Intramuscular fetal corticosteroid therapy short-term effect on maternal-fetal Doppler velocimetry

I. Babović[1], S. Plesinac[1], J. Opalić[1], I. Pilić[1], Z. Radojičić[2], M. Pervulov[1], N. Radunović[1], A. Ljubić[1]

[1]Institute for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade
[2]Faculty of Organizational Sciences, University of Belgrade, Institute for Statistics, Belgrade (Serbia)

Summary

Aim: The aim of the study was to assess the short-term effects of intramuscular (IM) corticosteroid therapy (CST) on fetoplacental and fetal circulation in high-risk pregnancies of preterm labor. *Method:* We evaluated the effect of IM fetal single-dose dexamethasone (4 mg/kg) on fetoplacental and fetal circulation two hours before and 0-4 hours after CST in 38 fetuses after the 32nd week of gestation. *Result:* Changes in the umbilical artery (UA) resistance index (RI) after fetal CST (AU RI1) were significantly correlated with gestational age after the 32nd week at recording r = 0.354; $p < 0.05$. There was a statistically significant difference of RI in the descending aorta (DAo) before and after therapy; $p < 0.001$ (-0.04-0.01), 95% confidence interval (CI) for differences. *Conclusion:* Short-time effects after fetal IM CST include an increased index resistance in DAO as well as decreased RI in UA after the 32nd week.

Key words: Fetal corticosteroid therapy; Fetoplacental; Fetal arterial velocimetry.

Introduction

Liggins [1] observed that fetal corticosteroid treatment trials resulted in early lung maturation in sheep. The pioneers of clinical trials, Liggins and Howie [2], documented that maternal antenatal corticosteroid treatment could decrease the incidence of respiratory distress syndrome in premature infants. Many studies have subsequently demonstrated that corticosteroids accelerate, in vitro and in vivo, the physiological, biochemical and morphological maturation of the fetal lung. Maternal administration of glucocorticoids has not been demonstrated specifically in intrauterine growth-restricted (IUGR) fetuses, whereas the use of antenatal glucocorticoid treatment has been widespread in this population, especially in cases of elective preterm delivery [3].

Knowledge of fetal hemodynamic effects of exogenous corticosteroids is limited. Sczabo and Cosmi [4] reported an 8-fold increase in relation to the initial value of fetal lung perfusion (by three-dimensional color power Doppler) which was observed within 10 min after fetal betamethasone injection of 0.5 mg/kg of estimated fetal weight. Cohlen *et al*. found, following antenatal betamethasone therapy, no significant change in the pulsatility index of any of the fetal blood vessels [5]. A new technique for artificial lung maturation – direct fetal IM CST was included very successfully in clinical practice by Ljubić *et al*. [6], but there is no information about its effect on fetal behavior. Betamethasone causes profound but transient suppression of fetal heart rate parameters, which can mimic fetal distress. Evaluating fetal wellbeing with Doppler waveform studies after direct fetal intramuscular administration is therefore important.

The aim of our study was to evaluate short-term effects (0-4 h), of direct fetal IM CST on the resistance index of the umbilical artery (UA RI), the middle cerebral artery (MCA RI), aortic isthmus (AI RI) and fetal descending aorta (DAo RI) .

Materials and Methods

Thirty-eight fetuses from singleton pregnancies after the 32nd week of menstrual age at risk of preterm delivery were prospectively included in the study at the Institute of Gynecology and Obstetrics, Clinical Center of Serbia, from June 2000 to June 2001. Gestational age was calculated according to the date of the last menstrual period and confirmed by first trimester ultrasound (US). If there was a discrepancy (more than five days), US was used to determine gestational age.

Preterm birth was anticipated on the basis of: 1. preterm contraction of the uterus (n = 20); 2. fetal intrauterine growth retardation (n = 11); 3. pregnancy-induced hypertension (n = 6); 4. preeclampsia (n = 4); and 5. premature rupture of membranes (n = 3).

