Reactivity of the Human Fetal Pulmonary Circulation to Maternal Hyperoxygenation Increases During the Second Half of Pregnancy

A Randomized Study

Juha Rasanen, MD; Dennis C. Wood, RDMS; Robert H. Debbs, DO; Jose Cohen, MD; Stuart Weiner, MD; James C. Huhta, MD

Background—The aims of the present study were to determine whether maternal hyperoxygenation affects human fetal pulmonary circulation and whether there is a gestational age-related response in the fetal pulmonary circulation to maternal hyperoxygenation during the second half of gestation.

Methods and Results—Twenty women between 20 and 26 weeks of gestation and 20 women between 31 and 36 weeks of gestation with normal singleton pregnancies were randomized to receive either 60% humidified oxygen or medical compressed air (room air) by a face mask. Fetal aortic and pulmonary valve; ductus arteriosus (DA); and right (RPA), left (LPA), and distal (DPA) pulmonary artery blood velocity waveforms were obtained by Doppler ultrasound before, during, and after maternal administration of either 60% oxygen or room air. Left and right ventricular cardiac outputs, DA volume blood flow, and RPA and LPA volume blood flows (Qp) were calculated. Foramen ovale volume blood flow (left ventricular cardiac output − Qp) was estimated. Pulsatility index (PI) values of DA, RPA, LPA, and DPA were calculated. Maternal hyperoxygenation did not change any of the measured fetal parameters between 20 and 26 weeks, whereas between 31 and 36 weeks, the PI values of RPA, LPA, and DPA decreased (P < .0001) and the PI of DA increased (P < .0001). In addition, Qp increased (P < .001), and DA volume blood flow (P < .01) and foramen ovale volume blood flow (P < .03) decreased. Left and right ventricular cardiac outputs were unchanged. All changes returned to baseline after maternal hyperoxygenation was discontinued.

Conclusions—Reactivity of the human fetal pulmonary circulation to maternal hyperoxygenation increases with advancing gestation; this suggests that fetal pulmonary circulation is under acquired vasoconstriction at least after 31 to 36 weeks of gestation. (Circulation. 1998;97:257-262.)

Key Words: blood flow • echocardiography • hemodynamics • oxygen • physiology
Methods

Forty women with uncomplicated singleton pregnancies were included in this randomized study, which was approved by the Research Review Committee of our institution. Before the study, each patient signed a written informed consent form. Each fetus was appropriate for gestational age in size (between 10th and 90th percentile growth curve) according to fetal biometry. Fetal standard anatomic survey did not reveal any abnormalities, and all the newborns were normal on the basis of physical examination.

Twenty fetuses were studied between 20 and 26 weeks of gestation, and 20 fetuses were studied between 31 and 36 weeks of gestation. Image-directed pulsed and color Doppler equipment (Acuson 128XP) with a 5-MHz sector probe was used to obtain blood velocity waveforms at the level of the AoV and PV, proximal RPA and LPA (immediately after the bifurcation of the main pulmonary artery), DPA (beyond the first bifurcation of the branch pulmonary artery), and DA. The lowest high-pass filter level was used (100 Hz), and the spatial peak temporal average power output for color and pulsed Doppler was kept at <100 mW/cm². An angle of ≤15° between the vessel and Doppler beam as assessed by color Doppler was accepted for later analysis. After the baseline Doppler study, randomization was performed with the use of sealed envelopes. Ten patients received medical compressed air (room air) and 10 patients received 60% humidified oxygen via face mask in each gestational age group. Room air and 60% oxygen, which were delivered from the wall units, were humidified oxygen via face mask in each gestational age group. Room air groups (n=20), and the correlation between two independent RVCO calculations (blood flow across the PV and the sum of QdA and QdL) was established at three different study points.

Statistical comparison of the measured parameters within the group between three different study points was performed by one-way ANOVA for repeated measurements, and if statistical significance was reached, further analysis was made with the Fisher PLSD test. Comparisons between different groups were done with Student’s t test. A value of P<.05 was selected as the level of statistical significance.

Results

Between 20 and 26 weeks of gestation, the mean gestational age was 23.5 weeks in the oxygen group (group I; n=10) and 22.7 weeks in the room air group (group II; n=10). Between 31 and 36 weeks of gestation, the mean gestational age was 33.6 weeks in the oxygen group (group III; n=10) and 33.4 weeks in the room air group (group IV; n=10). The gestational ages did not differ significantly between groups I and II or between groups III and IV.

