48-hours administration of fenoterol in spontaneous preterm labor – Doppler blood flow assessment of placental and fetal circulation

Mariusz Grzesiak [1,2], Piotr Hincz [1,2], Sebastian Forys [3], Rehana B. Ahmed [4], 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 Department of Radiology, "Polish Mother" Memorial Research Institute, Lodz, Poland
4 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 13 13; FAX: +48 42 646 96 40; E-MAIL: mariusz.grzesiak@gmail.com

Submitted: 2013-02-21 Accepted: 2013-06-19 Published online: 2013-11-25

Key words: **preterm labor; fenoterol; Doppler; fetal circulation; fetal cardiac function**

Neuroendocrinol Lett 2013; **34**(6):553–558 **PMID:** 24378443 NEL340613A04 © 2013 Neuroendocrinology Letters • **www.nel.edu**

Abstract

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

MATERIAL AND METHODS: Doppler evaluation of placental and fetal circulation was performed prior to fenoterol administration and then after 24 and 48 hours. Maternal heart rate and pulsatility index (PI) in uterine arteries were assessed. FHR, RI and PI of umbilical artery and middle cerebral artery were measured. E/A ratio for A-V valves, the myocardial performance index (MPI) and shortening fraction (SF) were calculated for both ventricles independently. The blood flow pattern in DV was assessed using PI, S/a ratio and peak velocity index for the vein. To determine changes over time in all study variable analysis of variance (ANOVA) for repeated measurements followed by Tukey-Kramer's multiple comparison test was used. The effects of additional clinical covariates were checked.

RESULTS: Uterine and fetal arterial blood flow patterns were not altered significantly during 48 hours of tocolysis. No significant changes were observed in fetal cardiac function parmeters as well. The evaluation of Doppler parameters in the DV revealed a significant increase in PVIV after 48 hours. Additionally after 48 hours of successful tocolysis S/a ratio values were significantly lower.

CONCLUSIONS: Short term intravenous administration of fenoterol seems not to alter uterine and fetal arterial blood flow pattern. Direct fetal cardiac function remained unaffected. However significant changes of selected Doppler parameters in DV may suggest further studies should be performed to assess more precisely fetal venous blood flow.

ORIGINAL ARTICLE

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
PVIV	- peak velocity index for the vein
RI	- resistance index
S/a	- systolic/a index
SE	- side effects
SF	- shortening fraction
UA	- umbilical artery
UtA	- uterine artery

INTRODUCTION

Present treatment strategy in spontaneous preterm labor is concentrated on prolongation of pregnancy for at least 48 hours. This specific time interval is mainly dedicated for two purposes; to administer steroids in order to induce fetal lung maturation and to transfer pregnant women to tertiary care departments if necessary. Making a decision about types of pharmacological tocolytic agents requires careful consideration about possible benefits and adverse effects. Among many drugs, Beta-adrenergic Agonists, with its advantages and disadvantages, they are yet to be used in preterm delivery prevention. The β-mimetic, fenoterol is one of the most commonly used tocolytic drugs in Poland and Germany in select groups of patients (Schleussner *et al.* 2003). Its pharmacological mechanisms for maternal clinical cardiovascular effects are well known. Positive inotropic effects are responsible for slightly increased heart rate and systolic blood pressure and peripheral vasodilation resulting in decreased diastolic pressure. Mean cardiac output increased by 26% and total peripheral vascular resistence decreased by 18% in the trial with healthy humans (Bouillon *et al.* 1996). Many investigators studied the problem of possible fenoterol impact on fetal heart. Kast and Hermer (1993) in their review of 92 publications concluded that fenoterol, at doses used in human tocolysis, has no cardiotoxic effect on fetal heart. Similar results were presented by Meinen *et al.* (1983) who did not find any myocardial damage in rabbits. Hasaart and de Haan (1987) did not observed any influence of fenoterol infusion on the fetal umbilical circulation in pregnant sheep. On the other hand, Krason at al. (2002) reported the presence of isolated functional tricuspid valve regurgitation in fetuses with normal heart anatomy after betamimetic tocolytic therapy. Hamela-Olkowska *et al.* (2012) presented a case of transient fetal right ventricular hypertrophic cardiomyopathy in the course of prolonged fenoterol treatment. Those reports, previously mentioned, encouraged us to investigate whether any changes in placental and fetal circulation occur during fenoterol tocolysis within the first 48 hours of therapy.

