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Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour

The Worldwide Atosiban versus Beta-agonists Study Group
Participants are listed in Appendix A*

Objective To compare the effectiveness and safety of the oxytocin antagonist atosiban with conventional beta-adrenergic agonist (beta-agonist) therapy in the treatment of preterm labour.

Design Three multinational, multicentre, double-blind, randomised, controlled trials.

Setting Hospitals in Australia, Canada, Czech Republic, Denmark, France, Israel, Sweden, and the UK.

Population Women diagnosed with preterm labour at 23–33 completed weeks of gestation.

Methods Seven hundred and forty-two women were randomised; 733 received atosiban ($n = 363$; intravenous (iv) bolus dose of 6.75 mg, then 300 μg/minute iv. for 3h and 100 μg/min iv thereafter) or beta-agonist ($n = 379$; ritodrine, salbutamol or terbutaline iv; dose titrated) for at least 18h and up to 48 hours. Uterine contraction rate, cervical dilatation and effacement were used to assess progression of labour. An all patients treated analysis, using the Cochran-Mantel-Haenszel test, was performed.

Main outcome measures Tocolytic effectiveness was assessed in terms of the number of women undelivered after 48 hours and seven days. Safety was assessed in terms of maternal side effects and neonatal morbidity.

Results There were no significant differences between atosiban and β-agonists in delaying delivery for 48h (88.1% *vs* 88.9%; $P = 0.99$) or seven days (79.7% *versus* 77.6%; $P = 0.28$). Tocolytic effectiveness was also similar in terms of mean [SD] gestational age at delivery (35.8 [3.9] weeks *vs* 35.5 [4.1] weeks) and mean [SD] birthweight (2491 [813] g *versus* 2461 [831] g). Maternal side effects, particularly cardiovascular adverse events (8.3% *vs* 81.2%, $P < 0.001$), were reported more frequently in women given β-agonists, resulting in more treatment discontinuations due to side effects (1.1% *vs* 15.4%, $P = 0.0001$). No statistical differences in neonatal/infant outcomes were observed with either study medication.

Conclusions In the largest study of tocolytic therapy to date, atosiban was comparable in clinical effectiveness to conventional beta-agonist therapy, but was associated with fewer maternal cardiovascular side effects. We conclude that atosiban has clinical advantages over current tocolytic therapy.

INTRODUCTION

Preterm birth of less than 37 completed weeks of gestation[1] occurs in 5% to 10% of all pregnancies, leading to an estimated 13 million preterm births worldwide[2]. Preterm birth is associated with an unfavourable neonatal outcome, accounting for more than two-thirds of all singleton neonatal deaths excluding congenital malformations[3,4]. In addition, the incidence of severe neonatal morbidity (e.g. respiratory distress syndrome, intraventricular haemorrhage) increases with decreasing gestational age at delivery[5], and 10% of infants born at < 28 weeks of gestation will be severely handicapped and require life-long care[6]. Delaying delivery enables the implementation of beneficial clinical strategies, such as the administration of antepartum corticosteroids[7] or *in utero* transfer to a specialised care facility[8]. At very preterm gestations, prolonging pregnancy by even a few days may improve neonatal survival, which before 26 gestational weeks increases by 3% per day[9].

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Strategies to prevent preterm birth in women in early preterm labour include the inhibition of uterine contractility through tocolysis[10]. Many different tocolytic agents have been used over the years and current clinical practice includes the administration of beta-adrenergic agonists, magnesium sulphate, prostaglandin synthetase inhibitors and calcium channel blockers, sometimes in combination[10]. Beta-agonists have been used extensively for the prevention of preterm birth and have been shown to be effective in prolonging pregnancy for at least 48 hours[11–12]. Due to their inherent lack of specificity, beta-agonists are associated with significant maternal and fetal adverse events[13]. Clinically relevant side effects, such as maternal tachycardia, and palpitation, and fetal tachycardia have caused treatment discontinuations in 14% of women[12]. Rare and life threatening maternal cardiovascular events such as myocardial ischaemia[14] and pulmonary oedema[15] are also well documented[13]. Consequently, there is a medical need to develop more uterine-specific tocolytic agents to overcome these potentially harmful systemic side effects[10].

It is well known that oxytocin is not only a potent initiator of uterine contractility at term[16] but also appears to have an

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important role in the onset of preterm labour[17–18]. Furthermore, the increase in oxytocin receptor density in the myometrium during late pregnancy correlates well with increased uterine activity[19]. Atosiban, an oxytocin antagonist, has been shown to inhibit preterm uterine contractions effectively in placebo-controlled clinical trials[20–21] without causing any significant cardiovascular, pulmonary or central nervous system side effects[20].

We report an analysis of the pooled data from three randomised clinical trials with the same study design that compared the tocolytic effectiveness and safety of atosiban with beta-agonists (ritodrine, salbutamol and terbutaline) in the treatment of preterm labour.

METHODS

This pooled analysis used the combined data from three randomised, double-blind, double-dummy, controlled trials conducted at 75 centres across eight countries comparing atosiban with the beta-agonist agent currently used in the participating country. The study protocols were approved by the ethics committees of the participating centres and conducted in accordance with the principles outlined in the Declaration of Helsinki[22] and Good Clinical Practice. Signed, informed consent was obtained from all participants at enrolment.