The baseline values of the measured parameters did not differ significantly between groups I and II or groups III and IV. FHRs remained unchanged in all the groups during the study period. The PI values of RPA, LPA, DPA, and DA did not change significantly in groups I and II during the study period (Fig 1). On the other hand, in group III, the PI values of RPA, LPA, and DPA decreased significantly (P<.0001) during maternal hyperoxygenation (Figs 2 and 3). The mean Doppler tracings, we calculated FHR (bpm) and TVI (cm). The TVI calculation, which is considered to be a measure of the length of the column of ejected blood, was performed by planimetry of the area underneath the Doppler spectrum. Three consecutive cardiac cycles were analyzed, and their mean value was used for further analysis. The AoV and PV annuli, DA, RPA, and LPA diameters were measured from frozen real-time images during systole by using the leading edge–to–leading edge method. Three separate measurements of the vessel diameters were made, and the mean values were calculated. Calculation of the CSA (cm²) of the vessel was based on the assumption that the cross-sections of the vessels were circular. Volumetric blood flow at the level of the AoV, PV, DA, RPA, and LPA was assessed by using the formula Q=TVI×CSA×RVCO. The volume blood flow through AoV equals RVCO, and the volume blood flow through PV equals RVCO. Total Qd is the sum of the RPA and LPA volume blood flows. QdA was estimated by subtracting QdL from RVCO. The PI values of DA, RPA, LPA, and DPA were calculated [|peak systolic velocity–end-diastolic velocity|/mean velocity during the cardiac cycle]. All the Doppler measurements were done during fetal apnea and in the absence of fetal body movements.

To analyze the intraobserver reproducibility of the Doppler measurements, room air groups (n=20) were combined. We calculated the correlation and intraobserver variability of the measurements, expressed as difference (in percent) between the three study points. To test the validity of the volume blood flow assessment, all the groups were combined (n=40), and the correlation between two independent RVCO calculations (blood flow across the PV and the sum of QdA and QdL) was established at three different study points.

Selected Abbreviations and Acronyms

AoV = aortic valve  
CSA = cross-sectional area  
DA = ductus arteriosus  
DPA = distal pulmonary artery  
FHR = fetal heart rate  
LPA = left pulmonary artery  
LVCO = left ventricular cardiac output  
PI = pulsatility index  
PV = pulmonary valve  
QdA = ductus arteriosus volume blood flow  
QdL = foramen ovale volume blood flow  
QdL = pulmonary volume blood flow  
RPA = right pulmonary artery  
RVCO = right ventricular cardiac output  
TVI = time-velocity integral
decrease in the PI values was 18.0% from the baseline value for RPA, 19.6% for LPA, and 21.2% for DPA (see Fig 7). At the same time, the PI value of DA increased significantly (P<.0001) (Figs 2 and 3). The mean increase was 14.4% from the baseline values (see Fig 7). After maternal hyperoxygenation was discontinued, all PI values returned to the baseline level (Figs 2 and 3). In group IV, the PI values of RPA, LPA, DPA, and DA remained unchanged throughout the study period (Fig 2).

CSAs and TVIs of AoV, PV, DA, RPA, and LPA in different groups are presented in Tables 1 and 2. In groups I and II, LVCO, RVCO, QDA, and QP did not change significantly during the study period (Fig 4). In group III, maternal hyperoxygenation increased QP significantly (P<.001) and decreased QDA significantly (P<.01) (Figs 3 and 5). The mean increase in the QP was 24.5% from the baseline value, and the mean decrease in the QDA was 17.1% (Fig 7). One fetus at 36 weeks of gestation developed a reverse (from the aorta to the pulmonary artery) diastolic blood flow in the DA during maternal hyperoxygenation. All these changes returned to the baseline values (see Fig 7). After maternal hyperoxygenation was discontinued, pulmonary arterial vascular impedance decreased and QP increased significantly. After maternal hyperoxygenation was discontinued, pulmonary arterial impedance increased and QP decreased to the baseline level. Invasive lamb studies have demonstrated that in late gestation, the increase in the fetal oxygen tension decreases pulmonary vascular resistance and increases QP, whereas the effects of decreased fetal oxygen tension are the opposite. However, the fetal lamb pulmonary vascular bed does not react to changes in oxygen tension in the beginning of the last trimester of pregnancy. The findings of this study support the concept that in the human fetus, the reactivity of the pulmonary arterial circulation to changes in oxygen tension in the beginning of the last trimester of pregnancy is different compared with study II.†,‡,§

In the combined room air group (group II plus group IV), the PI values and volumetric blood flow calculations did not change significantly during the study period. The intraobserver variability was <4% for PI values and <9% for volumetric blood flow calculations. The correlation between different study points was significant for PI values (P<.0001), with correlation coefficient values of ≥.96. Two independent RVCO calculations (n=40) demonstrated a significant correlation at every study point with an R value of ≥.95 (P<.0001).

