Acute Cardiovascular Effects of Fetal Surgery in the Human

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Background—Prenatal surgery for congenital anomalies can prevent fetal demise or alter the course of organ development, resulting in a more favorable condition at birth. The indications for fetal surgery continue to expand, yet little is known about the acute sequelae of fetal surgery on the human cardiovascular system.

Methods and Results—Echocardiography was used to evaluate the heart before, during, and early after fetal surgery for congenital anomalies, including repair of myelomeningocele (MMC, n=51), resection of intrathoracic masses (ITM, n=15), tracheal occlusion for congenital diaphragmatic hernia (CDH, n=13), and resection of sacroccygeal teratoma (SCT, n=4). Fetuses with MMC all had normal cardiovascular systems entering into fetal surgery, whereas those with ITM, CDH, and SCT all exhibited secondary cardiovascular sequelae of the anomaly present. At fetal surgery, heart rate increased acutely, and combined cardiac output diminished at the time of fetal incision for all groups including those with MMC, which suggests diminished stroke volume. Ventricular dysfunction and valvular dysfunction were identified in all groups, as was acute constriction of the ductus arteriosus. Fetuses with ITM and SCT had the most significant changes at surgery.

Conclusions—Acute cardiovascular changes take place during fetal surgery that are likely a consequence of the physiology of the anomaly and the general effects of surgical stress, tocolytic agents, and anesthesia. Echocardiographic monitoring during fetal surgery is an important adjunct in the management of these patients. (Circulation. 2004;110:1549-1556.)

Key Words: fetus ■ pregnancy ■ cardiac output ■ surgery

Fetal surgery is emerging as a viable clinical option for addressing congenital anomalies.1-13 Surgery before birth can be immediately life saving for the fetus at risk, or it may alter the course of organ system development, resulting in a more favorable condition after birth.

Promising results have been achieved with fetal surgery for a variety of congenital lesions. Surgical removal of an intrathoracic lung mass, such as congenital cystic adenomatoid malformation (CCAM), leads to resolution of hydrops fetalis and subsequent survival.3,4 Resection of giant sacroccygeal teratoma (SCT) in utero eliminates volume load and heart failure, with resolution of hydrops and survival.5-7 Occlusion of the tracheal airway to achieve lung growth in cases of fetal congenital diaphragmatic hernia (CDH) has been attempted in the fetus, albeit with mixed results.8,9 Recently, in utero repair of myelomeningocele (MMC) has been performed with the goal of protecting developing neural elements from potential trauma of exposure to the intrauterine environment.10,11 Although MMC is not a life-threatening anomaly, fetal MMC repair may reduce the need for ventriculoperitoneal shunt placement to treat hydrocephalus and potentially improve long-term neurological function.12,13

The techniques of fetal surgery and strategies for care of the fetus undergoing surgical intervention continue to evolve. Little is known about the acute consequences of these interventions on the fetal cardiovascular system. Anomalies such as large CCAM14 and SCT5-7 exert primary deleterious effects on the fetal cardiovascular system, with anticipated improvement after fetal surgery. However, other anomalies such as MMC have no direct impact on fetal heart structure or function.

We have systematically performed serial fetal echocardiography in our patients undergoing fetal surgery, with a focus on direct intraoperative echocardiography and early follow-up. In the present study, we report on the cardiovascular sequelae of fetal surgery and anesthesia for congenital anomalies in the human fetus.

Methods

Patients

Between February 1996 and November 2002, 83 fetuses underwent fetal surgery (Table 1). Mean gestational age at surgery was 23±3 weeks; mean estimated weight was 680±228 g. The types of fetal surgery and indications included the following: (1) repair of MMC in

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Continuous intraoperative echocardiographic imaging during fetal surgery commences after maternal abdominal incision and exposure of the uterus through hysterotomy, fetal incision, and until suture closure of the uterus. Using a sterile technique, a plastic sleeve is filled with ultrasound gel and a 7.5-MHz probe inserted within and secured with rubber bands. The probe is positioned on the exposed uterine wall and maneuvered for optimal image quality and angle of interrogation for Doppler echocardiography. Parameters are assessed in a sequential looping manner whenever possible, with a full set of data acquired approximately every 3 to 4 minutes.

