoid treatment[4]. This is despite the fact that antenatal administration of corticosteroids reduced the overall incidence of RDS in preterm infants by approximately 50% (OR 0.51, 95% CI 0.41-0.60) and IVH by 52% (OR 0.48, 95% CI 0.32-72)[5]. The women enrolled in the trials were relatively advanced in gestation (median 31 weeks at randomisation in the two largest studies[4,6].Therefore, the subgroup of extremely

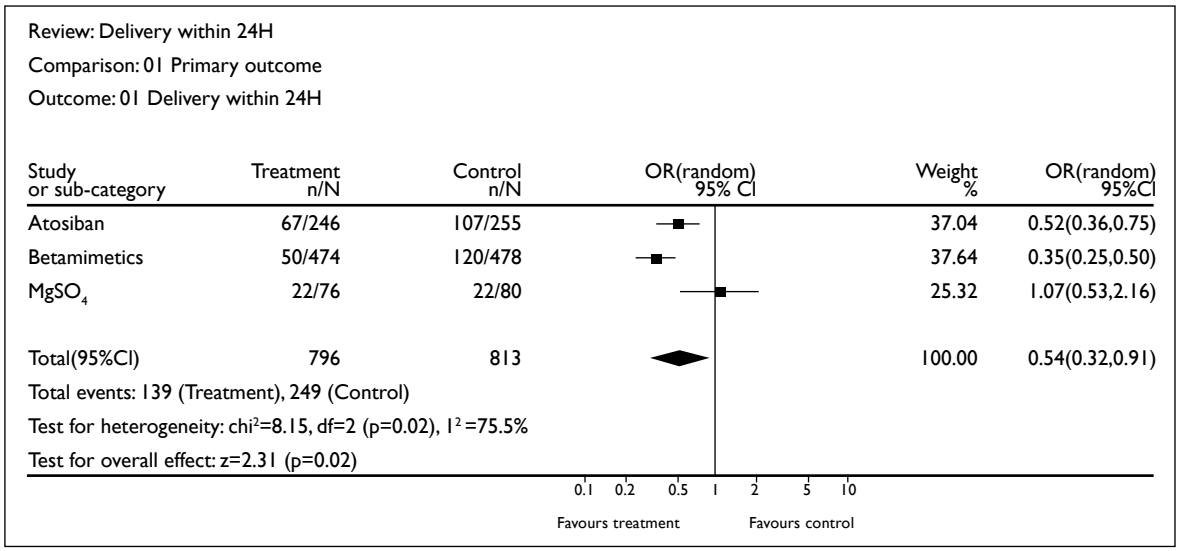

Fig. 1 Effect of tocolytic agents on the odds of delivery within 24 hours.

