Does corticosteroid therapy impact fetal pulmonary artery blood flow in women at risk for preterm birth?

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Abstract

Aim: Maternal corticosteroid administration in pregnancy is known to enhance fetal lung maturity in at risk fetuses. The aim of this study was to test the hypothesis that corticosteroid therapy alters fetal pulmonary blood flow in pregnancies at risk for preterm birth (PTB). **Material and methods:** We prospectively evaluated main fetal pulmonary artery (MPA) blood flow in pregnant women at risk for PTB and treated with corticosteroids (betamethasone), compared to an uncomplicated cohort without steroid therapy. The Doppler indices of interest included Peak Systolic Velocity (PSV), Resistive Index (RI), Pulsatility Index (PI), Systolic/Diastolic ratio (S/D ratio), Acceleration Time (AT), and Acceleration Time/Ejection Time Ratio (AT/ET ratio), with the latter serving as the primary outcomes due to its stability irrespective of gestational age. **Results:** When compared with controls, fetuses treated with corticosteroids demonstrated significantly decreased pulmonary artery acceleration time (median: 28.89 (22.22-51.11) vs. 33.33 (22.20-57.00), $p=0.006$), while all other indices remained similar. We found no difference in pulmonary blood flow between fetuses who developed respiratory distress syndrome (RDS) and those that did not (31.56 ± 6.842 vs. 32.36 ± 7.265 , $p=0.76$). **Conclusion:** Our data demonstrate altered fetal pulmonary blood flow with corticosteroid therapy, possibly due to increased arterial elastance brought on by medication effect, which leads to the decreased acceleration time or possible gestational age affect. Contrary to a recent report, we did not observe any Doppler differences in fetuses with RDS, which underscores the need for further examination of this proposed association.

Keywords: Fetal pulmonary artery Doppler, fetal lung maturity, corticosteroids, respiratory distress syndrome

Introduction

Premature delivery of a neonate carries with it a host of complications, including respiratory distress syndrome (RDS), pneumonia, infection, intraventricular hemorrhage (IVH), poor body temperature control, gastrointestinal problems (including necrotizing enterocolitis), and retinopathy of prematurity. Antenatal corti-

costeroid therapy has associated with improved neonatal outcomes, including a lower incidence of RDS in women at risk for preterm delivery [1-2]. Corticosteroids (such as betamethasone) administered antenatally increase production of surfactant in the lining of the fetal lungs, leading to reduced morbidity [3-5].

Fetal pulmonary artery Doppler has garnered increased attention of late. A recent study by Kim et al suggested that measurement of the fetal pulmonary artery blood flow is altered in fetuses that develop RDS at birth [1]. Indeed, Kim, along with other researchers [6], have suggested that pulse wave Doppler sampling of the fetal MPA could be used as a screening tool to help identify fetuses that are at a greater risk for developing RDS.

Consequently, our primary aim in this study was to estimate the impact of maternal corticosteroid adminis-

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tration on fetal pulmonary artery Doppler indices. Our secondary aim was to test the hypothesis that as suggested, there is a difference in pulmonary artery Doppler indices in fetuses that went on to develop RDS.

Material and methods

We conducted a prospective cohort study at one tertiary care center between 02/2013-10/2014. With respect to aim 1, we evaluated fetal pulmonary artery Doppler parameters in a cohort of 31 women at risk for preterm birth (cases) that received corticosteroids (betamethasone) for fetal pulmonary benefit, and compared them to a healthy referent cohort without corticosteroid therapy (n=43). For aim 2, within the cases, we compared the pulmonary artery Doppler indices between fetuses that went on to develop RDS (cases), and those that did not (referent). The examinations in the fetus corticosteroid group were made between 2-7 days following steroid administration, but not further out in order to capture the most immediate effect of the regimen. Institutional Review Board approval was obtained prior to data collection.

As part of routine ultrasound examinations we sampled the fetal pulmonary artery blood flow by pulse wave Doppler (GE Voluson E8 Expert). The pulse wave gate was set at 2 mm, and the angle of insonation was set between 0 and 15 degrees (angle correction was applied for angles other than 0). The pulse wave gate was placed distal to the pulmonary valve before the branching of the pulmonary arteries (fig 1). The sweep speed was increased to show adequate detail of the waveform for measurement of the time intervals (no more than five waveforms displayed). For measurement of the PSV, S/D ratio, PI and RI auto tracing was applied. If the trace did not meet our accuracy standards the manual trace option was utilized instead. Manual calipers were used for the time intervals with the dimensions set for measurement in milliseconds. The acceleration time was taken as the distance from the beginning of systole to peak systole and the ejection time was measured from the start of systole to the end of systole which is marked on the waveform (fig 2). From these two measurements the AT/ET ratio was calculated.

