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A Risk-Benefit Assessment of Therapies for Premature Labour

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Abstract

Prematurity is the leading cause of neonatal morbidity and mortality, yet the incidence of preterm birth has not declined despite the use of multiple pharmacological agents to treat preterm labour. After reviewing the literature we conclude the following.

β-Agonists have been shown to prolong gestation for 24 to 48 hours; however, these agents have not been shown to decrease neonatal morbidity or mortality.

Adverse effects are inevitable and can be life-threatening. There are no proven benefits to mother or fetus with long term therapy.

More data are needed regarding the tolerability and efficacy of calcium antagonists before routine clinical use can be recommended. Oxytocin antagonists should be considered investigational drugs and further studies are needed to evaluate their effectiveness in the treatment of preterm labour. Furthermore, the tolerability of oxytocin antagonists in both mother and fetus has not been adequately established.

Indomethacin, a prostaglandin inhibitor, has been shown to delay delivery in a limited number of randomised placebo-controlled clinical trials. Sulindac appears promising but has never been evaluated in a well controlled trial. Neonatal adverse effects appear to be minimal with prostaglandin inhibitors as long as the duration of treatment is short (<48 to 72 hours) and the gestational age is <32 weeks.

Magnesium sulfate appears to inhibit myometrial contractility but is ineffective at prolonging gestation or preventing preterm birth. Furthermore, magnesium has not been shown to decrease neonatal morbidity or mortality; in fact, some investigators have shown an increase in infant mortality with this agent.

There are no data to support adjunctive antimicrobial therapy for the treatment of preterm labour. Oral maintenance therapy with any of these tocolytic agents has not been shown to decrease the rate of preterm birth or recurrent preterm labour.

Prematurity continues to be the leading cause of neonatal morbidity and mortality. Preterm neonates are still the greatest contributors to the neonatal death rate.[1] The incidence of preterm birth (defined as delivery after <37 weeks of gestation) varies from 9 to 16%, depending on the population studied. During the past 40 years multiple pharmacological agents have been used to treat preterm labour, yet the incidence of preterm birth and low birth weight infants remains unchanged.

It is difficult to determine the efficacy of tocolytic agents for several reasons. First, the diagnosis of preterm labour is incorrect in up to 80% of patients.[2] This is because few investigators have based the diagnosis on the combination of uterine contractions and cervical change. By definition, both should be present to establish the diagnosis of preterm labour. The diagnosis has been shown to be in error in 40 to 70% of women when uterine contractions are the only criterion.[3]

Secondly, the cause of preterm labour is unknown, thereby preventing targeting of therapy to a specific cause. Uterine contractions are a normal physiological process during pregnancy. Of patients with regular uterine contractions, 30% have cessation of contractions without treatment.[1,4]

Thirdly, it is extremely difficult to evaluate many of the clinical trials in the literature. Most of the studies were not placebo-controlled and most did not have a strict definition of preterm labour. In addition, many studies have confounding variables: polypharmacy and inclusion of patients with multiple gestation and ruptured membranes. Furthermore, most of the studies did not adequately address fetal and maternal safety.

The improvement in perinatal mortality over the past 20 to 30 years is probably because of advancements in neonatal care rather than in tocolytic therapy. The enigma of preterm labour is best summed up by the words of Chekhov's character Gaev in *The Cherry Orchard*:[5] "When a lot of remedies are suggested for a disease, that means it can't be cured."

In this article we will try to present an overall assessment of efficacy and safety of the currently used tocolytic agents.

1. β-Agonists

1.1 Background and Mechanism of Action

The first published study with β-agonists in preterm labour was in 1961 using isoxsuprine.[6,7] Subsequently, buphenine (nylidrin), ritodrine, terbutaline, hexoprenaline, salbutamol, albuterol, orciprenaline (metaproteronol) and fenoterol have been used. Ritodrine is the only drug approved by the US Food and Drug Administration (FDA) for treating preterm labour. These drugs stimulate β-adrenoceptors throughout the body, including the uterus. There are 2 types of β-adrenoceptors in humans: β_1 receptors are located in the heart, small intestine and adipose tissue, and β_2 receptors are found in blood vessels, uterus, bronchioles and diaphragm. Many β-adrenergic drugs stimulate both receptors. They bind to smooth muscle membrane, activating the formation of cyclic adenosine monophosphate (cAMP) and resulting in a series of reactions which decrease intracellular calcium and reduce the sensitivity of the myosin-actin contractile unit to calcium. The inhibition of uterine smooth muscle occurs even in the presence of oxytocin.

Two potential problems with β-agonists are downregulation and desensitisation, making these agents less effective with prolonged exposure. The adverse effects reported with these agents are numerous.

1.2 Clinical Trials

There have been numerous published clinical trials using β-agonists. The majority are non-randomised clinical trials or retrospective studies. There have been several randomised controlled trials; however, they have serious methodological flaws.[4,8-17]

The study which led to the approval of ritodrine by the FDA was done in such a manner that the results are impossible to interpret.[13] There were 11 centres of which only 5 randomised to placebo. There were an inadequate number of control patients, many of whom were treated with ethanol. There were different protocols for route and schedule of administration at each institution. One centre, which contributed a significant amount of patients to the entire study, published their data separately and found no difference between ritodrine and placebo.[18] This landmark study by Merkatz et al.[13] would probably not pass peer review today in its current format.

There have been ten randomised placebo-controlled trials of β-agonists published to date, of which 9 used ritodrine and 1 used intravenous terbutaline. No benefit of β-agonists in prolonging pregnancy was shown in 7 of these studies.[18-27] The largest study was published by the Canadian Preterm Labour Investigators Group. They randomised 708 women by gestational age to ritodrine or placebo in 6 centres. They demonstrated that ritodrine could delay delivery by 24 to 48 hours, but time from randomisation to delivery was 27.8 ± 1.6 days in the ritodrine group and 24.5 ± 1.6 days in the placebo group (not significant). Furthermore, there was no difference in neonatal mortality or morbidity between the 2 groups.[24]

Three studies have shown β-agonists to be superior to placebo. The first study was by Wesselius-De Casparis et al.[25] They compared ritodrine with placebo in 91 patients. They also included patients with ruptured membranes but analysed them separately. In addition, their definition of preterm labour was not precise. Of patients with intact membranes, 77% were undelivered 7 days after treatment with ritodrine versus 48% in the placebo group ($p = 0.02$).

