

# Critical appraisal and clinical utility of atosiban in the management of preterm labor

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**Abstract:** Preterm birth is the major cause of perinatal morbidity and mortality in the developed world, and spontaneous preterm labor is the commonest cause of preterm birth. Interventions to treat women in spontaneous preterm labor have not reduced the incidence of preterm births but this may be due to increased risk factors, inclusion of births at the limits of viability, and an increase in the use of elective preterm birth. The role of antibiotics remains unproven. In the largest of the randomized controlled trials, evaluating the use of antibiotics for the prevention of preterm births in women in spontaneous preterm labor, antibiotics against anaerobes and bacterial vaginosis-related organisms were not included, and no objective evidence of abnormal genital tract flora was obtained. Atosiban and nifedipine are the main tocolytic agents used to treat women in spontaneous preterm labor, but atosiban is the tocolytic agent with the fewest maternal – fetal side effects. A well conducted randomized controlled trial comparing atosiban with nifedipine for their effectiveness and safety is needed.

**Keywords:** preterm labor, preterm births, management, tocolytics, atosiban

## Introduction

Spontaneous preterm labor (SPTL) – the onset of regular, painful, synchronous uterine contractions before 37 completed weeks of gestation – is a syndrome caused by a multifactorial etiology such as infection/inflammation, uteroplacental ischemia or hemorrhage, uterine overdistention, stress, and immunologically related conditions.<sup>1</sup> SPTL is the most common cause of antenatal hospitalization,<sup>2</sup> and of all preterm births (PTBs), about 40% to 50% are related to SPTL.<sup>3,4</sup> In contrast to preterm premature rupture of the membranes and iatrogenic PTB, about 32% of all SPTL is associated with intra-amniotic infection (IAI).<sup>5</sup> This article reviews the management of SPTL and the role of tocolytics.

## Diagnosis of SPTL

The accurate diagnosis of SPTL is difficult. Fetal fibronectin (FFN), a glycoprotein found in the chorioamniotic membranes, decidua and cytotrophoblast is elevated in cervicovaginal secretions of women who deliver preterm.<sup>6</sup> A multicenter trial of 763 women considered to be in SPTL, with a mean gestational age at sampling of  $30.3 \pm 3.0$  weeks, evaluated the negative and positive predictive values of FFN for PTB. The mean gestational age at delivery was  $38.4 \pm 2.6$  weeks, and at least 80% of these women remained undelivered up to 7 days later, irrespective of their FFN status.<sup>6</sup> The negative predictive value of the FFN test far exceeds the positive predictive value. A meta-analysis of 27 studies using cervicovaginal FFN as a marker for preterm

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delivery showed a low sensitivity for PTB occurring at less than 34 weeks' gestation.<sup>7</sup> A Cochrane systematic review on the use of FFN testing for reducing the risk of PTB showed that management of women in SPTL, based on knowledge of FFN results versus no knowledge, significantly decreased the risk of PTB.<sup>8</sup> It remains uncertain which interventions are most useful when a positive FFN test is obtained, but length of hospital stay might be reduced and unnecessary tocolytic therapy and in utero transfer prevented if a negative FFN is obtained. The combination of positive FFN test, and the transvaginal ultrasound scan (TVUSS) of women with a short cervical length (<30 mm) may identify those women who may benefit from interventions such as antibiotics and tocolytics which may reduce PTB.<sup>9–11</sup>

## Infection and PTL

Chorioamnionitis is often subclinical, and requires amniocentesis to establish the diagnosis.<sup>12,13</sup> Intraamniotic inflammation, defined as negative amniotic fluid (AF) culture with elevated levels of AF interleukin (IL)-1- $\alpha$ , IL 1- $\beta$ , IL-6, IL-8, tumor necrosis factor-alpha (TNF- $\alpha$ ) and IAI (positive AF culture) are both associated with an increased risk of adverse outcomes when compared with idiopathic SPTL.<sup>14–21</sup> These include clinical chorioamnionitis, funisitis, neonatal respiratory distress syndrome (RDS), neonatal pneumonia, intraventricular hemorrhage ( $\geq$ grade II), bronchopulmonary dysplasia and periventricular leucomalacia, and cerebral palsy.<sup>5,22–27</sup>

