48-hours administration of fenoterol in spontaneous preterm labor – Does it affect fetal preload?

Mariusz Grzesiak [1,2], Sebastian Forys [3], Malgorzata Sobczak [4], Rehana B. Ahmed [5], 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 Outpatient Department of Obstetrics & Gynecology, "Polish Mother" Memorial Research Institute, Lodz, Poland
5 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

OBJECTIVE: to investigate whether any changes in the preload index (PLI) occur within the first 48 hours of fenoterol intravenous tocolysis.

MATERIAL AND METHODS: Doppler evaluation of placental and fetal circulation was performed in 36 pregnant women prior to fenoterol administration and after 24/48 hours. Measurements were obtained from a longitudinal section of the inferior vena cava (IVC) and preload index was calculated. To determine changes over time, an 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: The maternal heart rate values were significantly increased after 24 hours and 48 hours in comparison to pre-treatment values. No significant changes in fetal heart rate were observed during treatment. The fetal IVC PLI values were significantly reduced after 24 hours and 48 hours of treatment. The increase in PLI values when comparing 24 and 48 hours results were not statistically significant. These observations were consistent with ANOVA post-hoc analysis.

CONCLUSIONS: 48 hours intravenous administration of fenoterol appears not to alter inferior vena cava blood flow by itself. The reduction in PLI values may reflect lower fetal preload conditions during the course of successful tocolytic treatment. Therefore, Doppler IVC PLI measurement should be considered as a possible additional assessment method of effectiveness of treatment. However, other Doppler venous blood flow parameters should be assessed to confirm the results and clarify whether maternal corticosteroids administration may be interfering with the results.

ORIGINAL ARTICLE

INTRODUCTION

Preterm birth is one of the most current problems in obstetrics and neonatology (Pryde *et al.* 2001). Factually, it is the leading cause of neonatal mortality and morbidity (Di Renzo 2007). Unfortunately, neither detailed knowledge about possible risk factors and mechanisms underlying preterm labour, nor the growing number of new medical strategies results in reduction of reported rates (Goldenberg 2008). Preterm birth still remains very high; ranging from 12–13% in the USA to 5–9% in European countries (Slattery & Morrison 2002). Over the years we have been debating in regards to tocolytic medications. We have come a long way from prolonged use of tocolytic drugs, to the most recent policy, concerning short time interval administration. Present clinical strategies let us prolong pregnancy for at least 48 hours. This allows induction of fetal lung maturation by maternal administration of corticosteroids and if nesessary to transport pregnant women to tertiary care departments (Pryde *et al.* 2001).

When making decision about tocolytic therapy, it is essential to carefully consider possible benefits and adverse effects. Among many drugs, Beta-adrenergic Agonists have its pros and cons and are still to be used in preterm delivery prevention. Although Beta-adrenergic Agonists appear to be worrisome in regards to potential maternal and fetal side effects, in practice, they appear to be relatively safe if administered properly and cautiously in select group of patients (Pryde *et al.* 2001). Therefore, beta mimetic therapy limited to 48 hours parenteral administration is consistent with present treatment strategies. The β-mimetic, fenoterol is still one of the most commonly used tocolytic drugs in Germany and Poland (Schleussner *et al.* 2003). Among many publications, taking into consideration fenoterol's impact on the fetal circulatory system, there is no research in regards to fetal blood flow in the inferior vena cava. This finding encouraged us to investigate whether any changes in IVC occurred during parenteral therapy, within the first 48 hours of therapy.