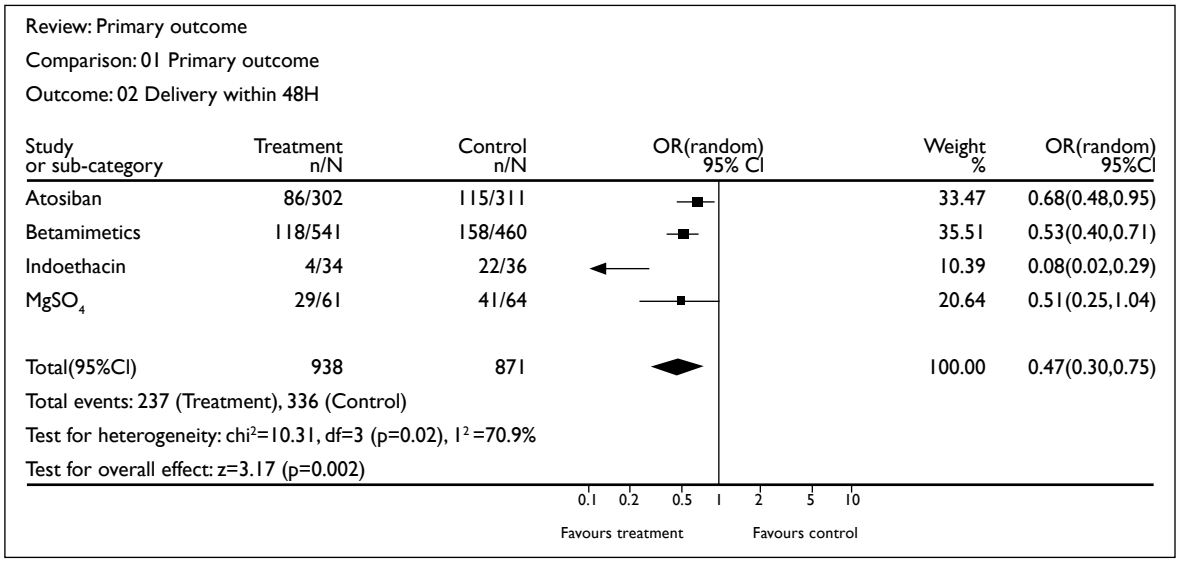

Fig. 2 Effect of tocolytic agents on the odds of delivery within 48 hours.

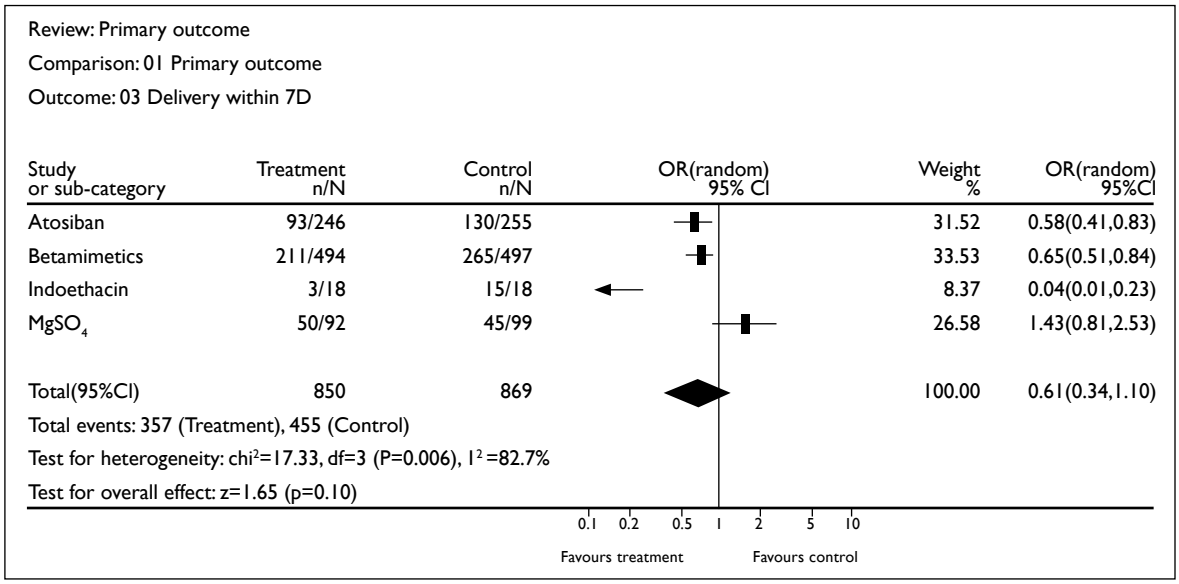

Fig. 3 Effect of tocolytic agents on the odds of delivery within seven days.

Table I. Randomised controlled trials included in this meta-analysis.