Data Analysis
Permission for data review was obtained from the Committee for Human Research of the Institutional Review Board at The Children’s Hospital of Philadelphia. Heart rate and CO were compared at the following time intervals: (1) interval #1: preoperatively, within 1 week of surgery; (2) interval #2: intraoperatively, after hysterotomy; (3) interval #3: intraoperatively, at fetal incision; and (4) interval #4: postoperatively, within 12 hours after surgery. CO was calculated as CO (mL·min⁻¹·kg⁻¹) = (1/2) × d³ × 3.14 × VTI × HR, where d = semilunar valve annular diameter, VTI = velocity-time integral, and HR = heart rate in beats per minute. HR and VTI tracings were used for serial measures only if at least 2 minutes of hemodynamic stability was present. The average of 3 to 5 beats for VTi was used. Right and left ventricular CO was summed for the combined cardiac output (CCO).

In addition, the following parameters were also recorded: (1) preoperatively, (2) intraoperatively, (3) early after surgery (<24 hours), and (4) late after surgery (>24 hours): (1) ventricular systolic dysfunction, defined as left ventricular shortening fraction <25% on 2D imaging; (2) atrioventricular valve insufficiency, graded as none, mild (grade 1), or greater than mild/mild hemodynamic importance (grade 2), defined as color Doppler regurgitant jet area ≥30% of atrial area; (3) ductal constriction, defined as narrowing noted on 2D imaging with Doppler pulsatility index <2; and (4) sustained bradycardia, defined as heart rate <80 bpm for ≥10 beats.

Values are recorded as mean and SD. Ten fetuses were randomly chosen for assessment of intraobserver and interobserver variability of data by 2 readers (JR, ZYT), each blinded to the other’s interpretation. Patients were categorized on the basis of the anomaly present. Wilcoxon signed-rank test was used for paired data when values were compared with the baseline preoperative values at different time intervals. Mann-Whitney rank sum test was used for unpaired analysis of data between groups with different diagnoses. Comparisons of categorial data were made between the different types of anomalies by χ² test. P < 0.05 was considered significant.

Results
Of the 83 fetuses, serial CO measures could not be calculated in 11 (12.5%; 7 MMC, 2 ITM, and 2 CDH) because of inadequate windows. In the ITM group, 8 fetuses died intraoperatively or within 24 hours of surgery; hence, postoperative data were available for 7.

Heart Rate and CO
Table 2 lists the mean and SD values for heart rate and CO. In all groups, heart rate increased at time #2 and #3 compared with time #1 and remained elevated or returned to baseline at time #4.

Compared with the MMC group, CCO before surgery was lower for the ITM (P < 0.05) and CDH (P < 0.01) groups and higher for the SCT group (P < 0.01). CCO decreased in the MMC, ITM, and CDH groups from time #1 to time #2 (P < 0.01), with a further decrease at time #3. There was a marked decrease in CCO from time #2 to #3, after resection of the SCT (P < 0.001). CCO was decreased for the MMC group at time #4 compared with time #1 (P < 0.01).

### Table 1. Types of Fetal Surgery Anomalies

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC</td>
<td>51</td>
</tr>
<tr>
<td>ITM mass</td>
<td>15</td>
</tr>
<tr>
<td>Right-sided CCAM</td>
<td>7</td>
</tr>
<tr>
<td>Left-sided CCAM</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary fibrosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Extralobar bronchopulmonary sequestration</td>
<td>1</td>
</tr>
<tr>
<td>CDH</td>
<td>13</td>
</tr>
<tr>
<td>Left sided</td>
<td>12</td>
</tr>
<tr>
<td>Right sided</td>
<td>1</td>
</tr>
<tr>
<td>SCT</td>
<td>4</td>
</tr>
</tbody>
</table>