The inclusion criteria were: regular preterm uterine contractions ($\geq$30 seconds duration at a rate of $\geq$ 4/30 min, confirmed by at least 1h external tocography), cervical dilatation of 0–3 cm (for nulliparae) or 1–3 cm (for multiparae), cervical effacement of $\geq$ 50%, $\geq$ 18 years of age or of legal consenting age, gestational age between 23–33 weeks (confirmed by ultrasound before 20 weeks and/or reliable menstrual dates). Exclusion criteria were high-order multiple pregnancy greater than twins, ruptured membranes, major vaginal bleeding, severe pre-eclampsia or hypertension, fever (body temperature $>$ 37.5°C), urinary tract infection, fetal/placental abnormalities (e.g. major congenital anomalies, placental abruption, intrauterine growth retardation), serious maternal disease, any contraindication to the use of β-agonists, alcohol or drug abuse, history of hypersensitivity to any component of the study drugs, previous exposure to any tocolytic therapy within six hours (or within 12 hours for indomethacin) of study entry, and participation in a clinical trial of an experimental drug within the previous month.

Two randomisation lists, prepared by SciAn Clinical, Toronto, Canada, were produced per country and stratification was carried out by gestational age $\leq$ 28 weeks and $>$ 28 weeks. Random block sizes of variable size were used. To blind the study treatment from the investigator/participant, a double-dummy technique was used, whereby the study medications had identical shape, size and colour. They were supplied in pre-randomised boxes labelled with the country code and case number by Ferring Pharmaceuticals, Malmö, Sweden. After randomisation to treatment group, women were administered atosiban or beta-agonist (ritodrine in Canada and Israel, terbutaline in the Czech Republic, Denmark, Sweden and the UK, or salbutamol in Australia and France) as follows. Atosiban (Ferring Pharmaceuticals, Malmö, Sweden) was given as a single iv bolus dose (6.75 mg in 0.9 mL normal saline), followed by an iv infusion of 300 μg/min atosiban in 5% dextrose for the first 3h and then 100 μg/min atosiban in 5% dextrose for at least 18h and up to 48h. Separately but simultaneously, a placebo iv infusion of 5% dextrose corresponding to beta-agonist was administered by dose titration at a rate of 100–350 μg/min for ritodrine (Yutopar, Bristol-Myers Squibb, Montreal, Canada), 5–20 μg/min for terbutaline (Bricanyl; Astra Draco, Lund, Sweden) and 2.5–45 μg/min for salbutamol (Salbuvent, Nycomed Pharma AS, Denmark [France]; salbutamol, Allen and Hanbury, Australia). For the beta-agonist group, a placebo (normal saline) was administered as a single bolus injection (0.9 mL) followed by an iv infusion at a rate corresponding to the atosiban infusion (see above). Separately but simultaneously, beta-agonist in 5% dextrose was given as an iv infusion by dose titration (see above).

The main outcomes of interest in the all patients treated analysis population were the effectiveness and safety of atosiban *vs* beta-agonist in conventional tocolytic therapy. Tocolytic effectiveness was assessed in terms of the total number of women undelivered after 48 hours and seven days of starting treatment. Safety was assessed by maternal side effects, with particular emphasis on cardiovascular adverse events (i.e. pulmonary oedema, chest pain, myocardial ischaemia, dyspnoea, palpitation, tachycardia, hypotension and syncope), and neonatal morbidity. Tocolytic efficacy and tolerability was assessed in terms of the proportion of women who did not deliver and who did not require alternative tocolysis within seven days of initiation of therapy, in addition to an assessment of the progression of labour (see below). For ethical reasons, a composite endpoint was used as a measure of efficacy (herein described as 'tocolytic efficacy and tolerability'), since many of the investigators were opposed to a protocol that did not allow administration of alternative tocolysis in the event of the progression of labour (treatment failure, see below). However, treatment failure also included women who discontinued treatment due to adverse events and, consequently, the efficacy endpoint used in this study was a composite of both efficacy and tolerability.

Secondary outcome measures were mean infant birthweight and mean gestational age at delivery.

Alternative tocolysis could be given as rescue therapy if treatment with the study drug failed, due to either progression of labour or side effects of the study drug, as judged by the investigator. The choice of alternative

tocolytic treatment was decided by the investigator and reflected local practice preferences. Combinations of alternative tocolytic agents could be given, but atosiban was not administered as 'rescue therapy' in the beta-agonist treatment arm (i.e. this was not a crossover study). Progression of preterm labour was assumed when any two of the following three criteria were met: a contraction rate $\geq$ 4/h, an increase in cervical dilation of $\geq$ 1 cm from the initial measurement, and an increase in cervical effacement $\geq$ 25% from the initial measurement. The administration of an alternative tocolytic agent was dependent on both efficacy and tolerability of study medication. An assessment of study treatments was optional at six or 12 hours after initiation of therapy if the investigator was concerned that labour was progressing despite study drug administration. If labour progressed, then study treatment was stopped and an alternative tocolytic agent was administered at the discretion of the investigator. At the end of the infusion period, labour progression was always assessed by a cervical examination and by recording uterine activity by external monitoring.

Uterine contraction frequency was monitored continuously for the first two hours after treatment initiation using an external tocodynamometer, and then for varying periods (usually one hour) at different intervals (24 or 48 hours), depending on country. Women who had a recurrence of preterm labour at any time after the cessation of study treatment could be re-treated with the same intravenous medication administered previously, provided that no alternative tocolytic therapy was given, gestational age was $<$ 34 weeks, and all other protocol eligibility criteria were still met.

Maternal, fetal and infant adverse events were reported until either discharge from hospital or neonatal death. Maternal and fetal tachycardia were defined as a heart rate of $>$ 120 and $>$ 170 beats per minute, respectively. The primary and secondary outcomes of this analysis were chosen based on the observations of The Canadian Preterm Labour Investigators Group[12].