A second study compared terbutaline with placebo in 30 patients. Of the 15 patients in the placebo group, 4 (27%) had arrest of labour for >7 days compared with 13 of 15 patients (87%) in the terbutaline group ($p < 0.01$).[26] A 1986 study randomised 125 patients to ritodrine or placebo.[27] The mean prolongation of pregnancy was 9.5 days greater in the ritodrine group, but there was no difference between the 2 groups in patients undelivered after 2 weeks. There are 2 problems with this study. First, 21% of patients were excluded after randomisation. Secondly, their diagnosis of preterm labour is suspect since 62% of patients in the

placebo group were undelivered after 2 weeks and 60% reached a gestational age of 36 weeks.

There have been two randomised placebo-controlled studies using the subcutaneous terbutaline pump.[28,29] Neither study demonstrated terbutaline to be better than placebo. Furthermore, in November 1997, the FDA issued the following statement about the terbutaline pump:

> *In the absence of data establishing the effectiveness and safety of the drug/device, FDA is alerting practitioners, home healthcare agencies, insurance carriers and others that continuous subcutaneous administration of terbutaline sulphate has not been demonstrated to be effective and is potentially dangerous.*

1.3 Adverse Effects

β-Agonists have been shown to cause more unwanted maternal and fetal adverse effects than any other tocolytic agent. β-Adrenoceptors are present in multiple organ systems; however, the cardiovascular system is most frequently involved. Common maternal symptoms are tremor, palpitations, headache, nausea, vomiting, thirst, restlessness and chest pain.

1.3.1 Maternal

Cardiovascular

The most common adverse effects are increases in heart rate, systolic blood pressure, stroke volume, pulse pressure and cardiac output. Cardiac output has been shown to increase 60% with terbutaline or ritodrine.[30,31] There is a simultaneous decrease in peripheral vascular resistance and diastolic pressure. Supraventricular tachycardia is the most common dysrhythmia. There have also been case reports of atrial fibrillation, premature atrial contractions and ventricular ectopy with these agents.[32-38] Electocardiographic changes are very common (in 75% of patients receiving ritodrine) and are often asymptomatic.[39,40] They usually resolve with discontinuation of the drug.

The terbutaline pump has also been associated with significant adverse effects. A recent study demonstrated 1 or more cardiopulmonary problems in 0.54% of 8709 patients on low-dosage continuous terbutaline infusion.[41] Furthermore, there has been a report of sudden death associated with the terbutaline pump.[42]

Pulmonary

Pulmonary oedema has been reported in up to 5% of patients given β-agonists despite corticosteroid administration.[32,43-49] Pulmonary oedema is thought to be either secondary to the antidiuretic effect of large doses of β-agonists or iatrogenic from fluid overload.

Another factor predisposing the patient to pulmonary oedema is the increase in sodium and water retention secondary to increased plasma renin and arginine-vasopressin caused by β-agonists.[50-52]

Metabolic

There are several marked metabolic changes that occur with high doses of β-agonists. First, serum potassium levels can fall precipitously after initiation of therapy, often 0.5 to 1.5 mEq/L below pretreatment levels.[53-55] The effect is transient, does not require treatment and serum levels normalise within 24 hours.

Secondly, β-agonists increase serum glucose and insulin levels.[56,57] The effect on blood glucose is more pronounced in patients with diabetes mellitus because of concomitant increased glucagon secretion.[56,58] β-Agonists also induce lipolysis, thereby predisposing patients with diabetes mellitus to severe metabolic acidosis. This effect is augmented by administration of corticosteroids. Both oral and subcutaneous terbutaline have been shown to decrease peripheral insulin sensitivity and increase endogenous glucose production in patients predisposed to gestational diabetes mellitus.[59,60]

Miscellaneous

Numerous other case reports have documented rare adverse effects including haemolytic anaemia, severe vulvar oedema, elevation of transaminase levels, postpartum cardiomyopathy, myotonic muscular dystrophy, acute cutaneous vasculitis, allergic dermatitis, agranulocytosis, cerebral oedema, second degree heart block, hypertensive crisis, adult respiratory disease syndrome, cardiac failure, respiratory arrest and maternal death.[61-80]

1.3.2 Fetal

β-Agonists readily cross the placenta.[81-90] Therefore, fetal effects are similar to those observed in the mother. Fetal tachycardia, increased cardiac output and redistribution of blood flow have been demonstrated.[91-98] Additionally, neonatal supraventricular tachycardia, nonimmune hydrops, myocardial ischaemia, myocardial necrosis and fetal death have been reported.[99-104] Metabolic complications include both hyperinsulinaemia and hypoglycaemia.[105,106]

The effect on utero-placental blood flow is unclear. Some investigators report decreased uteroplacental blood flow,[104-113] others increased blood flow,[114,115] and others no significant change.[116-118] The reasons for these differences are probably secondary to duration of treatment, the particular drug used, the concomitant use of other pharmacological agents and the particular method used to measure utero-placental blood flow. There has been long term follow-up (1 to 9 years) of infants exposed to β-agonists *in utero*. There were no demonstrable differences in developmental outcome between exposed infants and preterm controls.[119-124]

β-Agonists have been associated with an increased incidence of neonatal intraventricular haemorrhage (IVH).[125,126] One study looked at the incidence of IVH in 2827 neonates delivered between 25 to 36 weeks of gestation, comparing neonates of mothers who received β-agonists for preterm labour with those who received another tocolytic or no tocolytic therapy. These investigators showed a 2- to 4-fold increased risk [odds ratio (OR) 2.47, 95% confidence interval (CI) 1.34 to 4.56, p = 0.004] of IVH in neonates whose mothers received β-agonist treatment for preterm labour. Moreover, there was a trend toward an increased incidence of the more severe grades III/IV (OR 2.50, 95% CI 0.96 to 6.48, p = 0.06).[125]

2. Calcium Antagonists

2.1 Background and Mechanism of Action

Calcium antagonists have been shown to inhibit smooth muscle contractility in humans both *in vitro* and *in vivo*. These drugs inhibit the slow inward current of calcium ions through voltage-dependent calcium channels during the second phase of the action potential.[127] They may also inhibit the release of intracellular calcium from sarcolemmal stores and increase calcium efflux from the cell.[128] Calcium antagonists seem to have the greatest effect on myometrial relaxation.[129] Of these agents, nifedipine has been studied most often; the use of verapamil is limited because of its effect on atrioventricular conduction in the heart.

