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The present and future of tocolysis

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This chapter discusses the tocolytic agents currently in use for the treatment of preterm labour and considers them in light of the evidence base. These agents are the β2 sympathomimetic agonists, magnesium sulphate ($MgSO_4$), indomethacin, nifedipine and atosiban.

The available evidence for these agents shows that the β2 agents are effective but have significant maternal side effects and no effect on perinatal outcome. $MgSO_4$ and glyceryl trinitrate are clearly ineffective. Nifedipine is effective with a low maternal side effect profile and is associated with improved perinatal outcomes. Meta-analyses of the several randomized controlled trials of atosiban show that it is no more effective than other tocolytic therapies. Possible directions for the future will be discussed.

Key words: tocolysis; preterm delivery.

It has long been the desire of clinicians to have therapies that can interrupt premature labour and allow the delivery of more mature infants with lower morbidity and mortality, time to use antenatal corticosteroids and transfer to tertiary care centres for delivery. The promising therapies of each recent generation have often been tried and found wanting.

Observations from the 1990s have described preterm labour (PTL) as a syndrome rather than a distinct entity (as the causes are varied) reflecting the possible causes of a breakdown in the normal functional uterine quiescence with a short-circuiting or overwhelming of the normal parturition cascade. In many instances, PTL represents the need for the fetus to escape a hostile intrauterine environment.[1]

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A clinical review at the close of the 20th century by Steer and Flint described the incidence of preterm delivery [PTD] in the UK of 7%.[2] They noted that the precise diagnosis of PTL is difficult with the only absolute proof being progressive dilatation of the cervix, a point at which it may be too late to intervene. As a result two-thirds of women diagnosed as being in PTL will not have progressed to PTD within 48 h. Therefore, there are many situations when the use of tocolytics may be inappropriate. They also found no evidence that prophylactic tocolytics were of benefit. In the half decade since then, little would appear to have changed. Approximately 20% of all preterm births are iatrogenic and two-thirds of the remaining 80% are spontaneous PTL with or without preterm premature rupture of the membranes (PPROM). The final common pathway now appears to be activation of the inflammatory cascade.[3]

It is also important to keep in mind the expectations for any tocolytic drug. West et al in a retrospective study of women of >20 weeks' gestation in Minnesota, USA found the maximal benefit that could be expected from a new, safe, efficacious tocolytic therapy would be a reduction in PTD rates of about 12%.[4] In light of this it is interesting to consider how and why clinicians take up new treatments/therapies. Parer reviewed 11 technologies introduced into obstetrics over the past 30 years, specifically considering the evidence in the literature, the strength of the recommendations and an estimate of their acceptance or rejection.[5] With respect to PTL, he considered short-term tocolysis, single course of antenatal corticosteroids (betamethasone [BMZ]), thyroid-releasing hormone (TRH) and fetal fibronectin (fFN). Wherever the technologies were simple to apply, had a single endpoint and showed concordance with randomized controlled trials (RCTs) and clinical use, they were more likely be accepted. Generally, all have Level I evidence supporting their uptake or rejection and this is true for the acceptance of short-term tocolysis, BMZ and fFN, and rejection of TRH. However, this does not hold true for long-term tocolysis (despite the absence of any efficacy). Interestingly, Parer did not discuss the apparent continued use of $MgSO_4$ in the USA despite the clear evidence of its lack of effect as a tocolytic.

McLaughlin et al reported a survey of obstetricians (764) and neonatologists (89) in Australia and New Zealand in the light of the recommendations of the National Institutes of Health (NIH) that, 'Until data establish a favourable benefit-to-risk ratio, repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials'.[6] They found repeat corticosteroids were recommended by 44% of obstetricians and 21% of neonatologists. Obstetricians cited 'recommendations of a respected body or college', a 'respected authority in the area' and 'personal experience' for their decision-making. Neonatologists, however, were more likely to cite 'scientific presentations at meetings', 'ongoing RCTs', or 'scientific literature'. The use of repeat steroids was positively (in a linear trend) related to the seniority of an obstetrician (with trainees least likely). Practitioners who followed the NIH recommendations and who did not support repeat steroid use cited 'scientific presentations at meetings', 'ongoing RCTs', or 'scientific literature' as their basis for practice.