We used a free-hand technique with Doppler mapping in order to avoid maternal and fetal blood vessels. An effective single dexamethasone dose of 4 mg (fetuses up to 1,750 g of estimated fetal weight were given 3 mg and those above that limit 4 mg) was administered directly to fetuses by transabdominal US-guided IM injection from 9 to 12 a.m. Fetal weight was estimated using Hadlock's method based on measurements of the fetal head, body and femur. The site of application was the fetal gluteal musculature. A 22-gauge needle was used. The mothers were sedated during intervention (by diazepam). There were no incidents during or after corticosteroid applications. All women except one received additional medications: Partusisten (n = 20), antihypertensive drugs (n = 10), aspirin (n = 11), and antibiotics (n = 3). Tocolytic agents, used to stop preterm contraction of the uterus, were introduced before the first Doppler examination and discontinued after the last evaluation. Fenoterol (Partusisten Boehringer-Ingleheim) was administrated via an infusion pump. The initial infusion was 0.5-1 μg/min, with the rate increasing when necessary every 30-60 min to a maximum of 3.0 μg/min. The Ethics Commitee (no. 1262/99) approved the protocol. Patients were enrolled in the

Revised manuscript accepted for publication March 25, 2009

Fig. 1

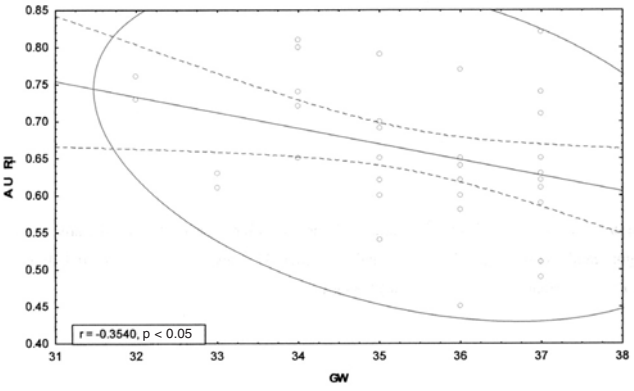

Fig. 2

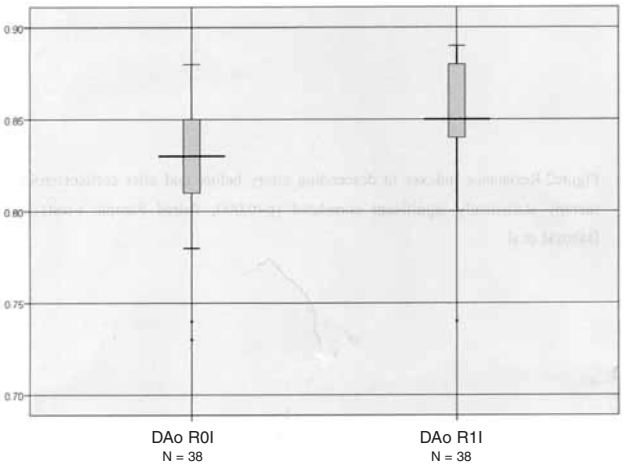

Figure 1. — Resistance indexes in the umbilical artery after corticosteroid therapy was significantly correlated with gestational age after the 32nd week at recording (r = 0.354; $p < 0.05$; Spearman's correlation test).

Figure 2: — Resistance indexes in the descending artery before and after corticosteroid therapy were statistically significantly correlated ($p < 0.001$); (Paired sample t-test).

study after informed consent had been obtained. Doppler examination was performed two hours before an IM corticosteroid therapy test (CST) and 0-4 h after therapy. A combined real-time pulsed Doppler system fitted with a 3.75 MHz curvilinear probe (Siemens) was used.The spatial peak temporal average power did not exceed 87 mW/cm. The Doppler angle of insonation was less than 30, sweep speed was 2.5 cm/s and pulse repetition frequency from 3.5 KHz to 5.0 KHz. The women rested in a semi-recumbent position during Doppler examination. All measurements were performed by the same physician during fetal apnea. Blood velocity waveforms were obtained from both the umbilical artery and fetal middle cerebral arteries. The umbilical artery was insonated close to its placental insertions and the middle cerebral artery about 1 cm distal to its origin from the internal carotid artery. The descending aorta (DAo) was insonated just below the aortic valve from frozen real time images during systole. Doppler recordings from the aortic isthmus, down-stream of the left subclavian artery and just upstream of the ductus artheriosus connection, were obtained in a sagital view simultaneously visualizing the aortic arch. We calculated the resistance index for each vessel by averaging the first two good quality resistance indexes obtained from two consecutive waveforms.