Nifedipine is rapidly and almost completely absorbed in the gastrointestinal tract; absorption is lower after sublingual administration.[128] The initial and maximal blood concen trations are reached in 6 and 15 minutes, respectively, with a duration of drug effect of up to 6 hours in nongravid women.[130] Parenteral nifedipine has not been used to treat preterm labour. The oral dose is 30mg initially followed by 20mg every 6 to 8 hours. Sublingual administration has also been used, starting with 10mg and repeating the dose every 20 minutes up to a maximum of 40mg in 1 hour. Patients were given oral nifedipine every 4 to 6 hours.[131,132]

2.2 Clinical Trials

Nifedipine has been compared with ritodrine in several small studies. Nifedipine was found to be equally or more effective than ritodrine in suppressing preterm labour with fewer adverse effects.[130,131,133-135]

Kupferminc et al.[127] performed a prospective randomised trial of nifedipine and ritodrine in 71 women and demonstrated a delay of delivery for 48 hours in 83% of nifedipine recipients and for 7 days in 67%; delivery was delayed until 36 weeks gestation in 50% of those receiving nifedipine. Corresponding figures for the ritodrine group were 77%, 63% and 43%, respectively (differences not significant). There were significantly fewer adverse effects in the nifedipine group compared with the ritodrine group (27 versus 77%, p < 0.001). Two other studies randomised patients to ritodrine or nifedipine with similar results.[131,136]

There is only 1 randomised placebo-controlled trial using nifedipine. 60 patients were randomised to either ritodrine, nifedipine or placebo. These investigators demonstrated nifedipine to be significantly better than placebo or ritodrine in prolonging gestation. However, their definition of preterm labour did not include cervical dilation or effacement, and one-third of patients in the nifedipine group also received ritodrine.[135]

2.3 Adverse Effects

2.3.1 Maternal

The adverse effects of nifedipine are substantially fewer than those of β-agonists. Transient facial flushing is the most common adverse effect. Calcium antagonists are frequently used for their vasodilatory and negative inotropic effects. A decrease in blood pressure has been observed in several studies.[127,130,132,135,137] One study demonstrated that even though blood pressure changes were statistically significant, the decrease was clinically unimportant and significantly less than the decrease associated with ritodrine.[127] Nifedipine produces a smaller transient increase in maternal heart rate than ritodrine.[127,130,132] In addition, nifedipine can cause maternal hepatotoxicity and can potentiate the toxicity of magnesium sulfate by causing neuromuscular blockade.[138] The metabolic effects of ritodrine (i.e. hypokalaemia and hyperglycaemia) are not seen with nifedipine.[132]

2.3.2 Fetal

Nifedipine is readily transported across the human placenta; however, reported fetal and neonatal adverse effects have been minimal. No significant changes in fetal heart rate have been shown when women have received nifedipine.[127,128] Nifedipine has been shown to have a significant effect on uterine and umbilical blood flow in animals, but not in humans.[139]

3. Oxytocin Antagonists

3.1 Background and Mechanism of Action

The exact role of oxytocin in term and preterm labour is unclear. The interest in oxytocin antagonists for the treatment of preterm labour was prompted by studies showing an increase in oxytocin receptors with the initiation of labour.[140,141] Although an increase in maternal plasma oxytocin levels in labour has not been demonstrated, Bossman et al.[142] suggest that there is increased excretion of oxytocin which is utero-feto-placental in origin and, therefore, not measurable in maternal serum. Oxytocin antagonists have been shown to inhibit myometrial contractions *in vitro*. The degree of inhibition correlates with the concentration of oxytocin receptors.[142]

The action of oxytocin antagonists is thought to be 3-fold: a competitive inhibitor of oxytocin binding to both myometrial and decidual receptors, and prevention of both second messenger formation and calcium mobilisation.[143]

Atosiban (antocin or 1-deamino-[D-Tyr(OEt)^2, Thr^4,Orn^8]oxytocin) is an analogue of oxytocin modified at positions 1, 2, 4 and 8. Because of its peptide structure, atosiban is primarily a parenterally administered drug with poor bioavailability after oral administration. An orally active nonpeptide oxytocin antagonist has been identified (L-366509), which may improve the usefulness of this agent.[129]

The dose of atosiban required for cessation of contractions varies. Rapid attainment of steady-state concentrations has been achieved by bolus administration. A 6.5mg bolus followed by infusion at 300 μg/min resulted in a significantly greater proportion of patients who stopped contracting within the first 2 hours of treatment compared with those who did not receive a bolus.[144] With a continuous infusion of 300 μg/min, plasma atosiban concentrations reach steady state within 1 hour of initiation of the infusion and the effective half-life is 18 ± 3 minutes.[145]

Atosiban does not appear to readily cross the human placenta. One study infused atosiban for up to 7 hours before elective caesarean section. The mean maternal/fetal serum ratio was 12 ± 0.03 and was not affected by length of infusion. In addition, there was no increase in maternal blood loss and no

adverse neonatal effects. Infants were followed until 1 year of age.[146]

Two additional studies have shown no effect on lactation or postpartum haemorrhage secondary to uterine atony in patients who received oxytocin antagonists.[129,144] Theoretically, oxytocin antagonists should be organ specific with limited adverse effects since oxytocin receptors are found primarily in the uterus and the breast.

3.2 Clinical Trials

Goodwin et al.[144] compared atosiban with ritodrine and found no significant difference in efficacy between these agents. There were significantly fewer maternal adverse effects with atosiban and no adverse effects in the newborn. Several small studies have shown atosiban to be effective in stopping preterm contractions.[147,148]

There has been 1 large randomised double-blind placebo-controlled study using atosiban.[149] Patients in preterm labour were randomised between 20 weeks and 33 weeks 6 days of gestation. There was no significant difference between atosiban and placebo in time to delivery (25.6 days for atosiban versus 21 days for placebo). However, the proportion of patients remaining undelivered and not requiring alternative tocolytic therapy within 7 days was slightly less in the antosiban group.