Data from all sites were entered onto a central database. Statistical analysis using SAS software (Version 6.12) was performed by the Biometrics Department, Ferring Pharmaceuticals. For analysis of the main outcomes of interest, an all patients treated population was defined and included all women who received any study medication (Fig. 1). The Cochran-Mantel-Haenszel test was used to control for the centre effect[23] in the analyses. Other secondary outcomes were analysed using the Wilcoxon Rank Sum test (normal approximation), χ^2 test, odds ratio with 95% confidence intervals and Kaplan-Meier survival analysis, where appropriate (i.e. according to the studied endpoint). Safety outcomes were analysed by descriptive statistics. Sample size was determined as follows: 240 women in each of the three component trials was sufficient to show an 18% increase from 38% in tocolytic efficacy, which was the reported proportion of women undelivered at seven days in The Canadian Preterm Labour Investigators Group study[12]. A level of significance of 5% ($\alpha = 0.05$) and a power of 80% ($\beta = 0.2$) was used.

RESULTS

A total of 742 women diagnosed with preterm labour between 23 and 33 completed weeks of gestation were enrolled during the study period (February 1994 to February 1997 inclusive) and randomised to receive either atosiban ($n = 363$) or beta-agonist ($n = 379$) (Fig. 1). Nine (1.2%) who did not receive study medications were excluded. Table 1 shows the reasons for discontinuation before study drug administration and the outcome. Consequently, 733 (98.8%) women were included in the study (Fig. 1).

Baseline characteristics (Table 2) of the atosiban and beta-agonist groups were comparable in terms of mean gestational age (30.1 weeks and 30.0 weeks, respectively), median number of contractions per 30 minutes (8 and 7, respectively) and median cervical dilation (1 cm and 1 cm, respectively). The groups were similarly balanced with regard to gestational age subgroups ($\leq$ 28 weeks and $>$ 28 weeks), mean maternal age, parity and ethnic origin (Table 2). However, more twin pregnancies were allocated to the beta-agonist group.

The proportion of women undelivered at seven days, used as a measure of tocolytic effectiveness, was 79.7% ($n = 287$) in the atosiban group and 77.6% ($n = 288$) in the beta-agonist group ($P = 0.28$). The equivalent unde-

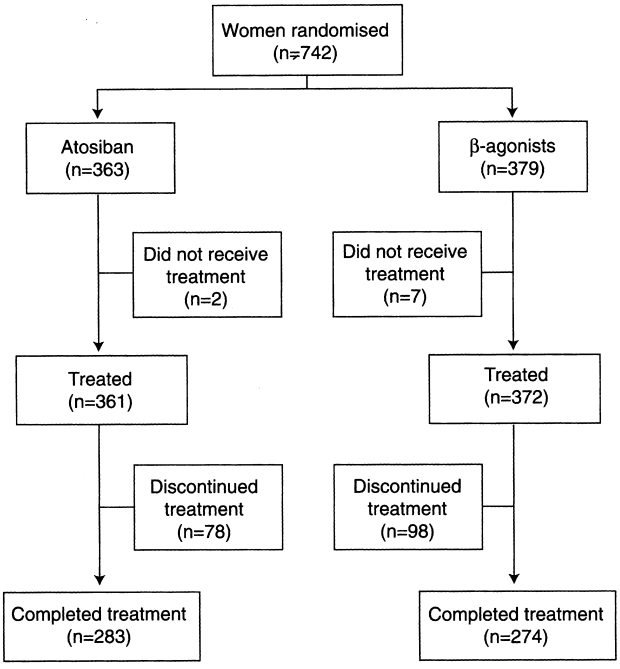

Fig. 1. Trial profile. Distribution of subjects.

Table 1. Outcome of the nine women who did not receive the study drug allocated. CS = caesarean section.

Study drug allocated	Reason for discontinuation before study drug administration	Outcome
Terbutaline	Rapid progress of labour	Breech presentation; delivered by CS on same day
Terbutaline	Rapid progress of labour	Breech presentation; delivered by CS on same day
Terbutaline	Rapid progress of labour	Delivery same day
Terbutaline	Rapid progress of labour	Delivery same day
Terbutaline	Contractions stopped	Delivery 45 days later
Ritodrine	Rapid progress of labour	Delivery same day
Ritodrine	Ineligibility according to protocol exclusion criteria[a]	Delivery same day
Atosiban	Woman withdrew consent	Delivery 10 days later
Atosiban	Ineligibility according to protocol exclusion criteria[b]	Delivery 39 days later

[a] Gestational diabetes. Since the woman was transferred from another hospital, this was noticed after randomisation, but before study drug administration.
[b] Age <18 years. This protocol violation was noticed after randomisation, but before study drug administration. Woman received magnesium sulphate instead.

livered rate at 48 hours was 88.1% ($n = 317$) and 88.9% ($n = 330$), respectively ($P = 0.99$). The proportion of singleton and multiple pregnancies undelivered at 48 hour and 7 days is shown in Table 3. The Kaplan-Meier curve for the relationship between delivery rate and the time to delivery for atosiban and beta-agonists is shown in Fig. 2.