## Antibiotics used in SPTL

Randomized placebo-controlled trials of the use of antibiotics for the treatment of SPTL have yielded conflicting results. The inclusion of antibiotics (clindamycin or metronidazole) which have activity against anaerobes and bacterial vaginosis (BV)-related organisms resulted in prolongation of pregnancy.<sup>28–30</sup> Using a combination of ampicillin and metronidazole,<sup>28</sup> Svare et al demonstrated that there was a significant prolongation of pregnancy (admission to delivery 47.5 days versus 27 days,  $P < 0.05$ ) and decreased incidence of preterm birth (42% versus 65%  $P < 0.05$ ). There was no significant effect on maternal and neonatal infection. Norman et al used ampicillin and metronidazole and showed that pregnancy was prolonged by at least 7 days compared to placebo (63% versus 37%,  $P = 0.03$ ) and neonatal morbidity was also decreased.<sup>29</sup> McGregor et al used clindamycin, and detected a statistically significant prolongation of pregnancy in the treated group compared to placebo (35 days versus 25 days  $P = 0.02$ ).<sup>30</sup>

Oracle II randomized 6295 women into 4 groups – erythromycin only, co-amoxiclav only, combination of erythromycin and co-amoxiclav, and placebo. The primary outcome measure was a composite of neonatal death, chronic lung disease or major cerebral abnormality on ultrasound before discharge from hospital. None of the antibiotics used showed any reduction in the composite outcome compared to placebo. There was no statistically significant difference in the prolongation of pregnancy between the four groups,<sup>31</sup> but the antibiotics used are not active against BV-related organisms,<sup>32–34</sup> and are not recommended for the treatment of BV.<sup>35</sup> In addition, no objective measure of abnormal colonization was used, and women with signs of infection were excluded. It is likely therefore, that a minority of women given antibiotics had any infection which needed correction. The median gestational age at delivery within the four groups was beyond 38 completed weeks which raises the question whether the women recruited were really in SPTL. In addition, other trials which did not use antibiotics which are active against BV related organisms and anaerobes have not shown any benefit.<sup>36–41</sup> A Cochrane systematic review of eleven trials on the use of antibiotics for inhibiting PTL concluded that antibiotic use showed no benefit,<sup>42</sup> partly because of small numbers of women included in the trials which used clindamycin or metronidazole compared to trials which did not use them, and mainly the overwhelming weighting of Oracle II.

## Antenatal glucocorticoids and PTL

Administration of a single course of antepartum glucocorticoids to women in SPTL at risk of PTB between 23 and 33 weeks gestation has been proven to reduce the incidences of neonatal RDS, intraventricular hemorrhage, neonatal sepsis, and need for admission to neonatal intensive care unit, necrotizing enterocolitis, and neonatal death.<sup>43</sup> However, antenatal exposure to glucocorticoids might result in insulin resistance when the offspring reach adulthood.<sup>44</sup> The benefit observed on the reduced incidence of neonatal RDS does not last beyond 7 days, which supports the importance of accurate diagnosis of SPTL. Repeat courses of antepartum glucocorticoids should be avoided since they can be associated with increased risk of small for gestational age, cesarean section,<sup>45</sup> and suppression of the maternal and neonatal hypothalamic–pituitary–adrenal (HPA) axis.<sup>46,47</sup> But the Cochrane review on repeat courses of antepartum glucocorticoids showed a reduction in occurrence and severity of any neonatal lung disease, and serious infant morbidity.<sup>45</sup> In a retrospective analysis of 713 infants (369 and 134 singleton