Discussion

Maternal hyperoxygenation with 60% oxygen did not affect the human fetal pulmonary arterial vascular impedance and Qp between 20 and 26 weeks of gestation, whereas between 31 and 36 weeks of gestation, the pulmonary arterial vascular impedance decreased and Qp increased significantly. After maternal hyperoxygenation was discontinued, pulmonary arterial impedance increased and Qp decreased to the baseline level. Invasive lamb studies have demonstrated that in late gestation, the increase in the fetal oxygen tension decreases pulmonary vascular resistance and increases Qp, whereas the effects of decreased fetal oxygen tension are the opposite. However, the fetal lamb pulmonary vascular bed does not react to changes in oxygen tension in the beginning of the last trimester of pregnancy. The findings of this study support the concept that in the human fetus, the reactivity of the pulmonary arterial bed to changes in the fetal oxygen tension develops after 21 to 26 weeks of gestation and is detectable by noninvasive Doppler ultrasound techniques between 31 and 36 weeks of gestation. Our results show that the human fetal pulmonary circulation is under acquired vasoconstriction at least after 31 to 36 weeks of gestation, and in this way blood flow is directed from the pulmonary circulation to the systemic circulation. Fetal oxygen tension has a role in the regulation of the pulmonary circulation and the distribution of fetal cardiac output during the latter part of the third trimester. In this study, DPA and proximal pulmonary arteries showed a similar decrease in the PI values during maternal hyperoxygenation, suggesting that the two sampling sites give the same information about the pulmonary vascular reactivity. The development of the reactivity of the pulmonary arterial circulation to oxygen with advancing gestation has been explained by an increasing amount of smooth muscle in small pulmonary
TABLE 1. CSAs of AoV and PV, DA, and RPA and LPA in Different Study Groups During the Baseline Study

<table>
<thead>
<tr>
<th>Group</th>
<th>CSA, cm²</th>
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<th>CSA, cm²</th>
<th>Group</th>
<th>CSA, cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>AoV</td>
<td>0.15±0.03</td>
<td>Group II</td>
<td>0.12±0.02</td>
<td>Group III</td>
<td>0.40±0.09</td>
<td>Group IV</td>
<td>0.39±0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV</td>
<td>0.19±0.06</td>
<td></td>
<td>0.15±0.03</td>
<td></td>
<td>0.52±0.08</td>
<td></td>
<td>0.56±0.09</td>
<td></td>
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</tr>
<tr>
<td>DA</td>
<td>0.08±0.02</td>
<td></td>
<td>0.07±0.01</td>
<td></td>
<td>0.20±0.04</td>
<td></td>
<td>0.20±0.02</td>
<td></td>
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<tr>
<td>RPA</td>
<td>0.05±0.01</td>
<td></td>
<td>0.04±0.01</td>
<td></td>
<td>0.14±0.03</td>
<td></td>
<td>0.15±0.01</td>
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</tr>
<tr>
<td>LPA</td>
<td>0.05±0.01</td>
<td></td>
<td>0.04±0.01</td>
<td></td>
<td>0.14±0.03</td>
<td></td>
<td>0.15±0.01</td>
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</tbody>
</table>

Values are mean±SD.

Maternal administration of 60% humidified oxygen (group I, 20 to 26 weeks of gestation; group II, 20 to 26 weeks of gestation; group III, 31 to 36 weeks of gestation) and room air (group I, 20 to 26 weeks of gestation; group IV, 31 to 36 weeks of gestation). CSAs of all the vessels are significantly greater (P<.0001) in groups III and IV than in groups I and II.