Overall, the most frequently reported maternal adverse event following beta-agonist administration was tachycardia (Table 4). Notably, the incidence of tachycardia in women receiving beta-agonist was similar across all three trials. Of clinical importance, one case of myocardial ischaemia and two cases of pulmonary oedema occurred in the β-agonist group. A third case of pulmonary oedema was reported after one woman received rescue therapy with a beta-agonist for seven days following atosiban administration. The incidence of at least one maternal cardiovascular side effect was 8.3% ($n = 30$) in the atosiban group and 81.2% ($n = 302$) in the beta-agonist group ($P < 0.001$). Maternal cardiovascular side effects included all reported cases of pulmonary oedema, chest pain, myocardial ischaemia, dyspnoea, palpitation, tachycardia, hypotension and syncope. An apparent increased incidence was observed in the beta-agonist group for vomiting, headache, anxiety, tremor, hyperglycaemia and hypokalaemia (Table 4). Four women (1.1%) in the atosiban group and 56 women (15.1%) in the beta-agonist group discontinued treatment due to maternal adverse events ($P = 0.0001$). The proportion of women who discontinued treatment due to maternal adverse events only will not be the same as the proportion of women who discontinued treatment *per se* (Fig. 1), since the latter includes all women who terminated drug therapy i.e. due to maternal/fetal adverse events, progression of labour, delivery etc. Mean [SD] heart rate (beats per minute) in women when study drug treatment was discontinued was 86.2 [13.9] ($n = 61$) in the atosiban group and 124.7 [19.6] ($n = 80$) in the beta-agonist group ($P = 0.0001$).

A measure of tocolytic efficacy and tolerability, defined as the proportion of women remaining undelivered and not requiring alternative tocolytic therapy after seven days of starting study treatment, was higher in the atosiban group (59.7% [$n = 215$]) compared with the beta-agonist group (47.4% [$n = 176$]; $P = 0.0003$) (Table 3), although the use of alternative tocolytic agents was lower in the atosiban group (37.1% [$n = 134$]) than in the beta-agonist group (46.5% [$n = 173$]; $P = 0.01$). The odds ratios (95% CI) for this comparison between atosiban and β-agonists were: ritodrine, 1.85 (1.06–3.21); terbutaline, 1.62 (0.94–2.77); salbutamol, 1.89 (1.10–3.24); pooled, 1.78 (1.30–2.43) (Fig. 3). Homogeneity tests for the differences between trials did not show significant differences: undelivered at 48 hour, $P = 0.82$; undelivered at 7 days, $P = 0.31$. In addition, the homogeneity of centre effects test also showed no significant difference between centres ($\chi^2 = 36.29$, df = 42, $P = 0.72$). A similar tocolytic efficacy and tolerability endpoint, defined as the proportion of women not deliver-

Table 2. Baseline characteristics of the participants who received study medication. Values are given as *n* (%), mean [SD] or median {range}.

	Atosiban ($n = 361$)	Beta-agonists ($n = 372$)
Maternal age (years)	26.8 [5.5]	27.0 [5.5]
Gestational age groups		
≤ 28 weeks	69 (19.1)	75 (20.2)
> 28 weeks	292 (80.9)	297 (79.8)
Ethnic group		
White	320 (88.6)	333 (89.5)
Black	16 (4.4)	12 (3.2)
Oriental	9 (2.5)	10 (2.7)
Other	16 (4.4)	17 (4.6)
Primigravidae	190 (52.6)	196 (52.7)
Pregnancy status		
Singletons	317 (87.8)	312 (83.9)
Twins	44 (12.2)	60 (16.1)
Gestational age (weeks)	30.1 [2.3]	30.0 [2.5]
Contraction frequency (*n*/30 min)	8 {4–48}	7 {4–22}
Cervical dilation (cm)	1 {0–3}	1 {0–3}

Table 3. Tocolytic effectiveness, and tocolytic efficacy and tolerability of atosiban and β-agonists at 48 hours and 7 days for singleton and multiple pregnancies. Values are given as *n* (%) of women.

	Atosiban	β-agonists	OR	(95% CI)	*P*
Singletons	***n* = 317**	***n* = 312**			
Tocolytic effectiveness					
Undelivered at 48 hours	284 (89.9)	274 (88.1)	1.30	0.77–2.20	0.33
Undelivered at 7 days	260 (82.3)	242 (77.8)	1.49	0.94–2.35	0.09
Tocolytic efficacy & tolerability[a]					
No failure at 48 hours	242 (76.6)	218 (70.1)	1.52	1.04–2.21	0.03
No failure at 7 days	193 (61.1)	151 (48.6)	1.88	1.33–2.66	0.004
Multiples	***n* = 44**	***n* = 60**			
Tocolytic effectiveness					
Undelivered at 48 hours	33 (75.0)	56 (93.3)	0.21	[b]	0.003
Undelivered at 7 days	27 (61.4)	46 (76.7)	0.24	0.05–1.13	0.07
Tocolytic efficacy & tolerability[a]					
No failure at 48 hours	26 (59.1)	42 (70.0)	0.05	0.14–1.78	0.28
No failure at 7 days	22 (50.0)	25 (41.7)	1.32	0.39–4.40	0.66

[a] Treatment failure = delivery within the time interval or need for alternative tocolysis.
[b] 95% CI not estimable.

ing and not requiring alternative tocolytic therapy after 48 hours of starting study treatment, was 74.4% ($n = 268$) in the atosiban group and 70.1% ($n = 260$) in the beta-agonist group ($P = 0.08$) (Table 3). The interaction between gestational age at randomisation and treatment was evaluated but no overall interaction was found ($P = 0.41$).