METHODS

The study was conducted in the Department of Feto-Maternal Medicine at the "Polish Mother" Memorial Research Institute, Medical University of Lodz, Poland. We established the following admission criteria: patients with singleton pregnancy, between 24–34 weeks of gestation with intact membranes and showing evidence of premature labor. This was diagnosed as painful and persistent contractions (at least four within 1 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 fenoterol treatment were excluded. The use of any tocolytic agents during pregnancy before admission to the hospital also met the exclusion criteria. After precise patients evaluation the fenoterol medication was started in accordance to the drug characteristic medical protocol and our clinical knowledge. The solution of one ampule Fenoterol Teva, consisting of 500 micrograms of Fenoteroli hydrobromidum and 250 ml of 5% glucose solution was prepared. Treatment was administered with intravenous infusion rate of 2 micrograms per minute. The previous mentioned therapy was maintained during the first 48 hours. Maternal steroid therapy was started right after admission to the hospital. Four intramuscular injections of 6 mg dexamethasone (Dexaven, Jelfa) were given every 12 hours (NIH Consensus Development Panel 1995). Doppler examination was performed prior to fenoterol 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. Blood flow in DV was visualized using color Doppler and pulsatile Doppler. 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 never exceeded 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

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(Arduini *et al.* 1990). The waveforms were assessed for possible presence of notch and uterine artery score was calculated (Ghosh *et al.* 2006). This technique was the same for both sides. When assessing the blood flow in umbilical artery, Doppler sampling site was located at 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, resistance and pulsatility index were calculated for both vessels. Finally, the cerebroplacental ratio 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-waves and A-waves were calculated. A-V valve regurgitation was recorded if it was 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 (Tei *et al.* 1995). M-mode technique was used to visualize the motion of the ventricular walls and intraventricular septum. Shortening fractions were calculated for both ventricles independently. The ductus venosus was presented in a median longitudinal section by color Doppler and the pulsed Doppler gate was placed in the distal portion of the umbilical sinus. With the same rules as mentioned above, peak velocity index for the vein (PVIV=(S–a)/D) and S/a ratio were calculated (Axt-Fliedner *et al.* 2004).

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 measurements 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

Thirty-six pregnant women were selected to join the study. The mean maternal and gestational age was 29.9±5.3 years and 29.1±3.1weeks, respectively. The median gravidity was 1 with a quartile range of 1–2 and the median parity was 1 with a quartile range of 1–2.

Tab. 1. Doppler indices in uterine arteries (UtA) before and after (24/48 hours) fenoterol treatment.

	before Mean±SD	**after 24 hours** Mean±SD	**after 48 hours** Mean±SD	***p*-value** (ANOVA)
Right uterine artery R-UtA PI	0.73±0.14	0.77±0.21	0.77±0.21	0.4478
Left uterine artery L-UtA PI	0.83±0.24	0.82±0.24	0.83±0.23	0.9406

Tab. 2. Doppler indices in umbilical (UA) and middle cerebral arteries (MCA) before and after (24/48 hours) fenoterol treatment.

	before Mean±SD	**after 24 hours** Mean±SD	**after 48 hours** Mean±SD	***p*-value** (ANOVA)
Umbilical artery				
UA RI	0.61±0.06	0.59±0.07	0.59±0.08	0.1004
UA PI	0.94±0.16	0.88±0.15	0.87±0.18	0.1030
UA PSV (cm/s)	43.3±10.8	49.9±11.5	46.6±12.2	0.1258
Middle cerebral artery				
MCA RI	0.80±0.06	0.78±0.06	0.78±0.06	0.1814
MCA PI	1.81±0.40	1.69±0.29	1.73±0.34	0.1654
MCA PSV (cm/s)	41.4±9.8	38.8±10.0	39.8±9.5	0.2591
CPR	1.96±0.46	1.99±0.55	2.04±0.75	0.8060

None of the patients delivered within 72 hours. No changes in uterine blood flow were detected during fenoterol tocolysis (Table 1). The measurements of resistance and pulsatility index as well as peak systolic velocity in umbilical and middle cerebral arteries did not result in significant alterations. The Doppler cerebroplacental ratio (CPR) calculations also did not revealed significant changes after 24 and 48 hours of fenoterol infusion (Table 2).

The maternal heart rate values were significantly increased after 24 hours (97.2±15.2 bpm) and 48 hours (95.8±14.2 bpm) in comparison to pre-treatment values (90.2±14.1 bpm). We noticed that there was no significant change in maternal heart rate when comparing 24 and 48 hours results. Fetal heart rate as well as E/A ratio, shortening fraction, myocardial performance index values, calculated separately for each ventricle, revealed no changes in fetal cardiac function during treatment (Table 3). In evaluation of blood flow in ductus venosus we noted significantly lower values of S/a ratio and a significant increase of PVIV after 48 hours of successful tocolysis, whereas PI values remained unchanged (Table 4). These observations were consistent with ANOVA post-hoc analysis. We did not observe the effect of gestational age and parity on the above results.