MATERIAL AND METHODS

The study was conducted in the Department of Feto-Maternal Medicine, "Polish Mother" Memorial Research Institute, Lodz, Poland. The following admission criterion was established: patients with singleton pregnancy, between 24–34 weeks' gestation with intact membranes and showing evidence of premature labor. Premature labor was diagnosed as painful and persistent contractions (at least four contractions within 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 fenoterol 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, fenoterol medication was started in accordance to the drug characteristic medical protocol and our own clinical knowledge. The solution of one ampule Fenoterol Teva containing 500 micrograms of Fenoteroli hydrobromidum and 250 ml 5% glucose solution was prepared. Treatment was administered with an intravenous infusion rate of 2 micrograms/minute. Such 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 12 hours apart (NIH Consensus Development Panel 1995). Doppler examination was performed prior to fenoterol 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 investigationes were performed by the same operator (M.G.) and the measurements were collected in the absence of fetal body and breathing movements. The high-pas filter was set at 100 Hz. 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 insonation angle was established as close to 0 degrees as possible and never exceeded more than 30 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) (Axt-Fliedner *et al.* 2004; Kanzaki *et al.* 1990). 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 internal Research Ethics Committee approved the project. All patients participating in the study had given a signed informed consent to be used as subjects.

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. None of the patients delivered within 72 hours.

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 were no significant changes in maternal heart rate when comparing 24 and 48 hours results. Fetal heart rate was not altered significantly during treatment (0h/146.2±8.9 bpm vs. 24 h/145.1±10 bpm vs. 48h/149.3±10 bpm, $p>0.05$). The primary PLI values were (0.59±0.3) and were significantly reduced after 24 hours (0.42±0.2) and after 48 hours (0.47±0.2) of treatment. The increase in PLI values when comparing 24 and 48 hours results was not statistically significant (Figure 1). These observations were consistent with ANOVA post-hoc analysis. We did not observe the effect of gestational age and parity on the above results.

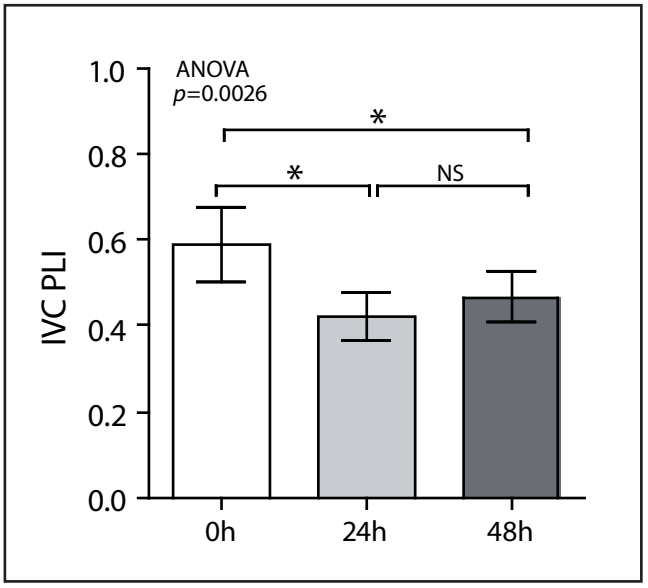

Fig. 1. Fetal Inferior Vena Cava Preload Index (IVC PLI) before and after (24/48hours) fenoterol treatment.