Significantly fewer women received alternative tocolytic treatment following atosiban administration compared with women given beta-agonists (Table 5). The number of women in each arm of the study who received alternative tocolytic treatment and the type of alternative tocolytic agent used are shown in Table 6.

The proportion of women who did not receive re-treatment with study medication during the duration of the trials was 79.8% ($n = 288$) and 77.7% ($n = 289$) in the atosiban and beta-agonist groups, respectively. The proportion of women requiring more than one re-treatment was 2.3% ($n = 8$) in the atosiban group and 3.8% ($n = 14$) in the beta-agonist group. Neither of these differences were statistically significant.

Mean [SD] gestational age at delivery was comparable in the two treatment groups, with values of 35.8 [3.9] weeks and 35.5 [4.1] weeks for the atosiban and β-agonist groups, respectively. The caesarean section rate was 14.1% ($n = 51$) in the atosiban group and 19.4% ($n = 72$) in the beta-agonist group. Mean [SD] birthweight was 2491 [813] g in the atosiban group and 2461 [831] g in the beta-agonist group ($P = 0.58$). Major congenital anomalies were reported in seven (1.7%) infants in the atosiban group and there were four cases (0.9%) identified in the beta-agonist group. none of these differences between treatment groups were statistically significant.

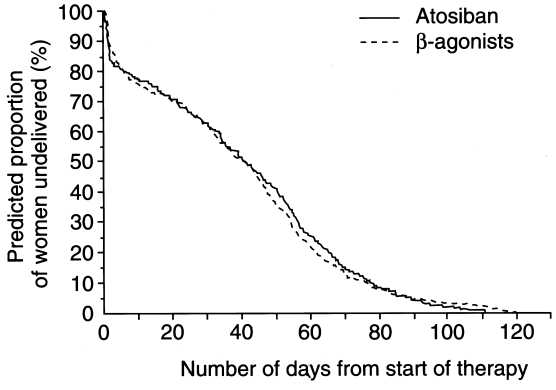

Fig. 2. Delivery rate and time to delivery for women administered atosiban or β-agonists.

Table 4. Frequency (%) of maternal side effects among treated enrolled women (APT population) according to treatment allocation.

	Atosiban ($n = 361$)	Beta-agonists ($n = 372$)
Pulmonary oedema	1 (0.3)[a]	2 (0.5)
Myocardial ischaemia	0	1 (0.3)
Chest pain	4 (1.1)	18 (4.8)
Palpitation	8 (2.2)	58 (15.6)
Tachycardia	20 (5.5)	281 (75.5)
Hypotension	12 (3.3)	21 (5.7)
Dyspnoea	1 (0.3)	27 (7.3)
Syncope	2 (0.6)	2 (0.5)
Nausea	43 (11.9)	59 (15.9)
Vomiting	25 (6.9)	81 (21.8)
Headache	35 (9.7)	69 (18.6)
Anxiety	4 (1.1)	11 (3.0)
Tremor	5 (1.4)	59 (15.9)
Hyperglycaemia	23 (6.4)	46 (12.4)
Hypokalaemia	3 (0.8)	24 (6.5)

[a] After 7 days rescue therapy with β-agonist.

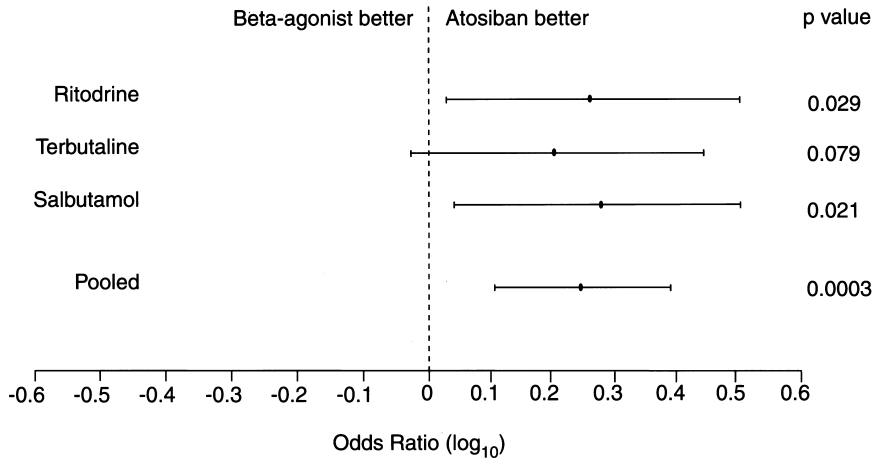

Fig. 3. Centre-stratified $\log_{10}$ odds ratios (with 95% CI) for the proportion of women undelivered and not requiring alternative tocolysis after 7 days of starting treatment in the three β-agonist trials and the pooled analysis

Fetal tachycardia was reported in 27.7% ($n = 103$) of women administered β-agonist and 3.3% ($n = 12$) receiving atosiban. Fetal bradycardia and fetal distress (i.e. meconium, repetitive, late or profound variable fetal heart rate deceleration) were reported in 3.8% ($n = 14$) and 3.8% ($n = 14$) of pregnancies, respectively, in the beta-agonist group and 6.4% ($n = 23$) and 3.6% ($n = 13$), respectively, in the atosiban group. Again, none of these differences between treatment groups were statistically significant.

The treatment groups were generally comparable with regard to neonatal morbidities such as respiratory distress syndrome, bradycardia, arrhythmia, patent ductus arteriosus, hypotension, sepsis and cerebral haemorrhage (Table 7). Admission to a neonatal intensive care unit was similar for both treatment groups (31.4% [127/405] of live births in the atosiban group and 29.8% [128/430] in the beta-agonist group), as was length of stay in a neonatal intensive care unit and ventilation therapy.