Not surprisingly therefore, for the current agents in use worldwide, there are regional differences that relate to historical practices, availability and cost.

CURRENT TOCOLYTIC AGENTS IN USE

The use of tocolytics has only infrequently been assessed on a widespread scale. Cook and Peek undertook a postal survey of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists[7]: 33% (813) of surveys were returned. The

response rate for Australia was 18.9% and 27.1% for New Zealand. Of these, 79% routinely attempted suppression of labour (to obtain steroid cover, 83%; and/or transfer to a tertiary center, 74%). The gestation of initiation of tocolysis was 20–37 weeks and tocolysis was discontinued at 32.9 ± 2.7 weeks. β-Mimetics were the drug of first choice for 73% followed by nifedipine 21% (more likely to be used in larger units) and other drugs < 5%. Interestingly, 34% used maintenance tocolysis (mostly β2 agonists). Steroid cover was achieved in a median of 80%, and prolongation of pregnancy ≥7 days in 50% and to term in 10%. Not surprisingly, there was a wide range of opinions and uncertainty regarding the effectiveness of tocolysis, the most appropriate drug to use and side effects. These are very similar results to a previous American survey, although the second choice drug in this survey was $MgSO_4$.[8]

β2 Sympathomimetics (β2 agonists)

An extensive review of β2 agonists compared to placebo has been undertaken by Anotayanonth et al of 11 RCTs involving 1332 women.[9] There was a significant decrease in the number of women giving birth within 48 h of administration of the β2 agonist (RR 0.63, 95% CI 0.53–0.75) but no reduction in deliveries before 37 weeks (RR 0.95, 95% CI 0.88–1.03) nor, when using sensitivity analysis, was there any effect on delivering within 7 days of administration (RR 0.67, 95% CI 0.48–1.01). There were significant increases in maternal adverse effects: cessation of treatment due to adverse reaction (RR 11.38, 95%CI 5.21–24.86), chest pain (RR 11.29, 95% CI 3.81–33.36), dyspnoea (RR 3.86, 95%CI 2.21–6.77), tachycardia (RR 4.08, 95%CI 1.55–10.73), palpitations (RR 10.11, 95% CI 6.56–15.58), tremor (RR 10.74, 95% CI 6.20–18.59), headaches (RR 4.07, 95% CI 2.60–6.35), hypokalaemia (RR 6.07, 95% CI 4.00–9.20), hyperglycaemia (RR 2.90, 95% CI 2.05–4.09), nausea/vomiting (RR 1.76, 95% CI 1.29–2.42) and nasal stuffiness (RR 2.90, 95% CI 1.64–5.12). Although there have been literature reports of maternal deaths, none was seen in these studies. With respect to perinatal outcomes there were no effects on perinatal deaths, respiratory distress (RDS), cerebral palsy (CP), neonatal death, infant death and necrotizing enterocolitis (NEC). Only one trial reported neonatal length of hospital stay and one other trial reported 18-month neurodevelopmental follow-up, and there were no differences seen in these two reports.

The authors hypothesized that there could be several reasons why β2 agonists were not seen to affect outcomes: namely, as most women were ≥32 weeks' gestation, increasing gestational age would be expected to have little effect; all trials in the review took place in tertiary care centres with neonatal intensive care units (NICUs); and all trials were conducted before 1990 when antenatal corticosteroids were not widely used.

They found insufficient evidence to support use of one β-mimetic over any other.