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

	before Mean±SD	**after 24 hours** Mean±SD	**after 48 hours** Mean±SD	***p*-value** (ANOVA)
FHR (bpm)	146.2±8.9	145.1±10.0	149.3±10.0	0.0892
TV E/A	0.64±0.07	0.63±0.07	0.61±0.07	0.2971
MV E/A	0.64±0.07	0.62±0.06	0.61±0.07	0.3352
RV SF (%)	35.2±3.5	34.6±4.1	35.8±3.9	0.2542
LV SF (%)	37.2±3.5	36.9±4.2	37.2±4.4	0.8804
RV MPI	0.48±0.12	0.44±0.12	0.46±0.12	0.2501
LV MPI	0.46±0.13	0.45±0.10	0.45±0.09	0.8089

Tab. 4. Doppler indices in Ductus Venosus before and after (24/48 hours) fenoterol treatment.

	before Mean±SD	**after 24 hours** Mean±SD	**after 48 hours** Mean±SD	***p*-value** (ANOVA)
PI	0.80±0.19	0.79±0.16	0.78±0.15	0.7816
PVIV	0.74±0.15	0.71±0.12	1.87±1.15	**<0.0001**
S/a	2.93±0.83	2.73±0.52	1.51±1.13	**<0.0001**

DISCUSSION

The efficacy and safety are the most important issues for modern tocolytic treatment policy. As beta-adrenoreceptors are located in many human organs, fenoterol as a representative of beta$_2$-adrenoreceptor agonists may be responsible for many effects, including those in the circulatory system (Gleiter 1999). Hemodynamic conditions are particulary different during pregnancy. The aim of our study was to detect any possible impact of intravenous fenoterol infusion on placental and fetal hemodynamic conditions. Our results did not reveal any potential effects on placental blood circulation. Analyses of blood flow dynamics showed no changes in uterine artery pulsatility index. The measurements of resistance and pulsatility index as well as peak systolic velocity did not result in significant changes. According to our results blood flow dynamics in the umbilical arteries were not altered. These observations are consistent with the findings of Hasaart and de Haan (1987). The study on their animal model showed no significant changes in uterine artery flow that were detectable. Cheung's and Wladimiroff's findings (1990) showed significant PI value reduction in the group of 25 pregnant patients with intravenous fenoterol administration in comparison to the control group. However we have no precise data about total period of treatment, the authors mentioned only that '...flow velocity waveforms were only recorded after complete suppression of premature labor was achieved'. Faber's *et al.* (1993) research demonstrated an increased pulsatility index value in both uterine arteries before and after 48 hours of fenoterol treatment. However they indicate that 1/3 of patients demonstrated pathological uterine perfusion before or during tocolysis. They conclude that this abnormality is not connected to the uterine contractions. PI values measured in umbilical and middle cerebral artery remained unchanged. Our data did not demonstrate any significant changes in vascular resistance in the uterine artery before starting tocolysis and after 24 and 48 hours of treatment. In our study, there were no patients with symptoms of abnormal uterine perfusion (elevated PI value, the presence of notch, high Uterine Artery Score value. This may explain differences which exist in uterine blood flow characteristics. Umbilical artery and MCA blood flow measurements (RI, PI, PSV) didn't reveal any changes during observation in both ours and Faber's *et al.* study group (1993). Due to umbilical artery and MCA blood flow not being altered, CPR didn't change significantly during tocolysis treatment in our research.

Fenoterol has been known for its cardiovascular side effects (SE). SE has been observed in pregnant women, due to its chronotropic and inotropic activity, resulting in tachycardia and increase of heart muscle contractility. Heart rate acceleration was also observed in fetuses (Gleiter 1999; Pryde *et al.* 2001). We have observed the effect of tachycardia in our pregnant women study group. However, surprisingly, this effect was not observed in fetuses. Fetal heart rate was higher after 48 hours of tocolysis but the change was insignificant. The possible explanation of this condition is based on pharmacokinetics. According to von Mandach et al studies (1989), after at least 12 hours of fenoterol intravenous infusion, average concentration of the drug in the fetuses was 40–60% of maternal concentration. It may suggest that the drug is not accumulated in the fetus especially when administered doses are similar to those that we used.