There were 18 fetal/infant deaths during the study period. Six deaths were reported in the atosiban group (four singletons and two twins) and 12 deaths in the beta-agonist group (five singletons and seven twins). Consequently, the perinatal mortality rate was 14.7 per 1000 in the atosiban group and 27.7 per 1000 in the beta-agonist group. The indicated causes of death were complications associated with prematurity, such as infection/sepsis, respiratory distress syndrome, necrotising enterocolitis and intraventricular haemorrhage. Of these deaths, three were intrauterine deaths, two in the beta-agonist group and one in the atosiban group. One unexplained stillbirth in the atosiban group occurred 11 weeks after treatment with atosiban. Two stillbirths occurred in the β-agonist group two days after initiating therapy, and had no obvious relationship to the administration of study drug. None of these deaths were regarded by the investigator to be related to the study medications.

Table 5. Proportion of women (%) who received alternative tocolytic treatment following atosiban or β-agonist administration.

	Atosiban ($n = 361$)	β-agonist ($n = 372$)	P
Use of alternative tocolytic treatment	134 (37.1)	173 (46.5)	0.01

DISCUSSION

We report the results of the largest clinical study programme of tocolytic agents carried out to date. This pooled analysis compared the clinical effectiveness and safety of atosiban, the first oxytocin antagonist tested in a

Table 6. Frequency and types of alternative tocolytic agents used following atosiban or β-agonist administration. NSAID = non-steroidal anti-inflammatory drugs.

Type of alternative tocolytic agent used[a]	Atosiban ($n = 361$)	β-agonist ($n = 372$)
β-agonist[b]	133	146
NSAID[c]	27	36
Progesterone	23	29
Magnesium sulphate	20	21
Phloroglucinol[d]	24	27
Calcium antagonists[e]	21	22
Tranquilizers[f]	2	2
Total	**250**	**293**

[a] Combinations of tocolytic agents were allowed.
[b] Ritodrine, terbutaline, salbutamol, fenoterol.
[c] Indomethacin, ketoprofen, diclofenac and sulindac.
[d] Spasfon.
[e] Nifedipine, nicardipine.
[f] Diazepam, clorazepam, hydroxyzine.

Table 7. Frequency of neonatal morbidity events (%) in the APT population according to the study medication received.

	Atosiban ($n = 406$)	Beta-agonists ($n = 432$)
Respiratory distress syndrome	79 (19.5)	85 (19.7)
Apnoea	36 (8.9)	20 (4.6)
Bradycardia	23 (5.7)	17 (3.9)
Arrhythmia	2 (0.5)	0
Patent ductus arteriosus	22 (5.4)	22 (5.1)
Hypotension	10 (2.5)	17 (3.9)
Sepsis	25 (6.2)	33 (7.6)
Cerebral haemorrhage[a]	18 (4.4)	23 (5.3)
Hypoxia/asphyxia	6 (1.5)	2 (0.5)
Retinopathy of prematurity	7 (1.7)	10 (2.3)
Anaemia	31 (7.6)	36 (8.3)
Thrombocytopenia	2 (0.5)	4 (0.9)
Hypoglycaemia	26 (6.4)	26 (6.0)

[a] Includes intraventricular haemorrhage

clinical setting, with three beta-agonists (ritodrine, terbutaline and salbutamol) in the treatment of preterm labour.

Our all patients treated analysis showed that the number of women remaining undelivered at 48 hours and seven days after treatment initiation was comparable between study medications, and this was used as a measure of tocolytic effectiveness. In addition, other established clinical endpoints, such as gestational age at delivery, were also similar. The relatively high proportion of undelivered women in both treatment groups is a reflection of the strict eligibility criteria used, which precluded women with ruptured membranes. However, the principal difference between atosiban and beta-agonists was the higher incidence of maternal side effects, particularly cardiovascular adverse events, in women receiving beta-agonists, which led to more than a tenfold higher treatment discontinuation rate in these women. This was supported by results from the tocolytic efficacy and tolerability endpoint used in the clinical trials, which showed that women were less likely to be changed from atosiban because of side effects. Notably, use of alternative tocolytic agents was significantly higher in women receiving beta-agonists. However, it should be borne in mind that the tocolytic efficacy and tolerability endpoint is a surrogate measure of efficacy since it is a composite outcome of both the efficacy of treatment and tolerability of women exposed to treatment. These data indicate that atosiban is comparable to conventional beta-agonist tocolytic therapy in delaying preterm delivery but is much better tolerated by the woman.

Earlier studies of atosiban in the treatment of preterm labour have shown that the inhibition of uterine contractility by intravenous administration was associated with a delay in delivery at least comparable to that of other tocolytic agents[20,21,24]. Goodwin *et al.*[24]. compared four different dosing regimens of atosiban with the standard dosage of ritodrine. They reported that there was no difference in delivery within 48 hours or the requirement for alternative tocolysis between the optimal dosing regimen for atosiban and ritodrine, although fewer side effects were associated with atosiban. More recently, a randomised, double-blind, placebo-controlled trial reported that maternal and fetal adverse events were similar following administration of atosiban or placebo, except for subcutaneous injection site reactions which occurred more frequently in maintenance therapy with atosiban[25]. Despite a significant difference in favour of atosiban in the proportion of women remaining undelivered and not needing alternative tocolysis at seven days (62% *vs*49%, odds ratio 1.70 [95% CI 1.17–2.46]), this trial showed no difference in the delay of delivery between atosiban and placebo. However, the trial was compromised by including women with gestational ages below 24 completed weeks and in advanced stages of preterm labour. In addition, alternative tocolytic agents were allowed to be administered after only one hour of starting study therapy and were used *ad hoc* before failure criteria were met (due to ethical reasons). All these factors may have potentially reduced the difference in outcomes between the placebo and atosiban treatments.

