

# Preliminary report of 48-hours Atosiban administration in spontaneous preterm labor – Doppler blood flow assessment of placental and fetal circulation

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## Abstract

**OBJECTIVES:** The aims were to investigate whether there are any changes in placental and fetal circulation during Atosiban tocolysis within the first 48 hours of therapy.

**METHODS:** Detailed Doppler evaluation of placental and fetal circulation was performed prior to Atosiban administration and thereafter at 24 and 48 hours. Maternal heart rate and the pulsatility index (PI) in both uterine arteries (R-UtA, L-UtA) were assessed. Fetal heart rate (FHR), the resistance (RI) and pulsatility index (PI) of umbilical (UA) and middle cerebral artery (MCA) were measured. Additionally cerebroplacental ratio was calculated. E-wave/A-wave ratio (E/A) for atrioventricular valves, the myocardial performance index (MPI) and shortening fraction (SF) for both ventricles were calculated for both ventricles independently. To determine changes over time in all study variables analysis of variance (ANOVA) for repeated measurements followed by Tukey-Kramer’s post hoc test was used. The effects of additional clinical covariates were checked.

**RESULTS:** Maternal heart rate and blood flow in (R-UtA/L-UtA) were not altered significantly during Atosiban administration. No significant changes in FHR as well as Doppler parameters (RI, PI, PSV) in UA and MCA were recorded after 24/48 hours of tocolytic treatment. The mean values of cerebroplacental ratio (CPR) remained unaltered during treatment. Detailed evaluation of fetal cardiac function parameters (E/A, SF, MPI) calculated independently for both ventricles, revealed no significant changes over the time.

**CONCLUSIONS:** To our best knowledge this study has been first evaluation of placental and fetal circulation with assessment of cardiac hemodynamic function during 48-hours administration of Atosiban. This kind of tocolysis treatment seems not to alter uterine nor fetal arterial blood flow pattern seriously. Hemodynamic cardiac activity in fetuses has remained unaffected. We cannot conclude definitely that there are absolutely no changes in the fetal hemodynamic condition due to Atosiban. Further studies should be performed to verify its possible influence on fetal venous blood flow.

**Abbreviations:**

A-V	- atrioventricular
E/A	- E- and A-wave ratio
CPR	- cerebroplacental ratio
DV	- ductus venosus
FHR	- fetal heart rate
Hz	- Herz
MCA	- middle cerebral artery
MPI	- myocardial performance index
PI	- pulsatility index
PSV	- peak systolic velocity
RI	- resistance index
S/D	- systolic/diastolic index
SF	- shortening fraction
UA	- umbilical artery
UtA	- uterine artery

## INTRODUCTION

Preterm birth, as one of the main perinatal complications of the pregnancy, is responsible for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities (Hack & Fanaroff 1999). Apart from great progress in medical care, the rate of preterm labor seems to increase in most of Western countries (Hoyert *et al.* 2004; Langhoff-Roos *et al.* 2006). As preterm labour is known as a complex perinatal problem, every year more health conditions are considered as potential risk factors. For example even periodontitis seems to be associated with higher rate of preterm low birth weights infants (Straka 2011). The above data are unquestionably a concern. Antenatal corticosteroids administration results in beneficial effects such as improved fetal lung maturation and neonatal outcome (Roberts & Dalziel 2006). Therefore postponing delivery for at least 48 hours is a main objective in present treatment of spontaneous preterm labor. This procedure enables 'in utero' transfer to the referral centre if neonatal intensive care unit (NICU) admission is highly probable. According to present investigations there is not one-trigger mechanism that initiates preterm labor sequence. It is evident that oxytocin and oxytocin receptors are involved in this process. Oxytocin antagonists have been regarded therefore as useful and specific therapeutic agents. Atosiban, 1-(3-mercaptopropanoic acid)-2-(O-ethyl-D-tyrosine)-4-L-threonine-8-L-orni-thine-oxytocin, is a synthesized cyclic nonapeptide that behaves as a competitive antagonist for oxytocin receptors. Its affinity is not only for oxytocin receptors but also for vasopressin receptors (V1a, V1b, V2) (Akerlund 2006). Atosiban inhibits the uterotonic action of oxytocin in animal and human models both in pre and term myometrium, in a complete, competitive and dose dependent way (Bossmar *et al.* 1994; Phaneuf *et al.* 1994; Reinheimer *et al.* 2005). Not only Atosiban efficacy but also its safety profile is a subject of many studies. Vomiting, nausea and headache were the most often reported side effects while Atosiban treatment had been started (Al-Omari