King also reported that there is no evidence of improved neonatal outcomes with ß2 agonists, but an association with severe maternal morbidity and mortality.[10]

β2 Sympathomimetics have also been used to relax the uterus for external cephalic version (ECV). An RCT of ß2 agonists for ECV reported a significant increase in cephalic presentation at delivery (RR 3.21, 95% CI 1.23–8.39) and reduced incidence of caesarean section (RR 0.33, 95% CI 0.14–0.80); the most marked effect was in multiparous women.[11]

Magnesium sulphate

$MgSO_4$ has historically been most used in North America, with only sparse and poor quality evidence supporting its use. Crowther et al reviewed 23 trials with > 2000

women but only nine trials were rated as high quality.[12] All trials and the nine high quality trials showed no effect on PTD $<$ 48 h after the administration of $MgSO_4$ compared with placebo, no therapy or other tocolytics (RR 0.85, 95% CI 0.58–1.25 and RR 0.87, 95% CI 0.61–1.24, respectively). All trials showed an increase in fetal and paediatric death, which was unexpected (but not seen in the nine high quality trials) (RR 2.82, 95% CI 1.20–6.62). No beneficial effect was seen for neonatal morbidity, including RDS, NEC or proven infection. One trial had 18 month follow-up data regarding CP and there was a non-significant reduction (RR 0.14, 95% CI 0.01–2.60). Crowther et al concluded that there was no evidence supporting the use of $MgSO_4$ as a tocolytic agent.

What is surprising is that recommendations were made in 1993 that $MgSO_4$ should not be used for tocolysis, with King repeating in 2004 that there was clear evidence from RCTs that its use as a tocolytic should be abandoned as there was an association with a higher risk of perinatal death.[10]

Non-steroidal anti-inflammatory agents

Non-steroidal anti-inflammatory (NSAI) agents, particularly indomethacin, have had a very bad press with respect to possible untoward fetal and neonatal outcomes. There may be a case for reconsidering this view. Panter et al reported a small placebo-controlled double-blinded RCT (34 women) comparing indomethacin and placebo. They found no increases in perinatal mortality or morbidity, namely NEC, bronchopulmonary dysplasia (BPD), interventricular haemorrhage (IVH) and periventricular leucomalacia (PVL). Indomethacin prolonged the gestation $>$ 48 h in 81% (vs. 56%). They concluded that there was no evidence of any benefits from indomethacin.[13] However, it can also be concluded that there were no detrimental effects.

The reports regarding indomethacin have been reviewed by Macones et al.[14] Although RCTs show indomethacin to be an effective tocolytic in delaying PTD for $>$48 h, 7–10 days, $\geq$37 weeks, and decreasing low birthweight, the studies are heterogeneous and some caution is needed in their interpretation. The question of its safety remains as the original studies were not appropriately powered. There may be an increased rate of IVH and NEC, but it is not possible to pool the results for neonatal outcomes. Premature closure of the ductus arteriosus occurs in 10–50% of fetuses exposed to indomethacin. It is more prevalent in later gestations ($>$32 weeks) and if additional maternal treatment is longer than 48 h. These effects can be reversible but pathological effects on fetal myocardial function have been reported (endocardial ischaemia, papillary muscle dysfunction, cardiac failure and death).

There have been conflicting results on the effect of indomethacin on middle cerebral artery (MCA) velocity. Review of these raises the possibility that indomethacin is not causally related to IVH and poor neonatal outcome. Indomethacin may be a confounding association with poor neonatal outcome, i.e. confounding by indication, where the indication for exposure is itself a risk factor but is not the cause. Where indomethacin has been used as an additive therapy, the failure of first-line tocolysis is a risk factor for adverse neonatal outcome. There is a recognized relationship between subclinical amniotic/chorioamniotic infection and refractory PTL. Intrauterine infection is strongly associated with neonatal complications. The authors postulate that observational studies highlight that exposure to indomethacin may be an indicator of more severe PTL (a clinical indicator that cannot be controlled or corrected statistically). Decision analysis techniques which trade-off the increased neonatal morbidity

at lower gestational ages suggest that indomethacin may result in a lower number of major neonatal morbid events.