Potential impact on cardiac function was evaluated by measurements of E/A ratio, myocardial performance index and shortening fraction. Early/Atrial ratio is a well known marker of ventricular diastolic function (Godfrey *et al.* 2012). Shortening fraction is a parameter representing cardiac contractility, while myocardial performance index is regarded as a measure of global cardiac function (Tei *et al.* 1995). Special attention was given to the last parameter as it is independent of fetal heart rate and ventricular structure (Pellett *et al.* 2004). The advantage of all these parameters is that both sides of fetal heart can be assessed independently. In our study after careful evaluation we found no significant changes in all above mentioned parameters. Therefore, a direct impact of fenoterol on cardiac function was not observed. However, we found a report presenting a problem of fetal hypertrophic cardiomyopathy with severe impairment of right ventricle function. It was

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observed during the course of prolonged fenoterol maintenance (Hamela-Olkowska *et al.* 2012). Our observations, limited to 48 hours of tocolysis, revealed no alterations in any cardiac activity in the fetus.

We should remember about conflicting data reporting a possible influence of corticosteroids on fetal hemodynamic condition. Chitrit *et al.* (2000) recorded a significant decrease in fetal middle cerebral artery (MCA) impedance after maternal steroid therapy. Urban *et al.* (2005) reported significant decrease in MCA PI and CPR index after dexamethasone. Senat and Ville (2000) examined 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. They found no significant changes in Doppler measurements. Although some authors present data about changes in fetal arterial hemodynamics after maternal corticosteroids, most of those effects were observed after 72 hours from the administration of the first dose. Our research was focused on the period of the first 48 hours of tocolytic treatment. On the basis of our results we may assume that steroid administration did not interfere with placental circulation, fetal arterial and cardiac hemodynamic condition.

Evaluation of venous blood flow is an important part of complex fetal hemodynamic assessment. Szunyogh et al (2006) assessed ductus venosus flow velocity patterns during the first stage of labor. They found clear evidence that while mean S velocity was stable, the mean velocity, significantly decreased during uterine contractions. It resulted in higher mean values of S/a ratio in the presence of contractions. Their observation corresponded to our study's results, in which after 48 hours of successful tocolysis S/a ratio values were significantly lower. Another hemodynamic parameter, Peak velocity index for veins (PVIV), is regarded as a reliable and useful venous Doppler index (Hecher *et al.* 1995; Wong *et al.* 2010). A significant decrease of its value was observed in the absence of uterine contractions during the first stage of labor (Krapp et al 2002; Krapp *et al.* 2012). Therefore, we decided to assess this parameter in our research additionally. We expected to find a similar trend of PVIV values as Krapp *et al.* (2002). Surprisingly, our data showed significant increase of PVIV after 48 hours of fenoterol medication. Baschat et al (2004) analysed different venous Doppler parameters to predict acid-base status in growth restricted fetuses was measured. They concluded that DV PVIV provided a significant prediction of low umbilical artery pH value at birth. Wong et al (2010) assessed ductus venosus (DV) blood flow in pregnancies complicated by pre-existing diabetes mellitus. In such pregnancies fetal acidemia was caused by elevated fetal blood glucose level. According to Wong's *et al.* study, in 30.5% of examined fetuses, abnormal PVIV in ductus venosus was found. Additionally, authors reported better sensitivity for DV PVIV to predict adverse pregnancy outcomes. It is difficult to find an assured explanation for significant increase of PVIV after 48 hours of fenoterol medication in our study. We have not observed myocardial hypertrophy nor cardiac dysfunction in our study group. Both are present in the diabetic pregnancies. However we should remember that beta-adrenergic-receptor agonists elevate maternal blood glucose level, promote gluconeogenesis and glycolysis (Caldwell *et al.* 1987; Spellacy *et al.* 1978). We cannot exclude that transient maternal hyperglycemia after 48 hours of fenoterol tocolysis may have an influence on carbohydrate metabolism and result in abnormal PVIV index in ductus venosus. Additionally, maternal corticosteroids administration may interfere with those findings, intensifying the results.

In conclusion, short term intravenous administration of fenoterol seems not to alter uterine and fetal arterial blood flow pattern. Our study has also shown that direct cardiac function remained unaffected. However, evaluation of Doppler parameters revealed significant changes in ductus venosus; an increase in peak velocity index for veins and decrease in S/a ratio after 48 hours of fenoterol treatment. Further studies should be performed to assess more precisely fetal venous blood flow and clarify whether maternal corticosteroids administration may interfere with these results.

ACKNOWLEDGMENTS

Dr Grzesiak's research project NN 407017035 was supported by Polish Ministry of Science and Higher Education.

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