DISCUSSION

Longo *et al.* (1986) published an interesting issue regarding the correlation between uterine contractions and placental blood flow. They showed in an animal model research that uterine artery oxygen concentration is reduced in the presence of contractions and becomes normal after contractile resolution. Since then, new reports about increased resistance in the uteroplacental circulation that occurs during Braxton-Hicks's contractions and possible fetal hypoxia, hypercapnia and acidosis in the case of excessive uterine contractility have also been published (Bower *et al.* 1991; Greiss & Anderson 1968; Oosterhof *et al.* 1992). However, most of the data has been focused on the relationship between uterine contractions and fetal afterload. Kanzaki and Chiba (1990) introduced a new hemodynamic parameter named preload index (PLI). It is calculated as the ratio of reverse flow during atrial contraction to flow during ventricular systole and is considered as a marker of preload of the fetal heart. There are several reports about possible implementation of this parameter in obstetric practice. Ott (1999) reported usefulness of PLI in predicting poor neonatal outcome. Some publications apprehended the evaluation of fetal preload in the case of twin to twin transfusion syndrome (TTTS) (Takahashi *et al.* 2003; Utsu *et al.* 1999). Takahasi *et al.* (2003) focused on a group of healthy fetuses in the presence and absence of uterine contractions. Their observed findings, suggested that the PLI in the fetus inferior vena cava increased significantly during uterus contraction. As PLI expresses fetal preload, they proposed that uterine contractions are responsible for temporary increases in fetal preload condition. They suggested that contractions are responsible for transient pumping of the residual volume of oxygenated blood, from the placenta to the fetal circulatory system. This mechanism was presumed as physiological and seems to be an additional oxygen supply for the fetus. We were very interested in studying if this effect was observed in undergoing tocolysis with intravenous fenoterol. The patients reported significant decrease in the number and intensity of uterine contractions after 24 hours of the treatment. Such condition was persistent within next 24 hours. In our study, assessment of fetal blood flow in inferior vena cava was started before treatment and after 24 and 48 hours respectively. The highest PLI values were observed 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. The changes in hemodynamic conditions seem to support the hypothesis that uterine contractions increase fetal preload. When treatment is successful and proves beneficial effect in diminishing uterine contractions, fetal preload is reduced. PLI mean value after 48 hours was insignificantly higher than after 24 hours. However, these findings may suggest that the first 24 hours of fenoterol treatment is a key point for effective tocolysis. Engelhardt *et al.* (1997) presented evidence that fenoterol tocolysis resulted in selective down regulation of myometrial β-adrenoreceptors, without a reduction in their mRNA concentrations. Desensitization of receptors appears to be responsible for the limited therapeutic benefits. Therefore, higher doses of fenoterol in intravenous infusion are necessary for maintaining a prolonged tocolytic effect (Spätling *et al.* 1989). This is a possible explanation of why in our study, the differences between mean PLI value after 24 and 48 hours are insignificant. Baschat *et al.* (2004) analysed different venous Doppler parameters to predict acid-base status in growth restricted fetuses. They concluded that among many of evaluated venous blood flow parameters, only IVC peak velocity index for veins (PVIV) did not provide a significant prediction of low umbili-

cal artery pH value at birth. Rizzo *et al.* (1996) underlined the important role of IVC PLI index in such cases. They reported that preload index has a high efficacy comparing to other inferior vena cava or ductus venosus indices. Higher reproducibility of this index or an even more direct relationship between IVC blood flow patterns and fetal condition were presented as possible explanation of this finding. We should consider a possible influence of corticosteroids on fetal hemodynamic condition. Both, transient maternal hyperglycemia after 48 hours of fenoterol tocolysis and maternal corticosteroids administration, may influence fetal venous blood flow. Kähler *et al.* (2004) assessed Doppler measurements in fetoplacental circulation after maternal steroid administration. They reported only transient changes in umbilical artery and ductus arteriosus. No changes in venous blood flow was detected. Nozaki *et al.* (2009) observed the reduction in pulsatility index of umbilical artery and ductus venosus after maternal betamethasone administration. The changes were maintained up to 48 hours. However they did not examine the blood flow pattern in the inferior vena cava and their study group consisted of growth restricted fetuses.

48 hours intravenous administration of fenoterol appears not to alter inferior vena cava blood flow by itself. The reduction in PLI values may reflect lower fetal preload conditions in a course of successful tocolytic treatment. Therefore, Doppler IVC PLI measurement could be considered as possible additional assessment method of effectiveness of treatment. However, other Doppler venous blood flow parameters should be assessed to confirm these results and clarify whether maternal corticosteroid administration may interfere with these results.