Although there have been a number of placebo-controlled clinical trials conducted to compare beta-agonists with placebo[13], most of these studies have investigated the use of beta-agonists in maintenance therapy. However, there is a paucity of similar trials for atosiban. This is not surprising considering the ethical implications associated with conducting a placebo-controlled arm of a trial. In order to perform such a trial in preterm labour, hospital ethics committees must be totally satisfied that the pregnant woman will be treated to accepted international ethical standards and not be denied alternative, effective treatment in harmful or potentially life-threatening situations. In many cases, this is very difficult to satisfy when both mother and baby are threatened. Therefore, we cannot currently quantify the effect of atosiban against placebo. In the future, it may be clinically relevant for placebo-controlled trials of all tocolytic agents to be allowed by research and ethics committees.

The success or failure of tocolytic therapy has become associated with a 48-hours threshold period since King *et al.*[11] published a meta-analysis of the randomised controlled trials using beta-agonists, which showed that these agents can significantly prolong pregnancy for up to 48 hours. This was subsequently confirmed by The Canadian Preterm Labour Investigators Group[12]. The time gained by the administration of tocolytic therapy until delivery can be used to transfer the woman to a tertiary neonatal care centre[9] or to administer corticosteroids in order to accelerate lung maturation[8]; corticosteroids show their beneficial effect when administered for at least 48 hours and up to seven days[26]. Therefore, when administered appropriately, tocolytic therapy may be of

clinical benefit, since prolongation of pregnancy, especially at very low gestational ages, can have a profound impact on neonatal survival[7].

The benefits of tocolytic therapy are not easy to demonstrate in clinical trials. At inclusion into a trial, most of the women have already been transported to a hospital offering highly specialised care for preterm birth and, in many cases, tocolysis has already been administered during transportation. Then there is the low rate of preterm delivery reported in randomised controlled trials, which is well documented and confirmed in this study. This presumably reflects the difficulties in diagnosing preterm labour, as well as the placebo effect. Should the labour progress, it is not possible, for ethical reasons, to withhold rescue therapy with alternative tocolytic agents. Therefore, it may be unrealistic to expect that improved infant outcome can be demonstrated in preterm labour trials complying with acceptable ethical standards. In addition, clinical trials may not have the necessary power to show significant differences between study treatments due to the large numbers of participants required. In this context, a *post hoc* power calculation showed that, given the total study sample size, the 95% confidence interval for the difference between atosiban and beta-agonists in terms of the proportion of undelivered women at seven days was –3.8% to +8.0%. In the clinical context, this analysis indicated that atosiban could have been up to 8.0% better, or up to 3.8% worse, than beta-agonist therapy for this endpoint.

Beta-agonists belong to a homogeneous class of pharmacological agents eliciting their therapeutic actions via the same type of beta-adrenergic receptors. Similarly, these receptors are also responsible for mediating the adverse events causing the poor tolerability of beta-agonist drugs in preterm labour. In our analysis, atosiban was shown to be well tolerated by women, whereas treatment-related adverse events were frequently reported after beta-agonist administration. As a result, many women discontinued beta-agonist treatment due to side effects. Beta-agonists are associated with a number of severe side effects including pulmonary oedema, cardiac arrhythmias and central nervous system disorders[13]. In our analysis, treatment with beta-agonist drugs was associated with the development of pulmonary oedema in three women, confirming the potential danger of beta-agonist use. A similar relationship could not be established for atosiban. One case of myocardial ischaemia and many cases of chest pain, palpitation, tachycardia and dyspnoea in the group treated with beta-agonists further underline the poor safety profile inherent with this class of pharmacological agent. On the contrary, atosiban was shown to have an excellent maternal safety profile, although this may have been affected unfavourably by the use of alternative tocolytic drugs (beta-agonists, indomethacin, magnesium sulphate and calcium channel blockers). In addition, trial design did not allow for cross-over of beta-agonist treatment failures to be given atosiban as an alternative therapy, even although the contrary was allowed. Fetal tolerability further supported the use of atosiban, with fetal distress and bradycardia similar to β-agonists, but with a much lower incidence of fetal tachycardia.

Neonatal and infant outcomes did not reveal any difference favouring either treatment type. Adverse events such as respiratory distress syndrome, bradycardia, arrhythmia, patent ductus arteriosus, hypotension, sepsis and cerebral haemorrhage were observed at a similar frequency in both treatment groups and are not unexpected considering the distribution of gestational age at delivery in these neonates. In addition, there was no significant difference between study drugs with regard to either the frequency of admission to or length of stay in a neonatal intensive care unit, or the requirement for ventilation therapy. The incidence of neonatal deaths was low and the causes of death were assessed as unlikely to be drug related; most cases were due to extreme prematurity.

In conclusion, we found that the clinical effectiveness of atosiban was comparable to conventional beta-agonist therapy. However, there were significantly fewer, clinically important maternal cardiovascular side effects following atosiban administration, and neonatal outcomes were similar. Therefore, atosiban would appear to represent an advance over current tocolytic therapy.