Maternal demographic and clinical information of interest were abstracted from the medical records. For the second aim of our study neonatal outcomes of interest (e.g. RDS) were abstracted from the neonatal medical records. RDS was defined as clinical findings of respiratory distress, and chest X-ray findings of a diffuse reticulogranular pattern with air bronchogram.

Data was analyzed using SPSS (version 20, IBM, Armonk, NY, USA). Descriptive statistics were used to examine the distribution of the data in each comparison group

Fig 1. Short-axis fetal heart image demonstrating optimal caliper placement. A: aorta, RA: right atrium, RV: right ventricle, PA: pulmonary artery.

Fig 2. Pulse-wave Doppler demonstrating acceleration (AT) and ejection time (ET).

for skewness, kurtosis, and normality of the distribution. Data were expressed as mean $\pm$ standard deviation for normally distributed data, and median with range otherwise. Mann-Whitney U test method was used for group comparisons. An alpha level of 0.05 was established for the study.

Using our pilot At/Et mean ratio of 0.24, we calculated a sample size of approximately 68 to provide approximately 95% power for detection of 20% difference between two equal-size groups (alpha 0.05).

Results

In the 75 women enrolled fetal pulmonary artery evaluation was successfully completed in all cases. The comparison groups were similar with respect to the gestational age at time of examination.

As presented in table I, fetuses from mothers treated with corticosteroids demonstrated significantly decreased pulmonary artery acceleration time compared to controls (median: 28.89 (22.22-51.11) vs. 33.33 (22.20-57.00), $p=0.006$), while all other indices were similar.

Among those fetuses exposed to corticosteroids, we found no statistical significant difference in pulmonary blood flow between fetuses who developed RDS and those that did not (table II). This relationship was not al-

Table I. Pulmonary artery Doppler indices in fetuses from mother that received steroid treatment compared to the control group (did not receive steroids).

Outcome Variable	Steroid group (n=31)	Control group (n=43)	p
PI	2.44 ± 0.31F	2.43 ± 0.34F	0.92
RI	0.91 (0.79 – 0.98)*	0.91 (0.77 – 1.17)*	0.39
S/D	11.05 (4.73 – 43.53)*	10.84 (4.41 – 31.52)*	0.22
PSV	68.61 (38.96 – 98.59)*	63.02 (48.11 – 107.12)*	0.79
AT	28.89 (22.22 – 51.11)*	33.33 (22.20 – 57.00)*	0.006
AT/ET	0.24 ± 0.05F	0.21 ± 0.04F	0.25
EFW	1378.50 (678.00 – 2454.00)*	1645.00 (587.00 – 3370.00)*	0.07
GA	30 (24 – 34)*	30 (24 – 39)*	0.47

F Denotes mean + standard deviation; * Denotes median with range (in parenthesis); PI: Pulsatility index; RI: Resistive index; S/D: Systolic/diastolic ratio; PSV: Peak systolic velocity; AT: Acceleration time; AT/ET: Acceleration time/ejection time ratio; EFW: estimated fetal weight; GA: Gestational age at time of pulmonary artery examination

Table II. Pulmonary artery Doppler indices in fetuses that subsequently did or did not develop respiratory distress syndrome (RDS).

Outcome Variable	RDS group (n=13)	No RDS (n=18)	p
PI	2.43 ± 0.34F	2.41 ± 0.23 F	0.90
RI	0.91 (0.77 – 1.17)*	0.91 (0.90 – 0.97)*	0.60
S/D	10.84 (4.41 – 31.52)*	11.09 (9.63 – 29.52)*	0.71
PSV	63.02 (48.11 – 107.12)*	62.44 (38.96 – 94.81)*	0.25
AT	33.33 (22.22 – 57.00)*	28.89 (24.44 – 50.00)*	0.53
AT/ET	0.21 ± 0.04 F	0.23 ± 0.05 F	0.90
EFW	1645 (587 – 3370)*	1005 (698 – 2283)*	0.28
GA	30 (24 – 39)*	28 (26 – 33)*	0.11

F Denotes mean + standard deviation; * Denotes median with range (in parenthesis); PI: Pulsatility index; RI: Resistive index; S/D: Systolic/diastolic ratio; PSV: Peak systolic velocity; AT: Acceleration time; AT/ET: Acceleration time/ejection time ratio; EFW: estimated fetal weight; GA: Gestational age at time of pulmonary artery examination

tered by controlling for time to delivery from examination; however, we must caution that this might be due to the small sample size.