Multifetal pregnancies, intrauterine fetal demise, and suspected fetal congenital malformations were excluded from the study.

Continuous variables are presented as mean (standard deviation as 95% confidence intervals) assessed for normality or not, and comparisons were made using the paired sample t-test to estimated differences between the resistance index (RI) in the umbilical artery (UA RI), middle cerebral artery (CM RI), aortic isthmus (AI RI) and descending aorta (DAo) before and after fetal IM corticosteroid therapy. A probability value below 0.05 was considered statistically significant. Spearman's correlation test was used to compare gestational week at recording and indexes of resistance in the umbilical artery, middle cerebral artery, descending aorta and aortic isthmus.

Results

The mean age of all women participating in the study was 29.2 years. Of the study women 26.3% 10/38) were older than 35 years.The majority were nulliparas (60.5%, 23/38). In 24 (63.2%) pregnancies, a cesarean section was performed and 14 neonates were born vaginally. Mean neonatal weight was 2,591.54 ± 639.33 g and there were the same number of male and female neonates (50.0%, 19/38).

Mean gestational age at dexamethasone administration was 35.13 ± 1.99 weeks (min = 27 weeks, max = 35 weeks). Most of the fetuses were above the 32nd week of gestation (92.1%, 35/38).

The mean RI in the umbilical artery was 0.66 ± 0.08 before the direct fetal IM steroid therapy (UA RI0), and 0.64 ± 0.09 after the therapy (UA RI1). Changes in the umbilical artery RI (AU R1I) was significantly correlated with gestational age after the 32nd week at recording (r = 0.3540; $p < 0.05$) (Figure 1).

There was not a statistically significant difference between umbilical artery index resistance before or after direct fetal CST ($p = 0.625$; 95% CI).

The mean RI in the middle cerebral artery was 0.80 ± 0.08 before fetal dexamethasone therapy (CM RI0) and 0.77 ± 0.08 after the therapy (CM RI1). Changes in the middle cerebral artery RI (CM R1I) were not significantly correlated with gestational age after the 32nd week at recording (r = 0.074). The main RI in the aortic isthmus was 0.89 ± 0.03 before the fetal IM steroid therapy (AI RI0) and 0.90 ± 0.04 after the therapy (AI RI1). No significant changes were observed between the middle cerebral artery index before (MCA R0I) and after CST (MCA RI1) (95% CI), as well as between resistance indexes of the aortic isthmus before (AI RI0) and after therapy (AI RI1) (95% CI).

The mean RI in the descending artery was 0.83 ± 0.03 before the direct fetal IM steroid therapy (DAo RI0) and 0.85 ± 0.03 after the therapy (DAo RI1). There was a statistically significant difference of index resistance in the descending aorta before and after therapy ($p < 0.001$; 95% CI) (Figure 2).

Discussion

In the study 77.3% of women were younger than 35 years and the majority were nulliparas. The synthesis and secretion of surfactant are a complex sequence of biochemical events involving lipids. Specific enzymes included in metabolism of surfactant use glucose, phosphate, and fatty acids as substrates for phospholipids synthesis. These reactions are determinated by fetal oxygenation [7]. Hypertensive disease is a frequent indication for preterm delivery. Almost one-third of all pregnancies in our study were complicated by maternal hypertensive disorders. Corticosteroids might initiate hypertension in normotensive women and aggravate it in those with already elevated blood pressure. The 48-hour postponement of delivery required to complete antenatal CST may be unacceptable because of the maternal risk of preeclampsia that is aggravated by CST. Only healthy fetuses without US signs of fetoplacental insufficiency at the time of administration IM fetal CST were considered. In over twice the pregnancies cesarean section was performed.

Lemons and associates [8] reported that of approximately 70% of neonates who received antenatal corticosteroids, 50% were delivered by cesarean section. After the 29th week birth weight appeared to be a better predictor of survival than gestational age [9]. Mean neonatal birth weight was 2,600 g.