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APPENDIX A. WORLDWIDE ATOSIBAN *VERSUS* BETA-AGONISTS STUDY GROUP

Steering Group and Writing Committee

J M Moutquin, D Cabrol, *N* M Fisk, A H MacLennan, K Maršál, and J Rabinovici. The Steering Group designed the study protocol, decided on scientific and ethical issues during the conduct of the studies, interpreted the data and constituted the Writing Committee.

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References

1. World Health Organisation. *International Statistical Classification of Diseases and Related Health Problems. (10th Revision)*, Volume 2. Geneva, Switzerland: WHO, 1993.
2. Hall MH, Danielian P, Lamont RF. The importance of preterm birth. In: Elder MG, Lamont RF, Romero R, editors. *Preterm labor*, New York: Churchill Livingstone, 1997:1–28.
3. Rush RW, Keirse MJNC, Howat P, Baum JD, Anderson ABM, Turnbull AC. Contribution of preterm delivery to perinatal mortality. *BMJ* 1976;**2**:965–968.
4. Scottish Stillbirth and Neonatal Death Reports: 1989, 1990, 1991, 1992, 1993, 1994. Edinburgh: ISD Publications, Trinity Park House, 1995.
5. Robertson PA, Sniderman SH, Laros RK, Cowan R, Heilbron D, Goldenberg RL. Neonatal morbidity according to gestational age and birthweight from five tertiary care centers in the United States 1983 through 1986. *Am J Obstet Gynecol* 1992;**166**:1629–1641.
6. Tin W, Wariyar U, Hey E. Changing prognosis for babies of less than 28 weeks' gestation in the north of England between 1983 and 1994 Northern Neonatal Network. *BMJ* 1997;**314**:107–111.
7. Crowley P, Chalmers I, Keirse MJNC. The effects of corticosteroid administration prior to preterm delivery: an overview from the evidence from controlled trials. *Br J Obstet Gynaecol* 1990;**97**:11–25.
8. Lamont RF, Dunlop PD, Crowley P, Levene MI, Elder MG. Comparative mortality and morbidity of infants transferred in utero or postnatally. *J Perinat Med* 1983;**11**:200–203.
9. Finnström O, Olausson PO, Sedin G, Serenius F, Svenningsen N, Thiringer K. 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**:503–511.

10. Cole RM, Lamont RF. Current perspectives on drug treatment for preterm labour. *J Obstet Gynaecol* 1998;**18**:309–314.
11. King JF, Grant A, Keirse MJNC, Chalmers I. Beta-mimetics in preterm labour: an overview of the randomized controlled trials. *Br J Obstet Gynaecol* 1988;**95**:211–222.
12. Canadian Preterm Labor Investigators Group. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. *N Engl J Med* 1992;**327**:308–312.
13. Besinger RE, Iannucci TA. Tocolytic therapy. In: Elder MG, Lamont RF, Romero R, editors. *Preterm labor*, New York: Churchill Livingstone, 1997. pp. 243–297.
14. Hadi HA, Albazzaz SJ. Cardiac isoenzymes and electrocardiographic changes during ritodrine tocolysis. *Am J Obstet Gynecol* 1989;**161**:318–321.
15. Lamont RF. The contemporary use of β-agonists. *Br J Obstet Gynaecol* 1993;**100**:890–892.
16. Fuchs AR, Romero R, Keefe D, Parra M, Oyarzun E, Behnke E. Oxytocin secretion and human parturition: pulse frequency and duration increase during spontaneous labor in women. *Am J Obstet Gynecol* 1991;**165**:1515–1523.
17. Bossmar T, Akerlund M, Fantoni G, Szamatowicz J, Melin P, Maggi M. Receptors for myometrial responses to oxytocin and vasopressin in preterm human pregnancy: effects of the oxytocin antagonist atosiban. *Am J Obstet Gynecol* 1994;**171**:1634–1642.
18. Kinsler VA, Thornton S, Ashford MLJ, Melin P, Smith SK. The effect of the oxytocin antagonists F314 and F792 in the in vitro contractility of human myometrium. *Br J Obstet Gynaecol* 1996;**103**:373–375.
19. Fuchs AR, Fuchs F, Husslein P, Soloff MS. Oxytocin receptors in pregnant human uterus. *Am J Obstet Gynecol* 1984;**150**:734–741.
20. Goodwin TM, Paul R, Silver H, Spellacy W, Parsons M, Chez R, et al. The effect of the oxytocin antagonist atosiban on preterm uterine activity in the human. *Am J Obstet Gynecol* 1994;**170**:474–478.
21. Goodwin TM, Valenzuela G, Silver H, Hayashi R, Creasy GW, Lane R. Treatment of preterm labor with the oxytocin antagonist atosiban. *Am J Perinatol* 1996;**13**:143–146.
22. World Medical Assembly. Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *Bull Pan Am Health Organ* 1990;**24**:606–609.
23. Stokes M, Davis C, Koch H. *Categorical data analysis using the SAS system*. Cary, North Carolina: SAS Institute Inc, 1995.
24. The Atosiban Study Group, Goodwin TM, Valenzuela GJ, Silver H, Creasy G. Dose ranging study of the oxytocin antagonist atosiban in the treatment of preterm labor. *Obstet Gynecol* 1996;**88**:331–336.
25. Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela G, Veille JC, Tabor B, et al. A double-blind placebo-controlled trial of an oxytocin-receptor antagonist (Antocin) in the treatment of preterm labor. *Am J Obstet Gynecol* 2000;**182**:1173–1183.
26. Anon A. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA* 1995;**273**:413–418.

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