preterm infants delivered at  $\leq 34$  and  $\geq 35$  weeks gestation respectively, and 210 multiple gestation) whose mothers were exposed to single or multiple courses of antenatal corticosteroids (2–12 courses), a significant reduction in the head circumference ( $4.6 \pm 1.9$  mm) was observed in the multiple course group.<sup>48</sup> A cohort of 541 very preterm infants from singleton pregnancies between 3 and 6 years of age were evaluated, using physical, cognitive, and psychological assessments. Three or more courses of antenatal corticosteroids were associated with increased rates of aggressive/destructive, distractible, and hyperkinetic behavior. The rate of cerebral palsy was, however, reduced.<sup>49</sup> Nevertheless, repeat courses of antepartum glucocorticoids should be avoided, and the single course should be selective and optimized.

## Pathophysiology/biochemical triggers of PTL

The precise mechanism of labor in women remains incomplete clinically, endocrinologically and biochemically. Relatively increased plasma levels of corticotrophin releasing hormone – a peptide produced by the placenta – is associated with increased risk of PTBs, but this observation is not specific to SPTL.<sup>50–54</sup> Detection of an early surge or increased levels of salivary estriol is also associated with SPTL, but this surge can occur about 3 weeks before the onset of SPTL.<sup>51</sup>

Experiments on parturition in sheep show that activation of the fetal pituitary adrenal axis results in increased fetal cortisol secretion. Cortisol leads to activation of p450 dependent placental 17 alpha hydroxylase and 17–20 lyase enzymes to cause conversion of C21 to C18 steroids.<sup>56</sup> Maternal estradiol levels rise, and progesterone levels fall, and this change in estrogen: progesterone ratio leads to increased production of prostaglandins (PGs). Consequently, there is cervical ripening and increased activation of oxytocin receptors, leading to myometrial contractility. However, neither the induction of the placental p450 enzymes nor the fall in progesterone levels has been demonstrated in humans. It is possible that the lack of expression in humans of the placental p450 C17 enzymes serves to maintain the placental production of progesterone, which is responsible for uterine quiescence and regulation of uterine activity during pregnancy.

Ovine and primate parturition studies show that increased levels of intrauterine cortisol, of maternal, fetal or the fetoplacental origin induce the expression of PG synthase type 2 (PGHS-2) in the amniochorion, and the suppression of the NAD<sup>+</sup>– dependent PG dehydrogenase in the amnion

predominantly from epithelial cells, and to a lesser extent mesenchymal cells. As a result, there is increased production of PGE-2,<sup>58</sup> and the increased activity of the fetal HPA axis leads to increased production of estriol which activates the PGHS-2 in maternal endometrial epithelium leading to increased levels of PGF2- $\alpha$ .<sup>57,59–61</sup>

In vitro studies on the regulation of PGHS-2 activity by glucocorticoids in the amnion have yielded conflicting results. Dexamethasone increases the PGHS-2 activity in confluent amnion cell cultures,<sup>62</sup> and has no effect on PGHS-2 activity in freshly cultured amnion cells.<sup>63</sup> In addition, dexamethasone suppressed cytokine induced PGHS-II expression and activity in amnion cells by blocking transcription factor binding at the nuclear factor kappa beta (NF- $\kappa$ B) and CRE 5' promoter sequences of the PGHS-2 gene.<sup>64</sup>

## The role of progesterone

The suppression of progesterone receptors (PR) – effectively a functional withdrawal of progesterone – is also linked to the initiation of labor in humans. Two types of PR (A and B) are expressed in the human myometrium at term. It is the expression of PR-A mRNA, relative to PR-B mRNA that leads to functional withdrawal of progesterone.<sup>65</sup> In vitro studies in mice demonstrate increased transcriptional activities of NF- $\kappa$ B, in response to inflammatory cytokines such as IL-1 $\beta$  produced by fetal macrophages. Activation of fetal macrophages is believed to be due to secretion into the AF of major lung surfactant protein A and the final effect of these activities is suppression of the PR.<sup>66</sup>