This conclusion was supported by a report from Suarez et al of 56 neonates with IVH compared with 224 gestational age matched controls, following the introduction of indomethacin.[15] The study was powered to detect a two-fold increase in IVH. Multivariate logistic regression analysis showed that only gestational age, vaginal delivery, chorioamnionitis and RDS were associated with IVH when adjusted for indomethacin alone (OR 1.3, 95% CI 0.5–3.3) or in combination with $MgSO_4$ (OR 2.0, 95% CI 0.8–4.8). They also concluded that the population most at risk (extreme prematurity) is preferentially exposed to indomethacin and recalcitrant PTL (more likely to have chorioamnionitis) is more likely to have combined therapy.

Loe et al identified 46 studies with 28 meeting the criteria for systematic review (using the guidelines of the Meta-analyses of Observational Studies in Epidemiology [MOOSE] Group and for RCTs the guidelines of the Quality of Reporting of Meta-analysis [QUOROM] conference).[16] Quite exhaustive and specific analysis using Mantel–Haenszel (for fixed effects), DerSimonian and Laird (for random effects), Egger Testing and funnel plots (assessment of publication biases) and Breslow–Day analysis (testing for homogeneity across studies) were used. The 28 studies included 6008 infants (1621 receiving indomethacin antenatally and 4387 not exposed). Pooled data from the RCTs showed no significant differences in IVH (OR 1.02, 95% CI 0.55–1.89), NEC (OR 2.43, 95% CI 0.73–8.03), premature closure of the ductus arteriosus (OR 1.25, 95% CI 0.64–2.54) or perinatal mortality (OR 1.39, 95% CI 0.65–2.97). Three elligable RCTs showed an increase in BPD (OR 2.80, 95% CI 1.07–7.31), heavily influenced by only one trial. The pooled observational studies did not show this effect or any other significant differences. There was no evidence suggesting publication biases. They also noted that in many of the observational studies indomethacin was used as a second line therapy after the failure of another tocolytic. The meta-analysis of the pooled observational studies did not show increased risks of neonatal morbidly or mortality and so the authors stated, 'We cautiously conclude that use of indomethacin at less than 34 weeks of gestation for tocolysis does not appear to increase the risk of adverse neonatal outcomes'.

Sulindac has been evaluated for ECV by Humphrey et al in 95 women (46 given sulindac and 49 placebo controls).[17] There were no outcome differences in the two groups but there was a reduction in amniotic fluid index (AFI) and deepest pocket of liquor at 14 days.

The possibility of cyclooxygenase-2 (COX-2) inhibitors as possible tocolytic agents has been investigated by several teams but the withdrawal of rofecoxib has prevented a thorough evaluation.

Nitric oxide donors

The possibility of glyceryl trinitrate or nitric oxide (NO) donors as tocolytics had great appeal and they entered the armamentarium of many practitioners on the grounds of small uncontrolled reports, such as that of O'Grady et al, who reported a 100% successful tocolysis.[18]

Duckitt and Thornton reviewed the available evidence in 2002 from five RCTs (466 women).[19] NO donors did reduce the risk of delivering before 37 weeks (RR 0.69, 95% CI 0.53–0.88) but did not delay delivery prior to 32 or 34 completed weeks, nor improve neonatal outcome when compared with placebo, no treatment or

alternative tocolytics. There were generally reduced side effects with NO donors (RR 0.47, 95% CI 0.37–0.61) but they were significantly more likely to cause headache (RR 3.36, 95% CI 1.29–8.76). They concluded there was insufficient evidence to support NO donors for tocolysis. NO donors were also less successful than terbutaline in women undergoing ECV.[20]