*et al.* 2006). However much less maternal side effects were reported comparing to beta adrenergic agonists and nifedipine (Al-Omari *et al.* 2006; French/Australian Atosiban Investigators Group 2001; Romero *et al.* 2000; The Worldwide Atosiban versus Beta-agonists Study Group 2001). Evaluation of maternal effects revealed no clinical data suggesting maternal adverse effects on the cardiovascular, renal and central nervous system. Most studies in human and animals do not show serious alteration in fetuses after Atosiban administration due to preterm labor symptoms (de Heus *et al.* 2009; de Heus *et al.* 2009; Thorp *et al.* 1999). However few controversial reports have been published till now (Romero *et al.* 2000; Simsek *et al.* 2012). Hemodynamic conditions are very specific and sensitive markers of any change in fetal wellbeing. Therefore it was our aim to evaluate placental and fetal hemodynamic conditions during 48-hours tocolytic administration of Atosiban.

## METHODS

The study was conducted in the Fetal Maternal Medicine Department at the Research Institute "Polish Mother's Memorial Hospital", Medical University, Lodz, Poland. We established the following admission criteria: patients with singleton pregnancy, between 24–34 weeks' gestation with intact membranes and showing evidence of premature labor. This was diagnosed as painful and persistent contractions (at least four in an hour) associated with cervical changes and/or effacement (Hincz *et al.* 2002). Exclusion criteria included multiple pregnancy, chorioamnionitis, intrauterine growth restriction, fetal congenital malformations, vaginal bleeding and acute fetal distress. The patients with circulatory system diseases (e.g. heart defects, hypertension) as well as diabetes (both pre- and gestational), symptoms of infection or any other specific maternal contraindication for Atosiban treatment were excluded. The use of any tocolytic agents during pregnancy before admission to the hospital met also exclusion criteria.

After precise patient evaluation, Atosiban medication was administered in accordance to the drug characteristic medical protocol and our clinical knowledge. The initial dose of Atosiban (Tractocile, Ferring Pharmaceuticals A/S, Copenhagen, Denmark) was given as a single intravenous bolus dose (6.75 mg in 0.9 ml isotonic sodium chloride solution). This was followed immediately by intravenous infusion of 300 µg/min of Atosiban in 5% glucose for 3 hours, then 100 µg/min for up to 48 hours. Maternal steroid therapy was started right after admission to the hospital. Four intramuscular injections of 6 mg dexamethasone (Dexaven, Jelfa) were given 12 hours apart from one another (NIH Consensus Development Panel on the Effect of Corticosteroids for Maternal Maturation on Perinatal Outcomes 1995). Doppler examination was performed prior to Atosiban and corticosteroid administration and repeated after 24 and 48 hours of the therapy. The patient was lying in a left