TABLE 2. TVIs of AoV and PV, DA, and RPA and LPA in Different Study Groups During the Baseline Study

<table>
<thead>
<tr>
<th>Group</th>
<th>TVI, cm</th>
<th>Group</th>
<th>TVI, cm</th>
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<th>TVI, cm</th>
<th>Group</th>
<th>TVI, cm</th>
<th>Group</th>
<th>TVI, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>AoV</td>
<td>8.1±1.2</td>
<td>Group II</td>
<td>8.2±0.7</td>
<td>Group III</td>
<td>11.9±2.1</td>
<td>Group IV</td>
<td>10.7±1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV</td>
<td>8.3±1.0</td>
<td></td>
<td>7.4±0.5</td>
<td></td>
<td>11.1±0.8</td>
<td></td>
<td>10.3±0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA</td>
<td>12.5±1.1</td>
<td></td>
<td>11.3±1.5</td>
<td></td>
<td>19.7±3.5</td>
<td></td>
<td>19.0±6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPA</td>
<td>7.3±1.0</td>
<td></td>
<td>7.0±0.7</td>
<td></td>
<td>8.6±1.8</td>
<td></td>
<td>8.7±1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPA</td>
<td>6.9±0.7</td>
<td></td>
<td>7.0±1.2</td>
<td></td>
<td>8.6±1.4</td>
<td></td>
<td>8.5±1.2</td>
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</tr>
</tbody>
</table>

Maternal administration of 60% humidified oxygen (group I, 20 to 26 weeks of gestation; group II, 20 to 26 weeks of gestation; group III, 31 to 36 weeks of gestation; group IV, 31 to 36 weeks of gestation). TVIs of all the vessels are significantly greater (P<.001) in groups III and IV than in groups I and II. Values are mean±SD.

Maternal administration of 60% humidified oxygen (group I, 20 to 26 weeks of gestation; group II, 20 to 26 weeks of gestation; group III, 31 to 36 weeks of gestation) and room air (group II, 20 to 26 weeks of gestation; group IV, 31 to 36 weeks of gestation). CSAs of all the vessels are significantly greater (P<.0001) in groups III and IV than in groups I and II. Values are mean±SD.

The decrease in the pulmonary vascular resistance is mainly caused by the release of endothelium-derived nitric oxide, which leads to vasodilatation of the pulmonary arterial bed.7

The decrease in the pulmonary vascular impedance and the increase in the Qp by maternal hyperoxygenation between 31 and 36 weeks of gestation was accompanied by opposite changes in the fetal DA. The PI values increased and the QDA decreased significantly; all these changes returned to the baseline values after maternal hyperoxygenation was discontinued. The decrease in the DA PI has been associated with the constriction of the DA, and the increase in the DA PI has been found in the cases with increased RVCO.10 This study shows that the changes in the DA PI may also reflect fetal pulmonary vascular impedance. The decrease in the pulmonary vascular impedance directs blood flow from the systemic circulation to the pulmonary circulation; mainly, this affects the diastolic flow component in the DA by decreasing it or even reversing the direction of the blood flow during diastole. This leads to increased PI in the DA because the end-diastolic velocity and the mean velocity during the cardiac cycle decrease. Under normal circumstances, the direction of the blood flow in the human fetal DA during the diastole is from the pulmonary artery to the aorta. This study supports previous animal data3,5,6 that the increase in the Qp and the decrease in the pulmonary vascular impedance during maternal hyperoxygenation are not caused by the constriction of the DA. In the presence of the ductal constriction, peak systolic, end-diastolic, and mean velocities across the DA are increased in the human fetus, leading to decreased PI value. Our findings also agree with the results of Burchell et al,11 who found in children and adults with patent DA and pulmonary hypertension that breathing of a low oxygen mixture either initiated or increased the blood flow from the pulmonary artery to the aorta and that breathing of 100% oxygen caused opposite changes.

During maternal hyperoxygenation, both the RVCO and LVCO remained unchanged. Rizzo et al12 found that maternal hyperoxycarbonation with 60% oxygen between 34 and 36 weeks of gestation did not affect the TVIs of the mitral and tricuspid valves, suggesting that the RVCO and LVCO remained unchanged. Maternal hyperoxygenation at 31 to 36 weeks of gestation causes redistribution of the RVCO from the systemic circulation to the pulmonary circulation. Morin et al13 found in fetal lambs that at near-term gestation, maternal hyperoxygenation decreased the proportion of RVCO distributed to the organs of the lower body and placenta without changing the RVCO.