Bisits et al reported a multicentre, multinational RCT (the RNOTT study) comparing IV β2 agonists with glyceryl trinitrate (GTN) dermal patches.[21] The 238 women were randomized to β2 agonists (117) or GTN patches,(121) with rescue tocolysis using β2 agonists after 2 h (35% of women in the GTN group). On an intention-to-treat basis there were no significant differences in time to delivery but fewer side effects were noted with GTN. However, if delivery or requirement for rescue tocolysis is regarded as a treatment failure, then there is a significant difference between the two arms ($p = 0.0032$), with GTN being less efficacious. In the infant follow-up of this study, Gill et al have reported that there are no differences in the Griffiths neurodevelopmental assessment of infants at 18 months of age.[22]

Calcium channel blocking agents (CCBs)

CCBs, initially proposed as tocolytics in the 1980s, have had a recent resurgence. Papatsonis et al in 2000 reported an open RCT of neonatal outcomes for women who received either oral nifedipine or IV ritodrine (with nifedipine as rescue therapy for ß2 agonist failure).[23] Entry criteria were regular objective uterine contractions with intact membranes; evidence of cervical change was not necessary. Nifedipine was associated with lower rates of admission rates to NICU (OR 0.51, 95% CI 0.28–0.93), RDS (OR 0.46, 95% CI .024–0.89), ICH (OR 0.48, 95% CI .024–0.96) and neonatal jaundice (OR 0.53, 95% CI 0.29–0.97), all after correction for gestational age at delivery. The results were thought to a combination of the more effective nature of nifedipine as a tocolytic plus the intrinsic benefit of nifedipine, or the lack of harmful effects of ritodrine. Nifedipine was associated with significant increase in mean gestational age at birth and a higher mean birth weight. In the ritodrine group 13% of women required cessation of therapy due to side effects; nifedipine was not withdrawn in any women. These results were quite significant, as ß2 agonists have never been shown to be associated with improved neonatal outcomes and furthermore have been shown to be associated with increased rates of IVH.

King et al[24] undertook a meta-analysis of all published and unpublished RCT's using CCBs for tocolysis for women between 20 and 36 weeks' gestation. No trials have compared CCBs with a placebo or no alternative tocolytic. CCBs are more effective than ß2 agonists with less maternal side effects and reduced neonatal morbidity. Most trials have used oral treatments for maintenance up to 34–37 weeks. The results show decreased delivery within 7 days (RR 0.76, 95% CI 0.60–0.97); decreased delivery before 34 weeks (RR 0.83, 95% CI 0.69–0.99); the number needed to treat (NNT) for benefit for birth within 7 days was 11 (95% CI 6–100); reduced adverse maternal drug reaction (RR 0.14, 95% CI 0.05–0.36); reduced RDS (RR 0.63, 95% CI 0.46–0.88); reduced NEC (RR 0.59, 95% CI 0.36–0.98); reduced IVH (RR 0.59, 95% CI 0.36–0.98); reduced admission to NICU (RR 0.78, 95% CI 0.64–0.95) and reduced neonatal jaundice (RR 0.73. 95% CI 0.57–0.93); giving a NNT for benefit of 14 (95% CI 7–100).

Concerns have been raised regarding maternal cardiovascular side effects resulting from nifedipine therapy.[25,26] Papatsonis et al have challenged these concerns since they

are extrapolated from findings in elderly patients and not healthy young pregnant women.[27] ß2 Agonists are associated with fluid retention and an increase in cardiac output of 40−60%, consistent with the recognized complication of pulmonary oedema. It has also been argued that nifedipine is not associated with severe hypotension other than that attributed to the underlying maternal condition because the maternal hypotension far outlasted the known half-life of oral nifedipine.