Discussions

In this study, we set out to 1) estimate the impact of corticosteroid therapy of fetal PA indices, and 2) replicate findings by Kim et al that suggested altered PA Doppler indices in fetuses who went on to develop RDS [1]. While our data demonstrated decreased acceleration time following steroid administration, we did not see any other Doppler indicates. Furthermore, we did not observe any Doppler differences in fetuses that went on to develop RDS.

Our finding of altered fetal pulmonary blood flow (decreased acceleration time) with corticosteroid therapy is possibly due to increased arterial elastance brought on by medication effect, which could lead to the decreased acceleration time or possibly due to gestational age affect [7]. All other parameters were unaltered in the treated group. In our review of the literature we found many dif-

ferent approaches to assessment of fetal pulmonary blood flow (measurements, gate placement, sweep speed, etc). Even among those with similar approaches the findings are not consistent [8,9]. Studies that did not include At/Et ratio have been excluded from the discussion. Fuke et al demonstrated that the At/Et ratio for pulmonary blood flow is consistent throughout gestation (20 – 39 weeks), although they sampled the pulmonary branches rather than the main pulmonary artery [9]. They found a reduced At/Et ratio in six fetuses that died from complication of pulmonary hypoplasia. Contrary to Fuke et al, Chaoui et al found, while also examining the pulmonary artery branches, that the At/Et ratio increases with advancing gestational age [8]. They state that the increasing value of the At/Et ratio reflects decreasing pulmonary resistance normal to advancing gestation. This statement is contrary to Kim et al who claimed that an increased At/Et ratio was seen in association with RDS [1] (in which the fetus would have increased pulmonary resistance). Azpurua et al demonstrated an inverse relationship between amniocentesis derived lecithin/sphingomyelin ratio and main pulmonary artery Doppler At/Et ratio [6]. However,

their study only had 29 participants and only one of the neonates developed RDS. That fetus had an At/Et ratio of 0.29 which would have been considered normal by Kim et al [1]. Considering the disparate findings above, further study is certainly warranted.

Contrary to the recent report by Kim et al [1], we did not observe any Doppler differences in fetuses that developed RDS. The discordance in the two studies may be due to a variation in study population or details of the ultrasound measurements and equipment. Both studies (ours and Kim et al) have relatively small sample sizes. Although our sample size was twice the size of Kim et al [1] (37 mothers) only 31 of our mothers received steroids. The effect of differing sonographic measurements and equipment may also be contributing to this discordance. Though we reviewed the methods described by Kim et al [1] in order to replicate the measurements, there is an obvious difference in the acceleration times recorded between the two studies (Kim et al ave. AT 42 – 92ms vs. our study 25 – 39ms). This difference also produced a discrepancy in the At/Et ratio between the two studies. All other parameters, however, were comparable. The acceleration time from the study by Kim et al may be overestimated due to suboptimal sweep speed which does not allow for accurate assessment of time intervals. The sweep speed should be increased to show no more than 5 or 6 waveforms to show adequate detail of the waveform for these types of assessments. Lastly, Kim et al only included women who delivered within 72 hours of ultrasound examination [1] whereas our Doppler samples were acquired any time after 24 weeks gestation and were included in the study even if the fetus was delivered more than 72 hours after the examination.

Our study has some limitations which merit further discussion. First, the sample size was small, and was based on detecting a difference in At/Et, which was our primary aim. Therefore, any interpretation of the examination of the RDS research question (aim 2) may be inherently affected by this limitation. Second, we measured the pulmonary flow before the branching of the pulmonary arteries, and indeed this does not represent the full pulmonary flow as most of the volume is directed toward the descending aorta. However, given the inherent inconsistencies (and non-reproducibility of obtaining measurements in the right branch), coupled with the need to find a non-invasive/sonographic predictive tool, we feel that measurements of the main trunk suffice. Lastly, in some cases, delivery of the fetus occurred weeks after ultrasound measurements were taken which may place some limitations on the utility of the measurement. It could be worthwhile to repeat the study with a larger sample size of premature infants (including a larger sample of those

who developed RDS and those that did not) excluding those who delivered more than a certain interval after ultrasound measurement.

Conclusions

Our data demonstrate altered fetal pulmonary blood flow with corticosteroid therapy, possibly due to increased arterial elastance brought on by medication effect, which leads to the decreased acceleration time [7]. Contrary to a recent report [1], we did not observe any Doppler differences in fetuses with RDS, which underscores the need for further examination of this proposed association. If pulse wave measurement of fetal pulmonary blood flow is to be of any predictive clinical utility, further studies will be needed to demonstrate a reliable association.

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