In an in vitro study of human tissue, Allport et al<sup>67</sup> showed that increased NF- $\kappa$ B transcriptional activity leads to activation of the cyclooxygenase (COX) enzyme in the amnion. Two isoforms, one constitutive (COX-1) and the other inducible (COX-2) exist, but in human labor it is the COX-2 enzyme that converts free arachidonic acid (produced from glycerophospholipids in the cell membrane by increased phospholipase activity) into the PG precursors – PGH-2 and PGG-2.<sup>68,69</sup> Triggers such as increased cortisol from maternal or fetal stress and/or inflammatory cytokines lead to increased production of PGs which override uterine quiescence, leading to functional withdrawal of progesterone.

## Role of oxytocin

Coupling of oxytocin (OT), endothelin or prostanoid receptors with the enzyme phospholipase C beta (PLC- $\beta$ ) through the G protein coupled receptors (the most abundant receptors in the uterus) hydrolyzes OT sensitive phosphatidylinositol 4, 5 bisphosphate (PIP2) in the cell membrane.<sup>58</sup> This process

generates two secondary messengers – inositol 1, 4, 5 triphosphate (IP<sub>3</sub>) and diacyl glycerol. IP<sub>3</sub>, coupled with specific receptors, releases stored intracellular calcium from the sarcoplasmic reticulum. Production of IP<sub>3</sub> may further induce influx of calcium (Ca<sup>2+</sup>) from the extracellular space through voltage gated channels.<sup>70</sup> Activated myosin light chain kinase, under the influence of released intracellular calcium – calmodulin complexes, causes phosphorylation of myosin which then interacts with actin to cause uterine contraction. Dephosphorylation of myosin by myosin phosphatase leads to uterine relaxation.<sup>58,70</sup>

The Rho kinases, which belong to the family of G-proteins, also cause uterine contractions by inhibiting myosin phosphatase activity, which leads to calcium sensitization.<sup>71</sup> In contrast, coupling of  $\beta_2$ -adrenergic and prostanoid receptors with the enzyme adenylyl cyclase (AC), possibly through G-protein coupled receptors, lead to production of cyclic nucleotides (cAMP and cGMP) and promotes uterine relaxation.<sup>58,72</sup> Phosphodiesterase (PDE)-4, an isozyme of PDE predominantly expressed in the pregnant uterus, inhibits cAMP production, but progesterone promotes AC and inhibits PDE-4 activity.<sup>73</sup> Summary of some of these biochemical events leading to PTL are shown in Figure 1.