Trial	Tocolytic	N	Control	n
Ingemarsson,1976 [17]	Terbutuline	15	Placebo	15
Spellacy et al,1979 [18]	Ritodrine	14	Placebo	15
Larsen et al,1980 [19]	Ritodrine	131	Placebo	45
Cotton et al,1984 [21]	$MgSO_4$	16	Control	19
	Terbutaline	19		
Zuckerman, 1984 [22]	Indomethacin	18	Control	18
Leveno et al,1986 [23]	Ritodrine	54	Control	52
Garite et al,1987 [24]	Ritodrine	39	Control	40
Cox et at, 1990 [25]	$MgSO_4$	76	Control	80
CPIG, 1992 [4]	Ritodrine	352	Placebo	356
Fox et al, 1993 [26]	$MgSO_4$	45	Control	45
Goodwin et al, 1994 [27]	Atosiban	56	Placebo	56
Panter et al, 1999 [28]	Indomethacin	16	Placebo	18
Mittendorf et al,1997 [29]	$MgSO_4$	29	Placebo	28
Sibai, 1997 [6]	Atosiban	246	Placebo	255

Table II. Tocolytics compared with placebo or no treatment on prolongation of pregnancy.

Outcome	No. of tocolytic trials	Tx	Control	OR	95% CI
Betamimetics					
Delivery within 24 hours[4,18,19,23,24]	5	50/474	120/478	0.35	0.25 to 0.50
Delivery within 48 hours[4,19,21,24]	4	118/541	158/460	0.53	0.42 to 0.71
Delivery within 7 days[4,17,18,21,23,24]	6	211/494	265/497	0.65	0.51 to 0.84
$MgSO_4$					
Delivery within 24 hours[25]	1	22/76	22/80	1.07	0.53 to 2.16
Delivery within 48 hours[21,26]	2	29/61	41/64	0.51	0.25 to 1.04
Delivery within 7 days[21,25]	2	50/92	45/99	1.43	0.81 to 2.53
Indomethacin					
Delivery within 48 hours[22,28]	2	4/34	22/36	0.08	0.02 to 0.29
Delivery within 7 days[22]	1	3/18	15/18	0.04	0.01 to 0.23
Atosiban					
Delivery within 24 hours[6]	1	67/246	107/255	0.52	0.36 to 0.75
Delivery within 48 hours[6,27]	2	86/302	115/311	0.68	0.48 to 0.95
Delivery within 7 days[6]	1	93/246	130/255	0.58	0.41 to 0.83

preterm babies is under-powered in these studies, and it is in this subgroup in which the benefits of prolongation of delivery are the most significant with neonatal survival improving by 3% per day between 23-26 weeks of gestation[7].

TOCOLYTIC AGENT USAGE

The benefits of tocolytic agents in prolongation gestation by 24 to 48 hours are unlikely to improve the neonatal outcome in terms of physical maturation. These "golden hours" need to be optimised by in-utero transfer of the mother to a tertiary centre with neonatal facilities and administration of antenatal corticosteroids to the mother. Magnesium sulphate is commonly used to treat pregnancy-induced hypertension and though unlicensed, is widely used for tocolysis in the USA[8]. It can decrease uterine activity, but the basis for this tocolytic action is unknown. One possible mechanism is that magnesium competes with calcium for entry into the myometrial cells through voltage-gated channels. From our systematic review, there were no statistically significant differences between magnesium sulphate and a placebo to prolong pregnancy. Thus, magnesium sulphate should not currently be recommended or licenced for the management of preterm labour. On the other hand, the use of beta-agonists, atosiban, and indomethacin was all associated with significantly reduced odds of delivery within 24 hours, 48 hours and seven days. As such, there is no clear first-line tocolytic drug[9].

Table III. Effect of tocolyic agents on adverse neonatal outcomes.

Tocolytic	Neonatal death OR (95% CI)	RDS OR (95% CI)	IVH OR (95% CI)	NEC OR (95% CI)
Betamimetics	1.08	0.76	0.70	0.36
	(0.72 to 1.62)	(0.57 to 1.01)	(0.43 to 1.15)	(0.05 to2.59)
$MgSO_4$	1.83	1.19	0.82	1.15
	(0.70 to 4.77)	(0.61 to 2.31)	(0.25 to 2.63)	(0.28 to 4.73)
Indomethacin	1.48	0.61	-	1.47
	(0.24 to 9.20)	(0.16 to 2.30)		(0.22 to 9.69)
Atosiban	-	7.66	-	-
		(0.78 to 75.15)		

Table IV. Comparison of trials of nifedipine versus betamimetics in delivery and neonatal outcomes.

