Doppler evaluation of blood flow in fetal inferior vena cava during 48-hours Atosiban administration in spontaneous preterm labor

Mariusz Grzesiak [1,2], Rehana B. Ahmed [3], Jan Wilczynski [1,2]

1 Department of Feto-Maternal Medicine&Gynecology, "Polish Mother" Memorial Research Institute, Lodz, Poland
2 3rd Department of Obstetrics & Gynecology, Medical University of Lodz, Poland
3 Division of English Studies, the Medical University of Lodz, Poland

Correspondence to: Mariusz Grzesiak, MD., PhD.
"Polish Mother" Memorial Research Institute
Department of Feto-Maternal Medicine&Gynecology
Rzgowska Str. 281/289, 93-338 Lodz, Poland.
TEL: +48 42 271 10 71; FAX: +48 42 271 10 10; E-MAIL: mariusz.grzesiak@gmail.com

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Abstract

OBJECTIVES: The aims were to evaluate whether any changes in blood flow in fetal inferior vena cava (IVC) are observed during Atosiban tocolysis within the first 48 hours of therapy.

METHODS: Detailed Doppler evaluation of blood flow in fetal IVC was performed prior to Atosiban administration and after 24 and 48 hours respectively. Maternal and fetal heart rate was assessed. IVC Doppler indices, such as, S/D (systole/diastole), PVIV (peak velocity index for the vein) and PLI (preload index) were calculated. To determine changes over time in all study variables, analysis of variance (ANOVA) for repeated measurements was used and followed by Tukey-Kramer's post hoc test. The effects of additional clinical covariates were checked.

RESULTS: Maternal heart rate was not altered significantly during Atosiban administration. No significant changes in FHR (fetal heart rate) as well as following IVC Doppler parameters (S/D, PVIV) were recorded after 24/48 hours of tocolytic treatment. The fetal IVC PLI values were significantly reduced after 24 hours and 48 hours of treatment. The changes in PLI values when comparing 24 and 48 hours results were not statistically significant.

CONCLUSIONS: As the questions about drug safety appeared after the animal study had been published about possible myocyte injury, detailed Doppler evaluation of IVC blood flow was performed. It revealed the changes in preload conditions which could be a reflection of successful Atosiban tocolytic treatment. No hemodynamic changes in IVC were noted, suggesting the presence of fetal acidemia due to possible heart damage was observed.

ORIGINAL ARTICLE

INTRODUCTION

Apart from great progress in obstetrical care the rate of preterm labor still seems not to be reduced. On the contrary, the recent presented data shows that it is an increasing problem in most Western countries (Hoyert *et al.* 2004; Langhoff-Roos *et al.* 2006). Preterm birth is one of the leading perinatal complications resulting in approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities (Hack *et al.* 1999). The key point of modern tocolytic policy is to gain time of at least 48 hours. Firstly, to administer corticosteroids in order to improve fetal lung maturation and neonatal outcome (Roberts *et al.* 2006). Secondly, to enable 'in utero' transfer to the referral centre when neonatal complications and admission to the intensive care unit (NICU) are highly probable. There is no doubt that such management results in perinatal beneficial effects. The choice of optimal tocolytic drug is still unquestionably a concern. Among first-line tocolytic agents Atosiban is suggested as one with the best maternal and fetal safety profile (de Heus *et al.* 2010). It is clear evidence that oxytocin and oxytocin receptors are significant elements of preterm labor mechanism. Atosiban is a synthesized cyclic nonapeptide that behaves as a competitive antagonist for oxytocin receptors. However Atosiban affinity is not only limited to oxytocin receptors but also for vasopressin receptors (V1a, V1b, V2) (Akerlund, 2006). This additional mechanism could be a concern about a safety profile.