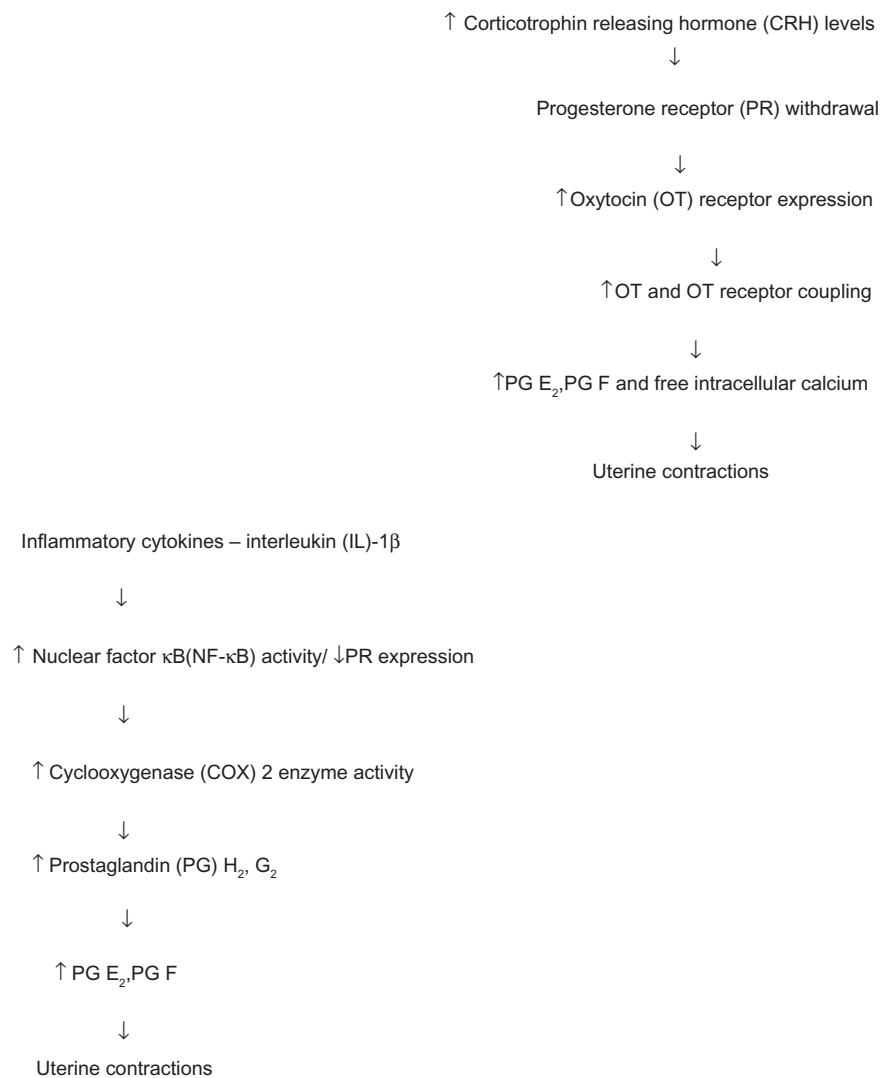
## Role of tocolytics – atosiban

OT is a potent uterotonic hormone that is secreted from the posterior pituitary gland. Although increased levels of OT are not evident during labor, the uterine contractile effect of oxytocin relies on activated OT receptors in the presence of increased estrogen and PG production.<sup>74</sup> Atosiban is a nonapeptide, desamino-OT analogue, and a competitive vasopressin/oxytocin receptor antagonist (VOTra).<sup>75–78</sup> Atosiban inhibits the OT-mediated release of IP<sub>3</sub> from the myometrial cell membrane.<sup>75</sup> As a result, there is reduced release of intracellular, stored calcium from the sarcoplasmic reticulum of myometrial cells, and reduced influx of Ca<sup>2+</sup> from the extracellular space through voltage gated channels. In addition, atosiban suppresses OT-mediated release of PGE and PGF from the decidua.<sup>79,80</sup>

## Phase II and III studies

Peak plasma concentrations of atosiban was achieved at 2 to 8 minutes following intravenous (IV) administration (10 nmol/kg body weight) compared to peak concentration at 10 to 45 minutes following intranasal administration of atosiban at 100 nmol/kg body weight.<sup>81</sup> Goodwin et al showed that following IV infusion of atosiban (300  $\mu$ /min) in women between 20 and 36 weeks' gestation, and in whom