Delivery outcome	No. of trials	Tx	Control	OR	95% CI
Delivery within 24 hours [11]	1	11/95	22/90	0.41	0.18 to 0.87
Delivery within 48 hours [11-13]	3	43/168	47/155	0.79	0.51 to 1.22
Delivery within 7 days [11-13]	3	69/168	77/155	0.71	0.50 to 0.99
Neonatal outcome					
Neonatal death [11-13]	3	9/168	10/143	0.75	0.27 to 2.06
RDS [11]	1	23/95	31/78	0.48	0.27 to 0.86

In recent years, calcium-channel antagonists have been used increasingly as a tocolytic agent. These agents act to inhibit calcium ions influx across the cell membrane, thereby decreasing the tone in the smooth muscle vasculature[10]. However, there has been no placebo-controlled trial involving calcium antagonists to date. Comparative trials with beta-agonists have shown more favourable neonatal outcomes and better prolongation of gestation (Table IV)[11-13].

The mechanism by which nifedipine achieves a reduction in the rate of respiratory distress syndrome is likely to be by prolonging pregnancy so that interventions, such as administration of antenatal corticosteroids that are known to reduce respiratory distress syndrome, have the opportunity to be effectively implemented. Another plausible mechanism is based on data from human adults that showed an improved five-year survival in patients with primary pulmonary hypertension. These patients responded to high-dose calcium channel blockers with a reduction in pulmonary artery pressure and pulmonary vascular resistance[14]. This led to the theory that neonatal respiratory distress syndrome may also be reduced by a direct effect of nifedipine on improving neonatal pulmonary perfusion[11,15]. Although nifedipine has been shown to have a more favourable neonatal outcome and better prolongation of gestation, it is not licensed for tocolysis, and there have been concerns about a theoretical risk to foetal and placental circulations with its use[16]. In addition, there is no consensus about the dosage, the route and the release formulation for a tocolytic regimen for nifedipine.

In contemporary obstetric practice, the use of tocolytic agents should be individualised and based on the maternal condition, potential side-effects of the tocolytic drug, and gestational age. Drugs such as beta-agonists, atosiban, and calcium channel blockers are the more popular tocolytic agents. The "choice" tocolyic agent, which could improve neonatal outcome with no maternal or neonatal side-effect, has not yet surfaced. Currently, we use the three-pronged strategy of tocolytic agents with in-utero transfer to a tertiary centre and concomitant use of antenatal corticosteroids in the management of preterm labour.

CONCLUSION

Although tocolytic therapy can prolong gestation in the management of threatened preterm labour, the time gained in-utero needs to be optimised. The neonatal effects of short-term prolongation of gestation with tocolytic agents have not been adequately evaluated in placebo-controlled trials, which have been characterised by low corticosteroid usage, enrolment at late gestations and lack of power. There is no clear first-line tocolytic agent. The use of

tocolytic agents should be individualised and based on maternal condition, potential side-effects and gestational age.