Most studies, both in human and animal, do not present data about possible fetal side effects after Atosiban administration due to preterm labor symptoms (de Heus *et al.* 2009; de Heus *et al.* 2009; Thorp *et al.* 1999). Although there are only few controversial reports published till now, unclear message can be worrisome (Romero *et al.* 2000, Simsek *et al.* 2012). One of the animal studies presented results about increased oxidative parameters as a result of heart tissues damage after Atosiban administration (Simsek *et al.* 2012). As ultrasound plays an important role in monitoring of fetal condition, sonographic valuation of blood flow can result in specific and sensitive results reflecting fetal wellbeing. Inferior vena cava is one of so called 'precordial veins'. Some IVC Doppler indices can offer us more detailed information about fetal cardiac function (Baschat, 2003). Therefore it was our aim to evaluate blood flow in the inferior vena cava 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 also met the 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 g/min of Atosiban in 5% glucose for 3 hours, then 100 g/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-pas filter was set at 100 Hz. The sample volume size was adjusted due to the diameter of the vessel. Blood flow in the fetal inferior vena cava (IVC) was visualized using color Doppler and pulsatile Doppler. The sample volume size was adjusted due to the diameter of the vessel. The isonation angle was established as close to 0 degrees as possible and never exceeded more than 20 degrees. Doppler measurements were obtained from a longitudinal section of the IVC in close distance, proximal to the right atrium. Three consecutive waveforms of best quality were used to measure parameters and calculate preload index PLI=a/S, S/D and PVIV=PV S–PV A/PV D (Axt-Fliedner *et al.* 2004; Kanzaki *et al.* 1990). Furthermore, 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±6.3 years and 30.1±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 during treatment (0h/85±12.9 vs. 24 h/89.1±19.1 vs. 48h/81.8±11.1 bpm, $p>0.05$). Fetal heart rate remained unchanged over the study time (0h/143.2±9.3 vs. 24h/140.4±11.9 vs. 48h/141.3±8.9 bpm, $p>0.05$). The mean values S/D and PVIV for IVC showed no significant changes over the time (Table 1). The primary PLI values were (0.58±0.19) and were significantly reduced after 24 hours (0.43±0.07) and after 48 hours (0.40±0.07) of treatment. The decrease in PLI values when comparing 24 and 48 hours results was not statistically significant (Figure 1).

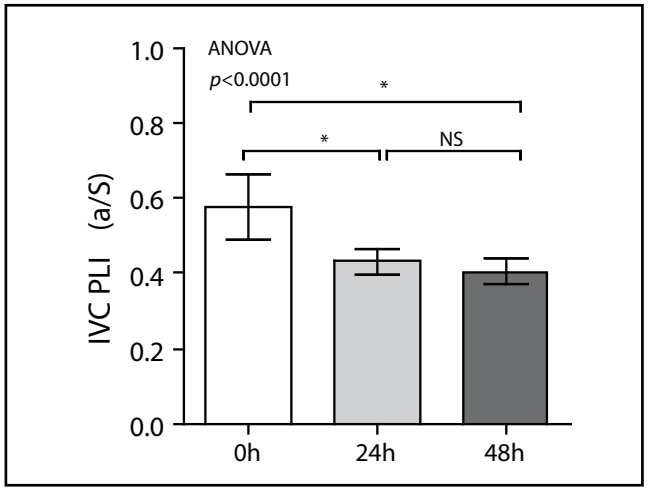

Fig. 1. Preload index in inferior vena cava (IVC) before and after (24/48 hours) Atosiban treatment.

Tab. 1. Doppler indices in IVC before and after (24/48 hours) Atosiban treatment.

IVC	before Mean±SD	after 24 hours Mean±SD	after 48 hours Mean±SD	*p*-value (ANOVA)
S/D	1.48±0.26	1.64±0.34	1.57±0.29	0.1427
PLI	0.58±0.19	0.43±0.07	0.40±0.07	**<0.0001**
PVIV	2.27±0.59	2.35±0.48	2.19±0.39	0.5124