3.3 Adverse Effects

There have not been any reported maternal or fetal adverse effects with oxytocin antagonists. However, the studies are limited.

4. Prostaglandin Inhibitors

4.1 Background and Mechanism of Action

There is substantial evidence that prostaglandins are of critical importance in both the initiation and maintenance of human labour. Elevated levels of prostaglandins have been demonstrated in both serum and amniotic fluid of patients in labour.[150-160] Prostaglandin levels are low or absent in serum and amniotic fluid of women not in labour at all gestational ages. Prostaglandin metabolites have been shown to decrease significantly in preterm labour patients who received indomethacin.[154,161]

Prostaglandins exhibit their effect by two mechanisms. First, they enhance the production of myometrial gap junctions. Secondly, they stimulate the cellular influx of calcium and calcium release from the sarcoplasmic reticulum, which leads to the activation of myosin light chain kinase and smooth muscle contraction.[162]

Prostaglandin inhibitors act by inhibiting the enzyme cyclo-oxygenase, the first step in prostaglandin synthesis. Cyclo-oxygenase converts arachidonic acid into the first prostaglandin intermediate, prostaglandin G_2. Nonsteroidal anti-inflammatory drugs (NSAIDs) compete with arachidonic acid for cyclo-oxygenase, but do not disrupt the enzyme. However, aspirin (acetylsalicylic acid) causes irreversible inhibition of cyclo-oxygenase by acetylation.

NSAIDs differ in chemical structure, mechanism of action, and adverse effects. These agents have analgesic, antipyretic and anti-inflammatory properties. They also suppress thromboxane and prostacyclin formation. These drugs appear more effective than β-agonists for preterm labour. Numerous studies have shown suppression of preterm labour in patients who failed to respond to tocolysis with β-agonists; however, no study has shown the opposite.[163-167]

Critical interest in prostaglandin inhibitors began 25 years ago. A retrospective study showed an increase in frequency of postmaturity and length of gestation in patients taking high doses of salicylates.[168] A subsequent study demonstrated a prolonged interval between injection and abortion in patients given aspirin or indomethacin before midtrimester abortion with hypertonic saline.[169]

4.2 Clinical Trials

The first clinical trial using prostaglandin inhibitors to treat preterm labour was published in 1974. Treatment of 50 patients in preterm labour with indomethacin delayed delivery by >7 days in 80% of patients.[170] Numerous subsequent studies have attempted to evaluate the efficacy of these agents

in the treatment of preterm labour, but most are uncontrolled clinical trials.[163,171-177]

There have been 2 double-blind randomised placebo-controlled trials using indomethacin for the treatment of preterm labour.[161,178] Both studies demonstrated that indomethacin could significantly prolong gestation compared with placebo (>48 hours in Niebyl et al.[161] and >7 days in Zuckerman et al.[178] However, some patients in both studies received additional tocolytic therapy when the initial treatment failed. Neither study reported maternal or neonatal adverse effects related to the use of indomethacin.

Sulindac is a prostaglandin inhibitor closely related to indomethacin, but with a much lower adverse effect profile. It has been used as a tocolytic therapy and found to be as effective as indomethacin.[179,180] Sulindac had minimal maternal and neonatal adverse effects in both studies. There was no significant effect on amniotic fluid volume, fetal urine output or fetal ductal velocity in patients who received sulindac. This may be due to 2 factors. First, sulindac has a complex metabolism; the parent drug is inactive and must be converted to the sulphide metabolite.[181,182] Secondly, sulindac has been shown to cross the placenta less readily than indomethacin.[183,184]

4.3 Adverse Effects

4.3.1 Maternal

Prostaglandin inhibitors can cause minor maternal adverse effects, including nausea, vomiting, diarrhoea, heartburn, headache and rash. More serious adverse effects are peptic ulceration, thrombocytopenia, bleeding and serious allergic reaction.

4.3.2 Fetal

Potential fetal adverse effects of prostaglandin inhibitors are decreased amniotic fluid volume, necrotising enterocolitis (NEC) and premature closure of the ductus arteriosus.

Two retrospective studies have shown an increased incidence of NEC in neonates of preterm labour patients treated for >48 hours with indomethacin,[185,186] although in 1 of the studies indomethacin administered for <48 hours duration and remote from delivery (>24 hours) was not associated with an increased incidence of NEC.[186] The study by Norton et al.[185] also showed an increased incidence of NEC in neonates of mothers who received indomethacin; however, some patients received up to 6000mg of indomethacin over a duration of 79 days, a dosage and treatment duration much greater than any of the other studies. It is unclear from this paper whether short-term therapy was associated with increased neonatal adverse effects, particularly an increased incidence of NEC. Furthermore, both of these studies were retrospective with relatively small sample sizes.

Another small retrospective study[187] found an increased incidence of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) in neonates of mothers who received ritodrine and indomethacin compared with patients who received ritodrine only. They did not demonstrate a statistical difference in NEC, patent ductus arteriosus or IVH, although the incidence of each was greater in the ritodrine only group. The significant limitation of the study, as well as being retrospective with a small sample size, is the lack of a stated method used to choose the control group. Moreover, the study patients received dual tocolytic therapy and received greater cumulative doses of ritodrine.

Several larger studies have not demonstrated significant adverse affects of prostaglandin inhibitors. Zuckerman et al.[188] treated 297 women in preterm labour with indomethacin alone for tocolysis. 15 neonates died from RDS and extreme prematurity. There were no neonatal adverse effects noted. Furthermore 246 infants had long term follow-up (up to 5 years) with satisfactory development. Another large study[189] evaluated neonatal outcomes of 818 women receiving indomethacin for preterm labour over a 7-year period. The overall rate of perinatal complications was 1.8%. Some of these patients received up to 17 weeks of drug treatment and many were treated beyond 35 weeks of gestation. There were no reported cases of NEC in this cohort of neonates. A subsequent study also did not find an increased risk of neonatal complica-

tions in mothers who received indomethacin for preterm labour.[190]

Indomethacin has been shown to decrease amniotic fluid volume. This reduction occurs in some patients and is unrelated to duration of therapy. Several investigators have successfully treated hydramnios with indomethacin and therefore this agent is often the preferred drug for treatment of patients in preterm labour with hydramnios.[191,192] Sulindac has not been shown to decrease amniotic fluid volume.[179,180]