Atosiban

Atosiban ([1-deamino-2-D-Tyro(OEt)-4-Thr-8-Orn]-oxytocin) is a competitive oxytocin receptor antagonist. Goodwin et al undertook a randomized, double-blind, placebo-controlled trial in 112 women (56 in each arm).[28] Inclusion criteria were four contractions per hour with no cervical change. Only a small number of women at <28 weeks were recruited. A significant decrease in uterine contraction frequency was seen over a 2-h period in the atosiban subjects.

Romero et al recruited 551 patients and randomized them to IV atosiban (246) or placebo (255), followed by subcutaneous maintenance. Standard tocolysis rescue occurred after 1 h if PTL continued.[29] There was no significant difference seen in time to delivery or therapeutic failure. The percentages of patients remaining undelivered at 24 h, 48 h and 7 days were significantly higher in the atosiban group than in the control group ($p < 0.008$). Atosiban was less effective at <28 weeks and the incidence of fetal deaths was higher at <24 weeks.

A European multicentre, double-blind, placebo-controlled RCT recruited 245 women diagnosed with preterm labor at 23−33 weeks who received IV treatment (116 with atosiban and 129 with terbutaline).[30] The inclusion criteria were regular contractions lasting ≥30 s at ≥4/30 min (confirmed by external tocography), cervical dilatation and effacement 0−3 cm (nulliparas) or 1−3 cm (multiparas). They were stratified by gestational age at ≤28 weeks and >28 weeks. Outcomes assessed were tocolytic effectiveness (those undelivered by 48 h and 7 days), efficacy and tolerability (number of women remaining undelivered and not requiring alternative tocolytic therapy after 48 h and 7 days), and safety (maternal side effects and neonatal morbidity). Atosiban had comparable efficacy and fetal and neonatal outcomes to terbutaline, but it had a superior safety profile in terms of maternal adverse outcomes. The most clinically important side effects (atosiban vs. terbutaline) were chest pain (0.9% vs. 2.3%), dyspnoea (0% vs. 7.8%), tachycardia (4.3% vs. 75.2%) and palpitations (0% vs. 9.3%). Termination of therapy because of adverse effects was 1.7% vs. 13.2%. Fetal tachycardia was seen (6% vs. 44.2%) with no difference in fetal bradycardias. None of the infant adverse effects was thought to be related to the tocolytic therapy; most could be attributed to the delivery process or prematurity and there were no differences in rates of admission to NICU or need for ventilation. The authors noted that the obvious side effect profile of terbutaline might have compromised blinding during treatment.

Moutquin et alreported a RCT of 363 women who received atosiban and 379 a β-mimetic (ritodrine, salbutamol or terbutaline).[31] There were no significant differences for delivery at 48 h or 7 days. There were reduced maternal side effects (particularly cardiovascular) in the atosiban group but no differences in neonatal/infant outcomes. Significantly fewer women required alternative therapy in the atosiban group.

The authors discussed the atosiban vs. placebo study of Romero et al.[29] (which showed no difference in the delay in delivery between atosiban and placebo) and discountedit because more women at <24 weeks were included in the atosiban group, and tocolytics rescue was used after 1 h and ad hoc before failure criteria were met.

There is still some degree of controversy regarding the use of atosiban or nifedipine for tocolysis. Discussion followed an editorial in the *BJOG* which questioned the evidence base for nifedipine compared to atosiban.[32] Papatsonis et al argued for nifedipine[33] citing the results of the Cochrane meta-analyses which suggested that nifedipine was preferable to β sympathomimetics, the cost of atosiban is high, atosiban has to be given parenterally, there may be a lower number of oxytocin receptors at lower gestational ages, and atosiban is not registered in many countries where nifedipine can be used. They stressed the need for an RCT comparing atosiban and nifedipine with a placebo arm and 2-year follow-up of the infants.