DISCUSSION

The questions about the safety profile of Atosiban are incorporated in spirited discussions about first-line tocolytic drugs in imminent preterm labor. The data presented by Romero *et al.* (2000) showed an increased rate of fetal and neonatal deaths in a group of mothers treated with Atosiban. However, the conclusion of this study remains ambiguous. The final message is unclear due to a greater number of extreme preterm pregnancies in the Atosiban group, increased rate of chorioamnionitis and the inability to exclude the mechanism of Atosiban's adverse effects. Experimental, animal studies brought us new information about possible threats. Houshmand *et al.* (2009) presented data about serious impairment of Oxitocin's cardio protective effect in the presence of Atosiban. Simsek *et al.* (2012) concluded that significant increased oxidative stress parameters are present in the plasma and heart tissue in newborns from Atosiban-treated gravid rats. Venous Doppler is involved in the assessment of fetal status in the course of many perinatal complications. As intrauterine growth restriction is a fetal pathology with complicated background some authors implemented additional venous Doppler parameters to characterize fetal well being and to predict possible complications. Rizzo *et al.* (1996) evaluated correlation between selected venous indices and fetal hypoxia/acidemia. They underlined that hypoxemia was predicted with the weakest efficiency. Their results were corresponding to other publications. Those studies presented data about superiority of peripheral arterial vessel Doppler assessment (Hecher *et al.* 1995; Rizzo *et al.* 1995). However, Rizzo's results obtained in combination of venous indices measurements with prediction of acidemia was peculiar. Inferior vena cava preload index (PLI) proved to be the most relevant among other IVC and DV Doppler parameters. The explanation is not ambiguous. One of the hypothesis underlines the anatomical background. The advantage of IVC over DV results from the proximity of the inferior vena cava to the heart. The other explanation is a greater sensitivity of blood flow in DV to various conditions (Kiserud, 2001). As changes in IVC preload index may reflect cardiac status this parameter is one of the main point of interest in our study. Preload index was a hemodynamic parameter introduced by Kanzaki and Chiba (1990) and presented as a ratio of reverse flow during atrial contraction to flow during ventricular systole. Since that time many reports presented data about different implementation of this index in fetal Doppler assessment (Ott, 1999; Utsu *et al.* 1999; Takahashi *et al.* 2003). Therefore, we decided to assess PLI and several other parameters of fetal blood flow in IVC. We were interested if any changes could be recorded before Atosiban treatment

and after 24 and 48 hours respectively. The calculated PLI values were highest at the moment of admission to the hospital due to premature labor manifestation. Doppler examinations, which were performed after 24 and 48 hours, revealed a significant decrease in PLI values in comparison to initial measurements. However we realized that this theory could be difficult to explain. We considered the cardiomyocyte injury mechanism described on animal model by Simsek *et al.* (2012). Atosiban administering resulted in increased oxidative stress conditions and impaired rat myocyte function. If similar changes had happened to human fetal heart, acidemia could probably be one of the symptoms of myocyte injury. According to Rizzo's *et al.* results (1996), PLI values should be significantly higher in the presence of acidemia. We tried to find a correlation between this fact and possibility of fetal acidemia. However as we mentioned above, in our study we observed absolutely contrary results. Looking for possible explanation of that finding we reviewed publication presented by Takahasi *et al.* (2003). They evaluated IVC PLI in a group of healthy fetuses in the presence and absence of uterine contractions. The increase of PLI values were recorded while contractions were observed. As PLI expresses fetal preload, they proposed that uterine contractions are responsible for temporary increases in fetal preload condition. We carefully assessed our results and noticed that IVC PLI values were the highest at the moment of patients' admission to the hospital. It corresponded to the presence of uterine contractions as symptoms of imminent premature labor. We started Atosiban intravenous administration as a tocolytic treatment. The next Doppler examinations were performed after 24 and 48 hours respectively and a significant decrease in PLI values was noticed comparing to initial values. These results can support the hypothesis that uterine contractions are responsible for moving the additional volume of blood from placenta to fetal circulatory system. When tocolytic treatment is successful, the fetal preload conditions are not increased anymore and PLI values are reduced. Baschat (2003) concluded that only IVC probably was the best reflection of cardiac function (101). We also additionally evaluated such Doppler parameters like S/D and PVIV. Observation of S/D and PVIV results didn't reveal any hemodynamic changes in blood flow in IVC.

However, this is only a preliminary report due to the number of patients, which was a limitation in our study. Although, there has been a few publications concerning Atosiban, which have been based on limited number of patients (de Heus *et al.* 2009; Neri *et al.* 2009).

According to the best of our knowledge, this study has been the first trial that has evaluated blood flow in fetal inferior vena cava during Atosiban administration Detailed Doppler evaluation revealed the changes in preload conditions which can reflect a successful tocolytic treatment. The questions about drug safety appeared after an animal study concerning possible myocyte injury had been published. We didn't find any hemodynamic changes in IVC, suggesting the presence of fetal acidemia, which could be observed if any heart injury would have had happened.

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