contractions were absent for 6 hours or maximum infusion length of 12 hours, plasma atosiban concentrations reached steady state within 1 hour of the start of IV infusion.<sup>82</sup> The decrease in uterine activity in the first 4 hours of IV infusion was directly proportional to the duration of infusion. At the completion of infusion, plasma atosiban levels declined in a bi-exponential manner with initial and terminal half lives of  $13 \pm 3$  and  $102 \pm 18$  minutes, respectively. In a phase II randomized placebo controlled trial of the effect of atosiban on premature uterine activity (20 to 36 weeks gestation), a 2-hour infusion of atosiban led to a statistically significant decline in the frequency of uterine contractions, suggesting that OT plays a role in the maintenance of PTL. The only adverse outcome reported in the atosiban group was nausea and vomiting in one patient.<sup>83</sup> In a phase III randomized controlled trial of the effect of atosiban on PTL (20 to 34 weeks), which allowed tocolytic rescue if after 1 hour of atosiban or placebo infusion, premature labor continued, the primary end-point was the time to delivery or therapeutic failure (progression of labor requiring an alternative tocolytic). There was no statistically significant difference between the two groups for the primary end-point. The secondary end-points were the proportions of women who were successfully treated at 24 hours, 48 hours and 7 days after commencing atosiban or placebo infusion. The proportions were significantly higher in the atosiban group: 73% versus 58% at 24 hours ( $P < 0.001$ ), 67% versus 56% at 48 hours ( $P = 0.008$ ), and 62% versus 49% at 7 days ( $P = 0.003$ ). Compared to placebo, the effect of atosiban on prolongation of pregnancy up to 7 days was more evident in pregnancies  $\geq 28$  weeks completed weeks of gestation; 65% versus 48%, and 51% versus 59% at  $< 28$  weeks.<sup>84</sup> These findings emphasize the fact that VOTras play a role in the maintenance of SPTL, yet other mechanisms are also involved. The perinatal mortality rate was 2.1% in the atosiban group, compared to 1.4% in the placebo group with or without tocolytic rescue.<sup>84</sup> However, the randomization was not stratified according to gestational age, which resulted in an excess of extremely premature infants at a more advanced stage of labor in the atosiban group, and the Cochrane Review<sup>85</sup> has been criticized for their use of these data.<sup>77</sup> In a randomized controlled trial of women who, after successful treatment with atosiban, had a maintenance subcutaneous infusion of atosiban or placebo, the use of atosiban resulted in a statistically significant prolongation of uterine quiescence, compared to placebo (median of 32.6 days versus 27.6 days). Women in the atosiban group had higher incidence injection site reactions (70% versus 48%) during the maintenance treatment.<sup>86</sup>



**Figure 1** Flow chart of biochemical events leading to preterm labor.

## Worldwide comparative trial of atosiban versus beta-agonists

A worldwide, multinational, multicenter, double-dummy, comparative controlled study compared the effectiveness and safety of atosiban with conventional beta-agonist therapy (ritodrine, salbutamol or terbutaline) in the treatment of SPTL. Alternative tocolytic therapy could be used, if there were unacceptable side effects or if labor progressed. The methodology also permitted re-treatment in cases in which tocolysis had been initially successful provided the patient still fulfilled the protocol requirements. The study showed that atosiban was as effective as the beta-agonists in delaying delivery for 48 hours or 7 days. The need for rescue therapy was significantly reduced in the atosiban group compared with the beta-agonist group, at 48 hours and 7 days after initiation of tocolytic therapy. Maternal side

effects, especially cardiovascular adverse events, occurred 10 times more frequently in the beta-agonist group (8.3% versus 81.2%,  $P < 0.001$ ). and there was a 15-fold increased need for discontinuation of therapy due to unacceptable side effects. There was no statistically significant difference in the perinatal morbidity and mortality rates.<sup>87</sup>

## Atosiban versus nifedipine

A meta-analysis using a “virtual” indirect comparison of atosiban versus the calcium channel blocker (CCB) nifedipine, included 9 randomized trials evaluating the effectiveness of nifedipine versus beta-agonists (different dosage, route and release formulation of nifedipine were used), and four trials of atosiban versus beta-agonists and concluded that the use of nifedipine was associated with a significant reduction in respiratory distress syndrome