In the absence of a direct comparison between atosiban and nifedipine Coomarasamy et al pooled analysis of odds ratios to provide an assessment of potential benefits of nifedipine vs. atosiban.[34] This technique generates pooled log ratios and their variances for performing adjusted indirect comparisons. These results have been shown to be 93% concordant with the results of direct comparisons. Nifedipine tocolysis was shown to be associated with a significant reduction in RDS (OR 0.55, 95% CI 0.32−0.97) and increased the number of women whose delivery was delayed by 48 h (OR 1.20, 95% CI 0.73−1.95); however, this was not significant.

Subsequently a meta-analysis has been undertaken by Papatsonis et al.[35] Six trials (1695 women) were included. Compared with placebo, atosiban did not reduce the incidence of preterm birth or improve neonatal outcome. In one trial (583 infants), atosiban was associated with an increase in infant deaths at 12 months of age compared with placebo (RR 6.15, 95% CI 1.39−27.22). However, this trial randomized significantly more women to atosiban before 26 weeks' gestation. Use of atosiban resulted in lower infant birthweight (weighted mean difference −138.31 g, 95% CI −248.76 to −27.86) and more maternal adverse drug reactions (RR 4.02, 95% CI 2.05 to −7.85, two trials, 613 women).

To date only one RCT has directly compared atosiban with nifedipine.[36] Eighty women (40 atosiban and 40 nifedipine) between 26 and 34 weeks were enrolled with PTL (four contractions in 20 min or eight in 60 min, cervical dilatation of >1 cm and ≤ 3 cm, cervical effacement of $\geq 50\%$). This was an unblinded study. The outcomes were delivery at 48 h and >7 days, and maternal safety. There were no statistically significant differences between the two groups. Atosiban was effective in 82.5% of cases and nifedipine in 75% ($p = 1.00$). There was a significant difference in maternal side effects (17.5% vs. 40%, $p = 0.027$). The duration of pregnancy after treatment was 29.03 ± 16.12 days vs. 22.85 ± 13.9 days ($p = 0.79$). The major side effects for nifedipine were hypotension (27.5%) and vertigo (22.5%). There was no neonatal follow-up. The power calculations for 40 women ($a = 0.05$, $b = 0.20$) were underpowered to fully assess all the hypotheses (P1 [atosiban] = 0.8, P2 [nifedipine] = 0.5). Although not included in the article, odds ratios for lack of response at <48 h were 0.64 (95% CI 0.22−1.88), delayed delivery for 48 h 1.57 (95% CI 0.53−4.65) and delayed delivery >7 days 1.62 (95% CI 0.61−4.25).

CHRONIC MAINTENANCE TOCOLYSIS

The final aspect to consider with tocolysis is whether or not there is any place for its use to maintain a pregnancy. Sanchez-Ramos et al found 12 trials with 1590 women (855 receiving maintenance tocolysis and 735 receiving placebo or no treatment) to be methodologically sound.[37] The odds ratio for preventing PTD was 0.95 (95% CI 0.77−1.17) and for preventing recurrent PTL was 0.81 (95% CI 0.64−1.03). There were no differences in rates of RDS, perinatal deaths or birthweights.

Progesterone

Da Fonseca et al reported a double-blind, placebo-controlled RCT evaluating the effect of prophylactic vaginal progesterone (100 mg pessaries) in decreasing both PTD and uterine activity in women at high risk of PTD (at least one prior PTD, prophylactic cervical cerclage or uterine malformation) between 24 and 34 weeks' gestation.[38] There was a significant reduction in uterine activity (23.6% vs. 54.3%, $p < 0.05$) and preterm birth (13.8% vs. 28.5%, $p < 0.05$), and fewer women delivered before 34 weeks in the progesterone group (2.7% vs. 18.5%, $p < 0.05$).

Sanchez-Ramos et al reviewed the evidence for progestational agents vs. placebo for patients at risk of preterm birth.[39] There were ten studies including 1339 subjects with either a history of previous preterm birth or multiple pregnancy. Analysis of all progestational agents was associated with lower rates of PTD (OR 0.45 95% CI 0.25–0.80). There is some debate as to whether 17-hydroxyprogesterone (17P) caproate is more effective than other progestational agents and 17P was also associated with a lower rate of birthweights < 2500 g (OR 0.50, 95% CI 0.36–0.71). However, there were no statistical differences in rates of admission for threatened PTL or perinatal mortality.