recumbent position to avoid orthostatic hypotension. A Voluson E8 ultrasound machine (GE, Medical Systems, Austria) with 3.5-MHz and 5-MHz convex probes was used. All scans were performed by the same investigator (M.G.) and the measurements were collected in the absence of uterine contractions, fetal body and breathing movements. The high-pass filter was set at 100 Hz. The sample volume size was adjusted due to the diameter of the vessel. The insonation angle was established as close to 0 degrees as possible and was never more than 30 degrees. Color flow imaging was used to visualize the flow through the main uterine artery medial to the external iliac artery. Furthermore the ascending branch was selected for PI calculation (Arduini *et al.* 1990). This technique was the same for both sides. For umbilical artery Doppler sampling site was located at the half of the distance between fetal and placental end of the cord. The circle of Willis and the middle cerebral artery were identified when a transverse view of the fetal brain was obtained. The measurements were taken in the middle part of MCA. Peak systolic velocity (PSV), resistance (RI) and pulsatility (PI) index were calculated for both vessels. Finally the cerebroplacental ratio (CPR) based on MCA-PI/UA-PI formula was calculated (Baschat & Gembruch 2003). The four chamber view of fetal heart was obtained from apical or basal approach. Color Doppler was used to identify blood flow across atrioventricular valves. The sample gate was placed distal to A-V valves at the brightest colors of the blood flow. Biphasic velocity waveforms were recorded with two diastolic peaks. The ratio between E and A waves were calculated. A-V valve insufficiency was recorded if present (Abuhamad & Chaoui 2010). The myocardial performance index (MPI) for right and left ventricle was calculated *in two steps*; the first time period (isovolumetric (a)) was calculated between the end of the A-wave and the beginning of the next E-wave during the ventricular filling phase, and the second period (b), the ejection time, was recorded in the aortic or pulmonary outflow tracts. MPI value was calculated using formula (a-b)/b (Pellet *et al.* 2004; Tei *et al.* 1995). M-mode technique was used to visualize the motion of ventricular walls and intra-ventricular septum. Shortening fractions were also calculated for both ventricles independently.

The results were analyzed according to well-known statistical methods by using StatSoft Statistica for Windows, release 6.0 (StatSoft, Inc., Tulsa, USA). To compare changes in response to treatment analysis of variance (ANOVA) for repeated measurement with the Tukey-Kramer's post hoc test were used. The  $p < 0.05$  was used as a definition of statistical significance.

The project was approved by local Research Ethics Committee. All patients participating in the study gave their signed informed consent.

## RESULTS

Twenty-one patients fulfilled inclusion criteria and were enrolled in the study. The mean maternal and gestational age was  $28.8 \pm 6.3$  years and  $30.1 \pm 2.6$  weeks, respectively. The median gravidity was 2 with a quartile range of 1–2 and the median parity was 2 with a quartile range of 1–2. Maternal side effect of Atosiban administration (nausea) was observed separately in 2 patients. No fetal or infant side effects related to the therapy were observed. None of the patients delivered within 72 hours. Maternal heart rate was not altered significantly while treatment (0h/ $85 \pm 12.9$  vs. 24 h/ $89.1 \pm 19.1$  vs. 48h/ $81.8 \pm 11.1$  bpm,  $p > 0.05$ ). The mean PI values for both uterine arteries showed no significant changes over the time (Table 1). Mean values of RI, PI and PSV in UA and MCA as well as cerebroplacental ratio remained unaltered after 24 and 48 hours of treatment (Table 2). Measurement of fetal heart rate and detailed evaluation of fetal cardiac function parameters (E/A, MPI, SF), calculated independently for both ventricles, revealed no significant changes over the time (Table 3).

**Tab. 1.** Doppler Pulsatility Index (PI) in uterine arteries (UtA) before and after (24/48 hours) Atosiban treatment.

	before Mean±SD	after 24 hours Mean±SD	after 48 hours Mean±SD	p-value (ANOVA)
Right uterine artery (R-UtA)	0.82±0.21	0.78±0.32	0.77±0.19	0.6399
Left uterine artery (L-UtA)	0.83±0.25	0.78±0.38	0.77±0.21	0.5846

**Tab. 2.** Doppler indices in umbilical (UA), middle cerebral artery (MCA) and cerebroplacental ratio (CPR) before and after (24/48 hours) Atosiban treatment.