Blood flow across the foramen ovale is technically very difficult to measure directly. However, we can indirectly estimate the QFO by subtracting the Qp from the LVCO. Our findings suggest that the QFO decreases during maternal hyperoxygenation at 31 to 36 weeks of gestation because the Qp decreases significantly without any change in the RVCO. In fetal lambs, the QFO decreases by an average of 50% during maternal hyperbaric oxygenation at near-term gestation.3

Immediately after birth, pulmonary vascular resistance decreases and Qp increases. The increase in the alveolar oxygen tension with the beginning of breathing is an important factor in this process.11 At least between 31 and 36 weeks of gestation, we can simulate by maternal hyperoxygenation the changes in the central hemodynamics occurring after birth. We speculate that this noninvasive technique may allow us to estimate...
prenatally whether the changes in the fetal pulmonary circulation will occur in a normal fashion during the postnatal period. Before the acquisition of increasing pulmonary vascular reactivity, the pulmonary blood velocity pattern should be useful for assessing fetal lung development and may be a tool for the assessment of lung hypoplasia. After the acquisition of pulmonary vascular reactivity, we speculate that fetuses with lung hypoplasia do not demonstrate similar vasodilatation in the pulmonary circulation as seen in normal fetuses during maternal hyperoxygenation.

Theoretically, one limitation of this study is that maternal physiological responses to oxygen may be different late in pregnancy and other factors, in addition to fetal hyperoxygenation, could have a role in the changes in human fetal central hemodynamics during maternal hyperoxygenation.

Maternal hyperoxygenation with 50% oxygen for 5 minutes increased maternal transcervaneous oxygen partial pressure about threefold. After 5 minutes of maternal hyperoxygenation with 100% oxygen, intervillous space oxygen tension rose from the baseline values. Transcutaneously measured fetal oxygen partial pressure has been found to increase during maternal hyperoxygenation. In addition, maternal administration of 55% humidified oxygen has been shown through fetal umbilical cord blood sampling to increase human fetal oxygen partial pressure. Based on these findings, our study protocol was sufficient to demonstrate the effects of increased fetal oxygen tension on fetal central hemodynamics.

This study, in which half of the patients were randomized to receive room air and the investigator who performed the Doppler ultrasound studies was unaware of the randomization, allows us to evaluate the methodological limitations related to both the calculation of vascular impedance and volume blood flow. In the combined room air group, all the measured parameters remained unchanged between the three study points. PI values are angle independent, and the variability among the PI calculations between different study points was the least, being <4%. In addition, the calculations of the volume blood flows showed good repeatability, and the intraobserver variability was <9%. Volume blood flow measurements based on Doppler ultrasound have been demonstrated to be valid in in vitro animal studies as well as in in vitro studies. The human fetal cardiac output measurements at the level of atrioventricular and semilunar valves have been shown to correlate significantly. To minimize the methodological problems related to volume blood flow calculations, the angle between the vessel and the Doppler beam was kept at ⩽15° as assessed by color Doppler and the vessel diameters were measured by using the well-established leading edge–to–leading edge technique. In the study of Kenny et al, the correlation coefficient between two observers for pulmonary arterial and aortic diameters was 0.98. Reed et al showed that maximal velocity tracings across cardiac valves could be obtained with a variation of <10%. To test the validity of the volume blood flow calculations, we correlated two independent RVCOs (blood flow across PV and QP) and showed a good correlation between these two independent calculations. These findings with previously published studies confirm that measurement of vascular impedance and calculation of the volumetric blood flow can be done accurately in the human fetus during the second half of gestation with the use of current ultrasound technology.

In conclusion, this study demonstrates that maternal hyperoxygenation decreases human fetal pulmonary arterial vascular resistance.
impedance and increases $Q_p$ between 31 and 36 weeks of gestation. Earlier in pregnancy, between 20 and 26 weeks of gestation, maternal hyperoxygenation does not alter human fetal pulmonary circulation. This finding shows that the reactivity of the human fetal pulmonary circulation to oxygen develops between these two study periods and that oxygen tension in the fetus has a role in the regulation of the fetal pulmonary circulation. During the latter part of the third trimester, the human fetal pulmonary arterial bed is under acquired vasoconstriction, directing RVCO from the pulmonary circulation to the systemic circulation. Maternal hyperoxygenation, at least between 31 and 36 weeks of gestation, mimics the changes in the fetal central hemodynamics that occur after birth. Finally, all the changes in the fetal central hemodynamics returned to baseline level after maternal hyperoxygenation was discontinued.

References

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