Meis reported a review of two large RCTs of 17P and stated that evidence supports the use of 17P up to 36 weeks in women with a history of a previous spontaneous PTD.[40] There is no evidence to support its use with multiple pregnancies, short cervix, or other high-risk conditions, nor was there any evidence for a tocolytic effect in PTL (four trials). One RCT (250 mg 17P or placebo IMI weekly) stopped enrolling because of significant reductions in deliveries at <37, 35 and 32 weeks with fewer birthweights < 2500 g. There was a trend towards reduced neonatal death, transient tachypnoea, RDS, BPD, patent ductus arterosus (PDA) and retinopathy of prematurity (ROP). There were significant reductions in rates of IVH (but not grades III and IV), need for ventilatory support, supplemental O_2 and NEC. It must be considered that if the study had continued to the proposed recruitment number it may have shown clear evidence of more improved perinatal outcomes. This highlights the need for studies into prevention of preterm birth that properly assess the primary outcomes. As of yet there is little data to support the optimal dose or route of administration of progestational agents.

In the same year Dodd et al reviewed seven RCTs of progesterone and showed that women who received progesterone were significantly less likely to deliver before 37 weeks (RR 0.58, 95% CI 0.48–0.70), have an infant ≤ 2500 g (RR 0.62, 95% CI 0.49–0.78) or an infant with an ICH (RR 0.25, 95% CI 0.08–0.82).[41] Because of the heterogeneity of the studies with respect to their age, timing of administration, populations studied and mode or dose of progesterone, further large studies are needed to detect any changes in maternal, neonatal and infant outcomes.

THE FUTURE

Diagnosis

Giles et al have demonstrated as part of a clinical audit the effectiveness of fFN as an adjunct in the diagnosis and management of threatened premature labour in women who have to travel large distances in Australia.[42] Development of more specific and selective diagnostic tools will help to diagnose true PTL and indicate who should

receive treatment and/or transport, and also allow any future tocolytic agents to be trialed in women in true PTL. Gomez et al considered the diagnostic performance of ultrasound measurement of cervical length and vaginal fFN in the prediction of premature delivery in patients with preterm uterine contractions and intact membranes.[43] They found a significant relationship between PTD, cervix length and fFN. Both tests performed comparably but their combined results were better in predicting PTD.

Treatment

Atosiban is a combined vasopressin V_{1A}/oxytocin receptor antagonist. Recently, a highly selective oxytocin receptor antagonist (barusiban) has been described.[44] Barusiban would appear in theoretical and in vivo studies to be more effective than atosiban. The medium inhibitory concentration of barusiban on preterm and term myometrium is about 100 times lower than that of atosiban.[45] Initial results of barusiban efficacy in a primate model where uterine contractions were stimulated with oxytocin are encouraging.[46]

Practice points

- there is no evidence to support $MgSO_4$ or NO donors as tocolytics
- ß agonists are effective in delaying delivery for 48 h but have no effect on perinatal mortality or morbidity, and do have significant maternal side effects
- indomethacin is an effective tocolytic but there are concerns regarding possible fetal and neonatal effects
- calcium channel blocking agents, specifically nifedipine, are effective tocolytics when compared with other tocolytic agents (but have not been assessed against placebo). They have a low maternal side effect profile and are the only tocolytics to have shown) positive effects on neonatal outcomes
- the oxytocin receptor antagonist atosiban is no better than other drugs in delaying or preventing preterm birth but has fewer maternal side effects

Research agenda

- further studies on the utility of progesterone with specific reference to neonatal and infant outcomes
- RCTs comparing any tocolytic (including nifedipine) must include a placebo arm

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