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REFERENCES

1 Axt-Fliedner R, Wiegank U, Fetsch C, Friedrich M, Krapp M, Georg T, *et al.* (2004). Reference values of fetal ductus venosus, inferior vena cava and hepatic vein blood flow velocities and waveform indices during the second and third trimester of pregnancy. Arch Gynecol Obstet **270**: 46–55.
2 Baschat AA, Güclü S, Kush ML, Gembruch U, Weiner CP, Harman CR (2004). Venous Doppler in the prediction of acid-base status of growth-restricted fetuses with elevated placental blood flow resistance. Am J Obstet Gynecol **191**: 277–284.
3 Bower S, Campbell S, Vyas S, McGirr C (1991). Braxton-Hicks contractions can alter uteroplacental perfusion. Ultrasound Obstet Gynecol **1**: 46–49.
4 Di Renzo GC (2007). Safety and efficacy of new drugs in preterm labor. Expert Rev Obstet Gynecol **2**: 19–24.
5 Engelhardt S, Zieger W, Kassubek J, Michel MC, Lohse MJ, Brodde OE (1997). Tocolytic therapy with fenoterol induces selective down-regulation of beta-adrenergic receptors in human myometrium. J Clin Endocrinol Metab **82**: 1235–1242.
6 Goldenberg RL, Culhane JF, Iams JD, Romero R (2008). Epidemiology and causes of preterm birth. Lancet **371**: 75–84.
7 Greiss FC Jr, Anderson SG (1968). Uterine blood flow during labor. Clin Obstet Gynecol **11**: 96–109
8 Hincz P, Wilczynski J, Kozarzewski M, Szaflik K (2002). Two-step test: the combined use of fetal fibronectin and sonographic examination of the uterine cervix for prediction of preterm delivery in symptomatic patients. Acta Obstet Gynecol Scand **81**: 58–63.
9 Kanzaki T, Chiba Y (1990). Evaluation of the preload condition of the fetus by inferior vena caval blood flow pattern. Fetal Diagn Ther **5**: 168–174.
10 Kähler C, Schleussner E, Möller A, Seewald HJ (2004). Doppler measurements in fetoplacental vessels after maternal betamethasone administration. Fetal Diagn Ther **19**: 52–57.
11 Longo LD, Dale PS, Gilbert RD (1986). Uteroplacental 0_2 uptake: continuous measurements during uterine quiescence and contractions. Am J Physiol **250**: 1099–1109.
12 NIH Consensus Development Panel on the Effect of Corticosteroids for Maternal Maturation on Perinatal Outcomes (1995). Effect of corticosteroids for maternal maturation on perinatal outcomes. J Am Med Assoc **273**: 413–418.
13 Nozaki AM, Francisco RP, Fonseca ES, Miyadahira S, Zugaib M (2009). Fetal hemodynamic changes following maternal betamethasone administration in pregnancies with fetal growth restriction and absent end-diastolic flow in the umbilical artery. Acta Obstet Gynecol Scand **88**: 350–354.
14 Oosterhof H, Dijkstra K, Aarnoudse JG (1992). Uteroplacental Doppler velocimetry during Braxton Hicks' contractions. Gynecol Obstet Invest **34**: 155–158.
15 Ott WJ (1999). Value of inferior vena cava Doppler waveform analysis for prediction of neonatal outcome. Am J Perinatol **16**: 429–434.
16 Pryde PG, Besinger RE, Gianopoulos JG, Mittendorf R (2001). Adverse and beneficial effects of tocolytic therapy. Semin Perinatol **25**: 316–340.
17 Rizzo G, Capponi A, Talone PE, Arduini D, Romanini C (1996). Doppler indices from inferior vena cava and ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. Ultrasound Obstet Gynecol. **7**: 401–410.
18 Schleussner E, Möller A, Gross W, Kähler C, Möller U, Richter S *et al.* (2003). Maternal and fetal side effects of tocolysis using transdermal nitroglycerin or intravenous fenoterol combined with magnesium sulfate. Eur J Obstet Gynecol Reprod Biol **106**: 14–19.
19 Slattery MM, Morrison JJ (2002). Preterm delivery. Lancet **360**: 1489–1497.
20 Spätling L, Fallenstein F, Schneider H, Dancis J (1989). Bolus tocolysis: treatment of preterm labor with pulsatile administration of a beta-adrenergic agonist. Am J Obstet Gynecol. **160**: 713–717.
21 Takahashi Y, Iwagaki S, Nakagawa Y, Kawabata I, Tamaya T (2003). Uterine contractions increase fetal heart preload. Ultrasound Obstet Gynecol **22**: 53–56.
22 Utsu M, Hirai T, Yamamoto N, Maeda K (1999). Flow dynamics of placenta shunt vessels in monochorionic diamniotic twins. In: Margulies M, Voto US, Eik-Nes S, editors Proceedings of the 9th World Congress of Ultrasound in Obstetrics and Gynecology (ISUOG), 147–152.