A recent decision tree analysis compared tocolysis with indomethacin with no tocolysis. These authors concluded that the benefits of indomethacin outweigh the potential risks to the neonate at gestational ages <32 weeks.[193]

Indomethacin is used to treat persistent patent ductus arteriosus in the neonate. Clinical response in the preterm neonate is variable and not related to serum indomethacin concentration.[194-197] Most studies demonstrate resistance of the ductus to closure at earlier gestational ages. Prostaglandin inhibitors cause constriction of the fetal ductus arteriosus *in utero*.[198-202] The constriction is usually transient and abates after cessation of the drug. However, prolonged exposure to indomethacin can cause pulmonary hypertension and tricuspid regurgitation. A randomised study comparing indomethacin with ritodrine showed minimal neonatal adverse effects in the indomethacin group. However, there were 3 cases of primary pulmonary hypertension in infants in the indomethacin group, allegedly caused by a prolonged duration of treatment.[203] Sulindac does not appear to have a significant effect on fetal ductal flow.[179,180]

5. Magnesium Sulfate

5.1 Background and Mechanism of Action

The mechanism of action of magnesium sulfate is unknown. It is thought to involve modulation of calcium uptake, binding and distribution within myometrial smooth muscle cells, resulting in decreased contractility. Magnesium also activates adenylate cyclase, resulting in increased cAMP levels. Magnesium sulfate has been shown to inhibit calcium-induced uterine contractions.[204,205] However, high serum concentrations of magnesium (4 to 8 mEq/L) are necessary to elicit a reduction in uterine contractility.

5.2 Clinical Trials

There are very few controlled studies evaluating the efficacy of magnesium sulfate for treatment of preterm labour. The first study was published in 1972. This investigation randomised 71 patients to intravenous magnesium sulfate, ethanol or dextrose. Success was defined as cessation of contractions for 24 hours and was 77% in the magnesium group. This study has several major flaws. First, the patients receiving dextrose were not randomised; only patients in the ethanol and magnesium groups were randomised. Secondly, only 9 patients received dextrose; therefore, the placebo group is too small to demonstrate statistical significance. Thirdly, their definition of preterm labour was inadequate, since 23 of 31 patients receiving magnesium had cervical dilation <1cm on enrolment.[206]

Three subsequent randomised placebo-controlled studies using magnesium sulfate have been published to date. The first study[22] randomised 54 patients to intravenous magnesium sulfate, terbutaline or placebo. Success was defined as prolongation of the pregnancy for 48 hours. There was no significant difference between the groups in prolongation of pregnancy or preterm birth. A second study by Cox et al.[207] randomised 156 women between 24 to 34 weeks of gestation to intravenous magnesium sulfate or placebo. Magnesium had no effect on prolongation of gestation, birth weight, neonatal morbidity or perinatal mortality. The authors concluded that infusions of magnesium sulfate at concentrations that could be tolerated were ineffective when used to prevent preterm birth.

The most recent study using magnesium sulfate was published in 1992.[208] This author randomised 65 patients to magnesium sulfate or placebo. The major flaw with this study is the definition of preterm labour. The author stated that one of the criteria for preterm labour was a short (<1cm) cervi-

cal neck or an opened cervical os, yet 23 of 30 patients receiving magnesium sulfate had a cervical os which was closed or fingertip on palpation. In fact, 28 of 30 patients had cervical dilation less than 2cm. Probably, most patients in the magnesium group were not in preterm labour. Magnesium sulfate was no better than placebo in prolonging gestation for >48 hours in patients with cervical dilation >2cm. The author did not provide adequate data regarding cervical dilation and effacement in the placebo group. Furthermore, there were 5 fetal deaths in this study (3 in the placebo group and 2 in the magnesium group).

5.3 Adverse Effects

5.3.1 Maternal

Magnesium sulfate has been shown to cause flushing, nausea, vomiting, visual disturbances, ileus, headaches, muscle weakness, lethargy, shortness of breath, urinary retention, hypocalcaemia and pulmonary oedema. High concentrations have been associated with subendocardial ischaemia, cardiac arrest and maternal death.[209]

5.3.2 Fetal

Fetal plasma concentrations of magnesium are comparable to maternal concentrations. Neonatal adverse effects include drowsiness, hypotonia, bony abnormalities and congenital rickets.[210,211] Furthermore, a recent study has raised grave concerns about magnesium sulfate. The Magnesium and Neurologic Endpoints Trial[212] was a randomised controlled trial initiated to determine whether antenatal magnesium sulfate exposure for preterm labour could prevent cerebral palsy. During the interim analysis, investigators noted a significant difference in mortality between the 2 arms. There were 7 paediatric deaths in 48 patients in the magnesium group and no deaths in 47 patients in the other group who received a different tocolytic. This risk difference was highly significant (15.2%; 95% CI 4.8 to 25.6; p = 0.006). Moreover, if the results of this study are combined with those of the study by Cox et al.[207] there is a highly statistically significant association between magnesium exposure and paediatric death (risk difference 10.7%; 95% CI 3.9 to 17.6; p = 0.002). Mittendorf et al.[213] estimated that there may be 1872 excess infant deaths annually in the US from magnesium exposure if a conservative measure of 3.9% excess deaths (lower 95% CI) is used and assuming the frequency of magnesium sulfate usage is 40%. However, using a more realistic excess infant death rate of 10% and magnesium sulfate usage of 40%, the excess infant death rate could be as high as 4800 per year with exposure to magnesium.[213] Another randomised placebo controlled trial also showed an increased perinatal death rate in mothers who received magnesium sulfate for preterm labour.[207] A retrospective case control study did not show an increased incidence of neonatal death in women given magnesium sulfate. However, not all women received magnesium sulfate for preterm labour. Some patients were given magnesium sulphate for pre-eclampsia (approximately 18% in the control group).[214]

6. Antimicrobials

6.1 Background and Mechanism of Action

Over the past 35 years there have been multiple unrelated studies that have demonstrated an association between infection and preterm birth. In 1961, Emig et al.[214] found histological evidence of inflammation in placentas of women who had preterm births. Since then, numerous authors have shown an association between funicitis and/or amnionitis with preterm birth. Furthermore, numerous investigators have shown that colonisation of the genitourinary tract with certain microorganisms is associated with prematurity, low birth weight and premature rupture of the membranes. These organisms include *Gardnerella vaginalis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, Group B β-haemolytic streptococci, *Bacteroides* species and *Chlamydia trachomatis*. There is evidence that these micro-organisms indirectly stimulate the production of cytokines, collagenases, prostaglandins and elastases.[215] Moreover, most patients found to have histological evidence of microbial invasion of the amniotic cavity do not fulfil

criteria for the diagnosis of intra-amniotic infection. These patients present with subclinical infection and therefore are not deemed candidates for antimicrobial therapy. These findings have led numerous investigators to study antimicrobial treatment as initial or adjunctive therapy for the treatment of preterm labour.