REFERENCES

1. Simpson AR. Introduction. The Nursling. P Budin. London: Caxton Publishing Co 1907:xix.
2. Hall D, McGaughey HS Jr, Corey E, Thornton WN Jr. The effects of magnesium therapy on the duration of labor. Am J Obstet Gynecol 1959; 78:27-32.
3. Bishop EH, Woutersz TB. Arrest of premature labor. JAMA 1961; 178:812-4.
4. CPIG. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. N Engl J Med 1992; 327:349-51.
5. Crowley P. Prophylactic corticosteroids for preterm birth. Cochrane Database Sys Rev 2000:CD 000065.
6. Sibai B. A double-blind, placebo-controlled trial of an oxytocin-receptor antagonist in the treatment of preterm labor. Am J Obstet Gynecol 1997; 176:S2.
7. Finnstrom O, Clausson PO, Sedin G, et al. The Swedish national prospective study on extremely low birthweight (ELBW) infants. Incidence, mortality, morbidity and survival in relation to level of care. Acta Paediatr 1997; 86:503-11.
8. Greenfield PJ, Lamont RF. The contemporary use of tocolytics. Current Obstet Gynaecol 2000; 10:218-24.
9. Management of Preterm Labour. ACOG Practice Bulletin No 43, May 2003.
10. BM S. Ion channels and the control of myometrial electrical activity. Semin Perinatol 1995; 19:31-40.
11. Papatsonis DN, Van Geijn HP, Ader HJ, et al. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. Obstet Gynecol 1997; 90:230-4.
12. Koks CHB, Kleine M, Manger P. A randomized comparison of nifedipine and ritodrine for suppression of preterm labor. European J Obstet Gynecol 1998; 77:171-6.
13. Kupferminc M, Lessing JB, Yaron Y, Peyser MR. Nifedipine versus ritodrine for suppression of preterm labour. Br J Obstet Gynaecol 1993; 100:1090-4.
14. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. An Engl J Med 1992; 327:76-81.
15. Papatsonics DN, Kok JH, Vann Geijn HP, et al. Neonatal effects of nifedipine and ritodrine for preterm labour. Obs Gynecol 2000; 95:477-86.
16. Blea CW, Barnard JM, Magness RR, Phernetton TM, Hendricks SK. Effect of nifedipine on fetal and maternal hemodynamics and blood gases in the pregnant ewe. Am J Obstet Gynecol 1997; 176:922-30.
17. Ingemarsson I. Effect of terbutaline on premature labor. A double-blind placebo-controlled study. Am J Obstet Gynecol 1976; 125:520-4.
18. Spellacy WN, Cruz AC, Birk SA, Buhi WC. Treatment of premature labor with ritodrine: a randomized controlled study. Obstet Gynecol 1979; 54:220-3.
19. Larsen JF, Hansen MK, Hesseldahl H, et al. Ritodrine in the treatment of preterm labour. A clinical trial to compare a standard treatment with three regimens involving the use of ritodrine. Br J Obstet Gynaecol 1980; 87:949-57.
20. Niebyl JR, Blake DA, White RD, et al. The inhibition of premature labor with indomethacin. Am J Obstet Gynecol 1980; 136:1014-9.
21. Cotton DB, Strassner HT, Hill LM, Schifrin BS, Paul RH. Comparison of magnesium sulfate, terbutaline and a placebo for inhibition of preterm labor. A randomized study. J Reprod Med 1984; 29:92-7.
22. Zuckerman H, Shalev E, Gilad G, Katzuni E. Further study of the inhibition of premature labor by indomethacin. Part II double-blind study. J Perinat Med 1984; 12:25-9.
23. Leveno KJ, Klein VR, Guzick DS, et al. Single-centre randomised trial of ritodrine hydrochloride for preterm labour. Lancet 1986; 493:1293-6.
24. Garite TJ, Keegan KA, Freeman RK, Nageotte MP. A randomized trial of ritodrine tocolysis versus expectant management in patients with premature rupture of membranes at 25 to 30 weeks of gestation. Am J Obstet Gynecol 1987; 157:388-93.
25. Cox SM, Sherman ML, Leveno KJ. Randomized investigation of magnesium sulfate for prevention of preterm birth. Am J Obstet Gynecol 1990; 163:767-72.
26. Fox MD, Allbert JR, McCaul JF, et al. Neonatal morbidity between 34 and 37 weeks' gestation. J Perinatol 1993; 13:349-53.
27. Goodwin TM, Paul R, Silver H, et al. The effect of the oxytocin antagonist atosiban on preterm uterine activity in the human. Am J Obstet Gynecol 1994; 170:474-8.
28. Panter KR, Hannah ME, Amankwah KS, et al. The effect of indomethacin tocolysis in preterm labour on perinatal outcome: a randomised placebo-controlled trial. Br J Obstet Gynaecol 1999; 106:467-73.
29. Mittendorf R, Covert R, Boman J, et al. Is tocolytic magnesium sulphate associated with increased total paediatric mortality? Lancet 1997; 350:1517-8.
30. 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. BJOG 2003; 110:1045-9.