We found that the changes in the umbilical artery resistance index (AU R1I) were significantly correlated with gestational age after the 32nd week at recording. But IR in MCA was insignificantly correlated with gestational age after that. We were not able to define a gestational age after the 32nd week as an age window in which the effect of dexamethasone was significant.

There was no statistically significant difference between umbilical artery RI before or after direct fetal CST. As Urban *et al*. [10] reported, animal data have shown that dexamethasone in fetal sheep reduced fetal partial pressure of oxygen in arterial blood, suggestive of umbilical artery vasoconstriction.

We found a statistically significant difference between RI in the DAo before and after direct fetal CST. The pusatility index of DAo was the only one where the peripheral vascular resistance index did not correlate with fetal cardiac output. The constant PI may indicate that descending aortic flow is integral for fetal development and may remain at a relatively low vascular resistance. Chang *et al*. [11] reported that changes of cardiac output did not influence the vascular resistance. However glucocorticoids increase blood pressure and vascular resistance in human neonates, and similar changes are likely to occur in human fetuses, although these may not be reflected by changes in the flow velocity waveforms of the UA and MCA [10]. In UA and DAo the acceleration time changed with fetal heart rate.

There was no control group since we were unable to recruit mothers.

Conclusion

Short-term effects of direct fetal CST include increased index resistance in the DAo and decreased resistance indexes in the UA after the 32nd gestational week. The short-time effects of IM fetal CST could be modified by intrauterine hypoxia and additional medication.

References

[1] Liggins G.C.: "Preterm delivery of fetal lambs infused with glucocorticoids". *J. Endocrinol.,* 1969, *45*, 515.
[2] Liggins G.C., Howie R.N.A.: "A control trial of antepartum glucocorticoid treatment in prevention of the respiratory distress syndrome in premature infants". Pediatrics., 1972, *50,* 515.
[3] Wijnberger D., Bilardo C.M., Hecher K., Stigter R.H., Wisser G.H.A.: "Effect of antenatal glucocorticoid therapy on arterial and venous blood flow velocity waveforms in severely growth-restricted fetuses". *Ultrasound Obstet. Gynecol.,* 2004*, 23,* 584.
[4] Sczabo I., Cosmi E.V.: "New developments in antenatal steroid therapy: in uterus administration of corticosteroids directly to the fetus". *Prenat. Neonat. Med.,* 2001, *6* (suppl.), 60.
[5] Cohlen B.J., Stigter R.H., Derks J.B., Mulder E.J.H., Visser G.H.A.: "Absence of significant hemodynamic changes in the fetus allowing maternal beta-methasone administration". *Ultrasound Obstet. Gynaecol.,* 1996, *8,* 252.
[6] Ljubić A., Cvetković M., Šulović V., Radunović N., Antonović O., Vukolić D. *et al*.: "New technique for artificial lung maturation. Direct intramuscular fetal corticosteroid therapy". *Clin. Exp. Obstet. Gynecol.,* 1999, *26,* 16.
[7] Jobe A.: "Fetal lung development". In: Creasy R., Resnik R. (eds.) Maternal-Fetal Medicine. Principles and Practice. Philadelphia, Saunders, 2004, 213.
[8] Lemons J.A., Bauer C.R., Oh W., Korones S.B., Papile L.A., Stoll B.J. *et al*.: "Very low-birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996". *Pediatrics,* 2001, *107,* E1.
[9] Iams D.J., Creasy K.R.: "Preterm labor and delivery". In: Creasy R., Resnik R. (eds.). Maternal-Fetal Medicine. Principles and Practice Philadelphia. Saunders, 2004, 623.
[10] Urban R., Lemancewicz A., Przepiesc J., Urban J., Kretowska M.: "Antenatal corticosteroid therapy: a comparative study of dexamethasone and betamethasone effects on fetal Doppler velocity waveform". *Eur. J. Obstet. Gynaecol. Reprod. Biol.,* 2005, *120,* 170.
[11] Chang C.H., Chang F.M., Yu C.H., Liang R.L.: "Systematic assessment of fetal hemodynamics by Doppler ultrasound". *Ultrasound Med. Biol*., 2000, *26*, 777.

Address reprint requests to:
I. BABOVIC, M.D.
63/27 Luke Vojvodica Street
Belgrade (Serbia)
e-mail: ivana.r.babovic@gmail.com