compared to atosiban. However, the number of women who remained undelivered by 48 hours was not statistically significantly different between the two groups.<sup>88</sup> The true effect of randomization can be lost when comparing the effectiveness of two tocolytics in this indirect way, and the authors acknowledged the shortcomings of such an analysis and that a number of assumptions were made in the comparisons. A small interventional randomized controlled trial, of 63 women, comparing atosiban with nifedipine for the treatment of SPTL (24 weeks to 35 weeks gestation) permitted tocolytic rescue after 1 hour for failed tocolysis by the assigned drug. Tocolytic agents were administered until uterine quiescence was achieved, and maintenance tocolytic regimes were not specified. The main outcome measure was the proportion of women who did not deliver, or who required alternative tocolytic therapy to avoid side effects 48 hours and 7 days after initiation of treatment. The study showed that there was no statistically significant difference between the two groups in delay of delivery for 48 hours up to 7 days. There was no statistically significant difference between the groups in the need for rescue tocolytic therapy. Nifedipine achieved uterine quiescence faster than atosiban (mean of 2.2 hours  $\pm$  0.93 versus 4.2 hours  $\pm$  1.1). Nausea occurred more frequently in the atosiban group. Headache, flushing, palpitation and hypotension were significantly increased in the nifedipine group. Perinatal and neonatal outcomes were not significantly different between the groups.<sup>89</sup> Another randomized controlled trial of 80 women, compared the efficacy of atosiban and nifedipine for the delay of delivery in women with PTL between 26 weeks and 34 completed weeks of gestation. Atosiban was as effective as nifedipine for delay of delivery for 48 hours and 7 days, and with minimal maternal side effects. Rescue tocolytic and maintenance therapy were not part of the protocol. Hypotension (27.5%), palpitations (7.5%) and maternal tachycardia (7.5%) were reported in the nifedipine group and none (0%) in the atosiban group.<sup>90</sup>

## Adverse effects of tocolytics

The posterior pituitary hormones, OT and arginine vasopressin, differ in structure by only two amino acids, and atosiban influences physiological effects of arginine vasopressin on the feto–maternal cardiovascular and renal systems.<sup>91</sup> In late-gestation sheep, the administration of atosiban for 1 hour failed to induce fetomaternal cardiovascular changes.<sup>92</sup> IV atosiban (300  $\mu$ g/min) used in women scheduled for elective cesarean section demonstrated no significant effect on the umbilical cord blood gases, and

maternal hematocrit.<sup>93</sup> In contrast Blea et al found that in pregnant ewes, IV nifedipine was associated with fetal hypoxia and acidosis.<sup>94</sup> There are also concerns with respect to the number of published reports of adverse feto–maternal events after the use of CCBs, compared to the use of atosiban.<sup>95–107</sup> In children aged 9 to 12 years who were exposed to nifedipine in utero compared to others with in utero exposure to ritodrine, measures of behavioural–emotional problems, motor function, parenting problems and education failed to demonstrate any significant difference between the two groups. The same comparison is needed to evaluate the long-term outcomes in children exposed to atosiban in utero, compared to nifedipine.<sup>108</sup>

For the treatment of SPTL, a complete course of atosiban is much more expensive than that of nifedipine.<sup>109</sup> There is no doubt that a well conducted randomized controlled trial of atosiban versus nifedipine is needed.<sup>110</sup>

## Conclusion

PTL is the most common event leading to PTB, but the prevention of SPTL remains challenging for clinicians. Accurate prediction of PTB in women admitted with threatened preterm labor remains difficult. Compared to traditional clinical methods, the combination of TVUSS and FFN may identify women who are in SPTL, and who are at increased risk of PTB, but further research is needed to identify factors that have better positive predictive values. The role of antibiotics for the prevention of PTB in women in SPTL remains unproven, but this should not be confused with prophylactic antibiotics given to women with abnormal genital tract colonization in early pregnancy. Studies that identify women with subclinical IAI may reveal women who are more likely to benefit from appropriate antibiotic administration. Tocolytic therapy is relatively ineffective in SPTL because of infection, and should be reserved for those in SPTL, of no obvious infective etiology. Compared to beta-agonists and CCBs, atosiban has the fewest maternal and fetal side effects. Unlike CCBs, atosiban has proven benefit over placebo, and is at least as effective as other tocolytics. The role of atosiban for the prevention of PTB in women with SPTL without subclinical IAI, and in gestations when VOTra are well established (>28 weeks' gestation) needs further evaluation. Such study should include protocols to identify women likely to be in SPTL using FFN and TVUSS of cervical length.

## Disclosures

The authors declare no conflicts of interest.

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