There exists a wide body of epidemiological, biochemical and clinical evidence supporting the role of subclinical infection in preterm birth.[215,216] Histological evidence of intra-amniotic infection has been found in up to 40% of patients with preterm birth.[217] Amniotic fluid cultures have been positive in up to 61% of patients with preterm labour and intact membranes.[218] A recent study has shown a strong correlation between the presence of bacterial vaginosis at 28 weeks gestation and preterm birth.[219]

Urinary tract infection has also been associated with preterm birth and low birth weight infants. Asymptomatic bacteruria is found in approximately 10% of pregnant women. A meta-analysis of 17 studies showed a higher rate of low birth weight infants in women with asymptomatic bacteruria than in women without bacteruria (OR 1.6, 95% CI 1.4 to 1.9; $p < 0.001$).[215] In addition, there was a higher rate of prematurity in women with asymptomatic bacteruria compared with women with no bacteruria in the 4 studies that presented data on preterm birth (OR 1.9, 95% CI 1.3 to 2.9; $p < 0.001$).[215]

Therefore, if subclinical infection is a major cause of failed tocolytic therapy, then it is not surprising that numerous investigators have studied antimicrobials as adjunctive therapy for the treatment of preterm labour.

6.2 Clinical Trials

There have been 10 randomised clinical trials published between 1986 and 1995 looking at adjunctive antimicrobial treatment in patients presenting with preterm labour:[220-229] 5 studies showed some benefit from adjunctive antimicrobial treatment[220-222,225,228] and 5 studies demonstrated no benefit.[223,224,226,227,229]

The first study[220] published in 1986 randomised 48 women with <34 completed weeks of gestation in preterm labour to either enteric-coated erythromycin base or placebo for 7 days in double-blind fashion. One-third of their patients were excluded after randomisation. These investigators were able to show a prolongation from treatment to delivery of 32.5 days in the erythromycin group versus 22.4 days in the placebo group ($p = 0.027$). However, they could demonstrate this difference only in women with <1cm of cervical dilation at the initiation of treatment. Moreover, there was no demonstrated neonatal benefit from treatment. A similarly designed study which randomised women to erythromycin versus placebo was also able to demonstrate a prolongation of pregnancy in patients who received antimicrobials.[221] However, neonatal morbidity and mortality were not addressed in this study.

A study by Morales et al.[222] randomised 150 women to ampicillin, erythromycin or no treatment. Antimicrobial therapy was prescribed for 10 days and was not altered by the results from cervical cultures. 25% of patients were excluded after randomisation. These investigators were able to demonstrate increased time gained *in utero* and increased birth weight in patients given either ampicillin or erythromycin compared with patients receiving no antimicrobial therapy. This study did not address neonatal morbidity.

A subsequent study in 1991[225] enrolled 117 women receiving tocolytic therapy to either intravenous clindamycin or placebo. The authors demonstrated an increased interval from treatment to delivery of 35 days in the antimicrobial group versus 25 days in the placebo group ($p = 0.02$). However, these investigators could not demonstrate any increase in neonatal birth weight or a reduction in neonatal morbidity or mortality in mothers who received antimicrobials.

Norman et al.[228] randomised 81 women in 3 perinatal centres in active preterm labour with uncomplicated singleton pregnancies between 26 to 34 weeks gestation. Patients were randomised to ampicillin and metronidazole or no therapy. These

investigators were able to demonstrate an increase in treatment to delivery interval in patients receiving antimicrobial therapy (median 15 days) versus patients receiving no therapy (median 2.5 days p = 0.04). There was no difference in mean gestational age at delivery or neonatal birth weight between the 2 groups. The only neonatal morbidity that was significantly different between the 2 groups was the incidence of NEC (5 neonates in the control group versus none in the antimicrobial group, p = 0.02).

The following studies have shown no maternal or neonatal benefit in patients receiving adjunctive antimicrobial therapy for preterm labour.[223,224,226,227,229]

Newton et al.[223] randomised 95 patients between 24 and 34 weeks gestation in preterm labour requiring treatment with parenteral tocolytic therapy to intravenous ampicillin plus concomitant enteric coated oral erythromycin for 7 days, or saline and identical lactose capsules in the placebo group. They determined that clinically significant outcome parameters would be an increase in mean birth weight of 250g or 7 days gained *in utero*. These investigators, however, could not find a difference in any outcome parameter between the 2 groups. Interestingly, at enrolment, 50% of patients had an elevated C-reactive protein level (defined as >0.6 mg/dl) which is felt to be a marker of early intra-amniotic infection and tocolytic failure,[220,223] and 41% of patients had bacterial vaginosis identified on Gram's stain. In addition, there was no difference in outcome parameters when patients were subgrouped according to the agent used for tocolytic therapy.

This same group of investigators published a subsequent follow-up study in 1991.[224] They randomised 86 patients in preterm labour between 24 and 34 weeks gestation who were receiving magnesium sulfate for tocolytic therapy to 1 of 2 study arms: intravenous ampicillin/sulbactam and indomethacin or the corresponding placebos. Again, these same investigators could not demonstrate any difference in gestational age at delivery, time interval from treatment to delivery, number of patients with recurrent preterm labour or maternal infection between the 2 groups. Furthermore, there was no difference in neonatal birth weight, perinatal morbidity or perinatal mortality between the 2 groups.