	before Mean±SD	after 24 hours Mean±SD	after 48 hours Mean±SD	p-value (ANOVA)
<b>Umbilical artery (UA)</b>				
RI	0.60±0.07	0.58±0.08	0.60±0.08	0.3363
PI	0.92±0.17	0.87±0.17	0.96±0.27	0.2506
PSV (cm/s)	43.6±10.5	44.0±10.7	45.0±7.2	0.8565
<b>Middle cerebral artery (MCA)</b>				
RI	0.77±0.05	0.79±0.07	0.84±0.22	0.2556
PI	1.70±0.27	1.84±0.36	1.70±0.36	0.2626
PSV (cm/s)	41.4±8.6	38.4±9.8	42.8±13.7	0.2552
Cerebroplacental ratio (CPR)	1.92±0.48	2.18±0.51	1.92±0.59	0.1106

**Tab. 3.** Fetal cardiac function parameters before and after (24/48 hours) Atosiban treatment.

	before Mean±SD	after 24 hours Mean±SD	after 48 hours Mean±SD	p-value (ANOVA)
FHR (bpm)	143.2±9.3	140.4±11.9	141.3±8.9	0.5542
TV E/A	0.64±0.08	0.61±0.08	0.62±0.09	0.1446
MV E/A	0.61±0.10	0.64±0.10	0.60±0.07	0.1951
RV SF (%)	36.3±4.1	36.8±4.0	38.7±3.8	0.2079
LV SF (%)	38.7±4.1	38.9±4.1	39.7±3.2	0.7952
RV MPI	0.47±0.12	0.43±0.14	0.49±0.09	0.1872
LV MPI	0.44±0.11	0.43±0.09	0.47±0.11	0.4732

## DISCUSSION

Recent publication, based on animal studies, presented new data about elevated cardiac oxidative stress in newborn rats from mothers treated with Atosiban (Simsek *et al.* 2012). This is an important voice in discussion, which was started by Romero *et al.* (2000). In randomized, double blinded, placebo-controlled trial they presented data about increased rates of fetal and infants deaths in the Atosiban group. The explanations for that fact are ambiguous. From one point of view a greater number of extremely preterm pregnancies were allocated to Atosiban group. Seven of ten infants deaths occurred in extremely immature infants group with birth weights less than 650 grams. Additionally an important role of increased rate of chorioamnionitis is to be underlined. From the opposing point of view, the authors didn't exclude the possibility of an adverse effect mechanism (Romero *et al.* 2002).

There is a clear evidence that role of Oxytocin (OT) in humans is not only limited to the reproductive system. OT synthesis process in the hypothalamus was well known, however, the heart was reported to be another site of Oxytocin synthesis and release as well (Jankowski *et al.* 1998). The possible impact of intrinsic OT system in regulation of vascular tone and cardiac function was suggested (Gutkowska *et al.* 2000; Jankowski *et al.* 2000). Oxytocin is also known as antioxidant agent inhibiting production of reactive oxygen products (Dusunceli *et al.* 2008; Iseri *et al.* 2005; Tugtepe *et al.* 2007). It has been probably participating in release of atrial natriuretic peptide (ANP), which is a potent vasodilator and antioxidant (Gutkowska *et al.* 1997). Houshmand *et al.* (2009) presented an experimental animal model of cardiac ischemia/reperfusion injury during analgesia. They presented data about serious impairment of Oxytocin's cardio protective effect in the presence of Atosiban. Finally, Simsek *et al.* (2012) have demonstrated significant increased oxidative stress in the plasma and heart tissue in newborns from Atosiban-treated mothers in animal model. In all these

publications, the relationship between Oxytocin, Oxytocin antagonists and the circulatory system were highly suggested. All findings about Atosiban, presented in animal models, may suggest its direct influence on the circulatory system and resulting in blood flow changes in different compartments.

Therefore, we decided to directly estimate placental and fetal circulation during 48-hours administration of Atosiban in spontaneous preterm labor. In our study analysis of blood flow dynamics; there was no change in uterine artery pulsatility index. The measurements of resistance and pulsatility index, as well as peak systolic velocity in umbilical artery, did not result in any significant changes. Our assessment suggested that uteroplacental circulation remained unaffected during Atosiban treatment. The evaluation of blood flow in middle cerebral artery (MCA) didn't reveal any hemodynamic changes. As in our results umbilical artery and MCA pulsatility index ratio were not altered, cerebroplacental Doppler ratio (CPR) didn't change significantly during tocolytic treatment. De Heus *et al.* (2009) presented the similar conclusions. In their research, blood flow assessment in umbilical and middle cerebral artery was a part of fetal biophysical evaluation. They didn't observe any significant effects of Atosiban in fetal movements and heart rate. They reported that tocolytic treatment appeared to have no direct fetal adverse effects. Neri *et al.* (2009) performed a computerized evaluation of fetal heart rate (FHR) during tocolytic treatment with Atosiban and Ritodrine independently. They reported the changes in FHR pattern when Ritodrine treatment was administered while neutral effect of Atosiban was observed. This conclusion is relevant to our study results. We recorded no significant changes in both maternal and fetal heart rate when Atosiban was administered. The potential impact of Atosiban on cardiac function was an important concern; we evaluated several hemodynamic parameters such as E/A ratio, myocardial performance index (MPI) and shortening fraction (SF). Early/Atrial ratio is well known as a marker of ventricular diastolic function while shortening fraction is a parameter representing cardiac contractility (Godfrey *et al.* 2012). We evaluated myocardial performance index, a precise tool to assess global cardiac function. That parameter was not dependent of fetal heart rate and ventricular structure (Pellet *et al.* 2004; Tei *et al.* 1995). The advantage of all these parameters is that both sides of the fetal heart can be assessed independently. In our study after careful evaluation we found no significant changes in all of the above mentioned parameters. We did not find any alterations of cardiac function, therefore a direct impact of Atosiban on fetal heart was not observed. In literature review we found only one publication concerning influence of Atosiban on cardiac function, resulting large arteries and resistance vessels. Fabry *et al.* (2011) observed no effects of Atosiban on the cardiovascular system. However, this evaluation

was performed in non-pregnant women and authors were unsure if those results could be totally the same in pregnancy. In our study, maternal corticosteroids administration was a part of general tocolytic protocol. Therefore, an important question arose, if steroids may interfere with hemodynamic changes. Conflicting data, concerning different observations, are presented by few authors. They reported modification of fetal heart rate, significant decrease in MCA PI and CPR after maternal steroid therapy (Chitrit *et al.* 2000; Lunshof *et al.* 2005; Urban *et al.* 2005). Senat and Ville (2000) assessed blood flow in uterine arteries, umbilical arteries, descending aorta and middle cerebral arteries in the group of growth restricted fetuses after maternal management of bethamethasone or dexamethasone. No significant changes were found in Doppler measurements. We should underline that if any alterations in fetal arterial hemodynamics were reported, in most cases they appeared after 72 hours from the administration of the first dose. Our research was focused on the period of first 48 hours of tocolytic treatment. On the basis of our results we may only assume that steroid administration did not interfere with placental and fetal circulation. We indicate a limitation of our research concerning a number of patients in study group. However, this is a preliminary report as well as a few publications concerning Atosiban have been based on limited number of patients (de Heus *et al.* 2009; Fabry *et al.* 2011; Neri *et al.* 2009).

According to the best of our knowledge, this study has been the first evaluation of placental and fetal circulation, whilst also combining the assessment of cardiac hemodynamic function. Administration of Atosiban seems not to alter uterine nor fetal arterial blood flow pattern seriously. Hemodynamic cardiac activity in fetuses has been also unaffected during treatment. We cannot definitely conclude that there is absolutely no change in the hemodynamic condition due to Atosiban. Further studies should be performed to verify its possible influence on fetal venous blood flow.

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