McCaul et al.[226] randomised 120 patients between 19 and 34 weeks gestation, either in preterm labour with intact membranes or not in labour with premature rupture of membranes, to ampicillin or placebo. There were 36 women in the preterm labour group and 84 women in the premature rupture of membranes group. In the premature rupture of membranes group, patients who received placebo had a longer treatment to delivery interval than patients receiving antimicrobial therapy (17.8 versus 8.1 days respectively, p = 0.04). However, in the patients in preterm labour with intact membranes who were randomised to antimicrobial therapy or placebo, there was no significant difference in treatment to delivery interval, chorioamnionitis, birth weight, neonatal RDS, sepsis, mode of delivery or the number of neonatal hospital days.

In 1993 a multicentre randomised, double-blinded, placebo-controlled trial was designed, implemented and published by the Maternal-Fetal Medicine Units Network at the National Institute of Child Health and Human Development.[227] 277 women with singleton pregnancies in preterm labour with intact membranes between 24 and 34 weeks gestation were randomised to receive either tocolysis, corticosteroids and antimicrobials, or tocolysis, corticosteroids and placebo. Patients randomised to the control group received corresponding placebos for each drug both parenterally and orally. The primary maternal outcome measure was prolongation of pregnancy. Secondary outcome measures were frequency of preterm premature rupture of the membranes, infectious related morbidity, number of readmissions for preterm labour and associated maternal complications observed in patients with preterm labour. The primary neonatal outcome measures were perinatal mortality and morbidity. Secondary outcomes included birth weight and days of hospitalisation in the neonatal intensive care unit. A composite morbidity score was calculated on the basis of the number of

the following serious adverse outcomes: RDS grades III or IV, IVH, NEC, neonatal sepsis and stage III or higher retinopathy of prematurity. There were 133 patients randomised to the antimicrobial group and 144 patients to the placebo group. The overall frequency of microbial invasion in the amniotic cavity, defined as either a positive amniotic fluid culture for micro-organisms or a positive Gram's stain for bacteria, was 5.9%. The rate of microbial invasion was doubled in patients allocated to the antimicrobial group compared with those patients in the placebo group; however, this difference was not statistically significant ($p = 0.09$).

These investigators could find no significant difference in maternal outcome between the 2 groups, including duration of randomisation to delivery, preterm delivery (<37 weeks gestation), frequency of preterm premature rupture of the membranes, clinical chorioamnionitis, endometritis or the number of subsequent admissions for preterm labour. Similarly, no significant difference in neonatal outcome could be detected between the 2 groups, including RDS, BPD, IVH, sepsis and admission and duration of newborn intensive care unit hospitalisation. These authors concluded that the results from their study did not support the routine use of adjunctive antimicrobial therapy in women with preterm labour and intact membranes.[227]

The most recent randomised study looking at adjunctive antimicrobial therapy was published in 1995.[229] These authors randomised 117 patients to either ceftizoxime or placebo. Women with preterm labour between 24 and 35 weeks of gestation who met the study criteria for tocolytic treatment were evaluated for randomisation. They used a separate randomisation schedule for twin gestations to assure equal distribution of twins between the 2 groups. All patients received intravenous magnesium sulfate for tocolytic therapy. All patients received an intravenous solution of either study medication or placebo every 8 hours initially for 5 days of therapy, but this was subsequently changed to 3 days of therapy because of patient refusal of prolonged intravenous antimicrobial therapy. The primary end-point was days gained *in utero*. There was no difference in the interval to delivery (34.5 ± 21.1 days in the ceftizoxime group versus 34.6 ± 24.5 days in the placebo group, $p = 0.99$) and no difference in the rate of delivery before 37 weeks gestation (60% in the ceftizoxime group versus 58% in the placebo group, $p = 0.91$). Furthermore, subanalysis of twin gestations who received >9 doses of therapy and were Group B streptococci negative or were <32 weeks gestation showed no difference in time gained *in utero* or delivery at <37 weeks gestation between the 2 groups. These authors concluded that ceftizoxime had no effect on interval to delivery or duration of pregnancy in women treated for preterm labour. Furthermore, the sample size of this study was sufficient to detect a 9-day difference in prolongation of pregnancy ($\alpha = 0.05$, $\beta = 0.2$).

A meta-analysis published in 1995[230] looked at the efficacy of adjunctive antimicrobial treatment in patients with preterm labour. These authors searched 18 medical databases, including MEDLINE from 1964 and EMBASE from 1974, to identify all literature included under preterm or premature labour and antimicrobials. In addition they scanned all abstracts from computer printouts, retrieved full text reports, the references from each retrieved report and review articles to identify studies meeting their inclusion criteria. There were 7 studies that met their inclusion criteria.[223-229] They extracted quantitative outcome data and calculated both the OR and the 95% CI for each. The 7 trials included a total of 795 patients. Adjunctive antimicrobial therapy appeared to reduce the risk of neonatal pneumonia and NEC and to increase the risk of neonatal mortality, but it had no effect on neonatal sepsis, RDS and IVH. None of the effects observed reached a significance level of $p < 0.05$ and all CI values overlapped 1. The authors concluded that the results from the meta-analysis did not support the routine use of adjunctive antimicrobial treatment in patients with preterm labour.[230]

6.3 Adverse Effects

The adverse effects of antimicrobials are numerous and depend on which study and which particular agent was used. The most common adverse effects were maternal and related to the gastrointestinal tract: nausea, vomiting and diarrhoea. However, most studies did not adequately address maternal adverse effects. Other potential adverse effects include rash, urticaria, hepatic dysfunction and potentially life-threatening reactions such as pseudomembranous colitis and anaphylactic reactions. One study demonstrated larger infants in the placebo-treated group compared with the antimicrobial-treated group.[226] There was also an increased risk of neonatal mortality in the meta-analysis (OR 3.25, 95% CI 0.93 to 11.38) in neonates treated with antimicrobials compared with placebo.[230] In addition, a theoretical neonatal adverse effect is isolation and overgrowth of resistant bacteria secondary to treatment of mothers with antimicrobials. However, none of the randomised studies adequately address this issue.

7. Outpatient Maintenance Tocolytic Therapy

Outpatient tocolytic therapy is commonly used; however, the benefit of this treatment has not been established. These agents have not been shown to decrease preterm birth. The success of inpatient parenteral tocolytic therapy is very limited; however, it is associated with much higher serum concentrations of the administered agents than is oral therapy.[231] Therefore one would expect that outpatient treatment would be less effective.

β-Agonists are the agents most commonly used for maintenance therapy. In 1995, a meta-analysis was published of the efficacy of oral β-agonist maintenance therapy for preterm labour.[232] There were 6 studies evaluated of which 4 met inclusion criteria. These authors concluded there are no data to support the use of β-agonist maintenance therapy after resolution of an acute episode of preterm labour in reducing the incidence of preterm delivery, increasing the time interval to delivery or reducing the incidence of recurrent preterm labour. Furthermore, long term β-agonist therapy has been associated with significant adverse effects.[41,42,52,59,61,233]

Subsequently, there have been 4 published randomised placebo-controlled studies evaluating β-agonists for maintenance therapy.[234-237] The first study[237] randomised 184 patients between 24 and 35 weeks of gestation to continued bed rest with or without oral terbutaline. Patients were stratified into 4 groups based on cervical Bishop score. Patients were treated until 37 weeks of gestation. There was no difference in the number of readmissions, unscheduled hospital visits, neonatal outcome or deliveries at <37 weeks between the groups. The authors concluded that oral terbutaline does not improve pregnancy outcome.

A second study[235] randomised 203 women between 24 and 35 weeks gestation to either oral terbutaline or placebo after successful intravenous tocolysis. Patients were treated until 37 weeks of gestation. There was no difference between the 2 groups in time gained *in utero*, mean gestational age at delivery, delivery within 1 week or the incidence of recurrent preterm labour. However, post hoc evaluation of women <32 weeks gestation showed that terbutaline was associated with pregnancy prolongation ($p = 0.01$). The authors concluded that oral terbutaline maintenance therapy was not associated with a reduction in the incidence of preterm labour or with prolongation of pregnancy.

Rust et al.[236] randomised 248 patients between 24 and 34 weeks gestation to either placebo, oral terbutaline or magnesium chloride after successful acute tocolytic therapy. Maintenance oral tocolytic therapy did not decrease uterine activity, reduce the rate of recurrent preterm labour or preterm birth or improve perinatal outcome.

The final study[234] randomised 95 women at <35 weeks gestation who had arrest of preterm labour with intravenous ritodrine to either placebo or sustained released ritodrine capsules. Patients received oral therapy for 1 week. These authors demonstrated a reduction in recurrent preterm labour with ritodrine ($p = 0.003$). However, there was no

difference in prolongation of pregnancy, incidence of preterm birth or perinatal outcome between the 2 groups.

Magnesium oxide has been compared with oral terbutaline for maintenance therapy. These authors found both drugs to be equally effective, with magnesium causing fewer adverse effects. However, their definition of preterm labour was not precise. This is further substantiated by the low incidence of delivery at <36 weeks gestation (approximately 18% in each group).[238]

The prostaglandin inhibitor sulindac has been evaluated in a randomised, double-blind, placebo-controlled trial. These investigators found no significant difference in time gained *in utero*, preterm birth, recurrent preterm labour, birth weight or time spent in the neonatal intensive care unit between the 2 groups.[180]

A meta-analysis of all oral maintenance therapy studies has been published recently.[239] Out of 14 studies, 10 met inclusion criteria. There were 1409 patients included (765 receiving maintenance therapy and 644 controls). Compared with placebo or no treatment, the pooled OR for preventing preterm delivery was 0.99 (95% CI 0.80 to 1.23) and the OR for preventing recurrent preterm labour was 0.80 (95% CI 0.63 to 1.02). Furthermore, maintenance tocolytic therapy did not decrease the rate of RDS or perinatal death, or increase birth weight or time gained *in utero*.

8. Conclusions

The rate of preterm birth has not declined over the past 40 years despite the use of multiple pharmacological agents for the treatment of preterm labour. It is estimated that in the US approximately 116 000 women are treated each year with ritodrine for preterm labour.[240] Kubli[43] had previously reported that in the (then) West Germany over 1 million ampoules and 6 million tablets of fenoterol are used each year to treat patients in preterm labour. However, there had been no reduction in preterm deliveries or low birth weight infants in that country. Furthermore, fenoterol has never been tested in a randomised controlled study for this indication.

Most patients presenting with preterm labour are not candidates for tocolytic therapy, even if an ideal inhibitor were available. Furthermore, tocolytic treatment of patients deemed to be eligible for tocolytic therapy had minimal impact on the number of low birth weight infants.[241] Less than 20% of neonatal mortality associated with preterm birth occurs in patients who are candidates for tocolysis, and virtually all of the mortality occurs in neonates <32 weeks gestation.[242] Moreover, no published study to date has demonstrated any neonatal benefit from treatment beyond 32 weeks of gestation.

It is extremely difficult to determine the efficacy of the various pharmacological agents used to treat preterm labour, since the definition of success varies from study to study. Many drugs have been used, but seldom in randomised controlled clinical trials. A sample size much greater than any study reported in the literature would be required to demonstrate a significant reduction in preterm birth or perinatal mortality.

Prostaglandin inhibitors appear to be effective in the treatment of preterm labour; the risks appear minimal if treatment is short in duration and the drug given before 32 weeks of gestation. Newer agents such as sulindac appear very promising because of a lower adverse effect profile, and need to be tested in larger controlled trials. Calcium antagonists and oxytocin antagonists appear to inhibit uterine contractions, but the number of clinical studies is insufficient to recommend routine use of these drugs. The reported adverse effects appear to be lower with these agents. Magnesium sulfate is ineffective in preventing preterm delivery; the potential for adverse effects is substantial and this agent should no longer be used to treat preterm labour. Moreover, infant mortality may be increased in fetuses exposed to magnesium sulfate *in utero*.

There has been no proven benefit to mother or neonate from the use of antimicrobials as adjunctive therapy for the treatment of preterm labour. Oral maintenance therapy has not been shown to decrease preterm birth, recurrent preterm labour or neonatal morbidity. Furthermore, long term use of

some agents is associated with significant maternal and neonatal morbidity. β-Agonists can prolong gestation for 24 to 48 hours. However, they have not been shown to decrease perinatal morbidity or morality. Furthermore, mother and fetus are placed at substantial risk because of the high incidence of serious, often life-threatening, adverse effects.

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