### Technique and Anesthesia for Fetal Surgery

The techniques used to perform fetal surgery are described elsewhere.1–8,12 Patients are admitted before the operation for obstetrical monitoring and initiation of tocolysis (indomethacin 50 mg 1 to 2 doses every 6 hours). An epidural catheter for regional anesthesia is inserted in 1 of the lower lumbar interspaces. Thiopental (4 to 5 mg/kg) and succinylcholine (2 mg/kg) are given intravenously, and the trachea is intubated. Desflurane or isoflurane is used to provide maintenance anesthesia. Initially, 0.5 MAC (mean alveolar concentration) of inhaled anesthesia is used. Oxygen and nitrous oxide are provided in a 1:1 ratio. Muscle relaxation is augmented with 2 to 3 mg/kg of vecuronium intravenously. Before incision, the inhaled agent is increased to 2 MAC to optimize uterine relaxation.16 Mean blood pressure is preserved with incremental doses of ephedrine or phenylephrine as needed. Just before uterine incision, the mother is placed on 100% oxygen. With exposure, the fetus is injected with 20 mg/kg fentanyl, and 200 μg/kg vecuronium intramuscularly.

Depending on the surgical procedure planned, fetal intravenous access is established such that packed red blood cells or saline can be given intravenously. After closure of the uterus, the mother is given 6 g of magnesium sulfate intravenously with continuous infusion at 2 g/h for 24 to 48 hours. The epidural catheter is incrementally dosed with 0.25% bupivacaine with 1:200 000 epinephrine to a maximum of 20 mL. Neostigmine (5 mg) and glycopyrrolate (0.6 mg) are given to reverse neuromuscular blockade at the end of the procedure. Indomethacin is continued as a 50-mg rectal suppository every 6 hours for 24 hours, then 25 mg orally every 6 hours for a total of 48 hours.

### Echocardiography Protocol

Fetal echocardiography is performed before surgery, intraoperatively, and after surgery with a Siemens Acuson Sequoia ultrasongraph. Images are recorded on 0.5-inch VHS tape for review.

All fetuses undergo a detailed fetal echocardiographic evaluation before consideration for surgery to rule out the presence of congenital heart disease and to perform morphometric measurements for estimation of fetal weight. Aortic and pulmonic annulus diameters are measured in systole. Doppler interrogation is performed at the level of the aortic and pulmonic valves, and the velocity-time integral is recorded for purposes of calculation of cardiac output (CO).17 Heart rate is determined by the time interval from the onset of flow between consecutive beats.
Bradycardia was seen in every group intraoperatively and not at any other time period. It occurred intraoperatively in 8% of MMC (4/51), 67% of ITM (10/15), 15% of CDH (2/13), and 50% of SCT (2/4) patients.

### Intraobserver and Interobserver Variability

Intraobserver and interobserver variability in CO measures were <5% and <10%, respectively. There was no difference between the readers in categorical determination of ventricular dysfunction, ductal constriction, or grade of valvular regurgitation.

### Discussion

The diagnosis and treatment of congenital anomalies before birth is evolving as a new form of medical care. The benefit of fetal intervention lies in the ability to treat pathological processes at an early stage of development, thereby preventing fetal demise or arresting the progression of disease to a more deleterious and difficult-to-treat state. Our understanding of the condition of the cardiovascular system during fetal surgery has been theoretical and derived primarily from animal models. This study is the first report on cardiovascular findings noted during human fetal surgery. By observing the cardiovascular system with echocardiography, we have identified derangements in a variety of parameters, including heart rate, CO, ventricular function, valvar function, and ductal patency.

The present study reports on fetal surgery for a variety of congenital anomalies. In MMC, the cardiovascular system is normal; hence, these fetuses act as a control for observation of the general effects of surgery and anesthesia.
on the normal cardiovascular system. The other anomalies studied all exert secondary effects on the fetal cardiovascular system. Alterations in diastolic filling properties and tamponade physiology exist before surgery in the fetus with ITM and CCAM, which may explain the development of hydrops. Mechanical compression and impaired filling of the left ventricle occur in CDH. Volume overload, ventricular dilation, and high-output failure are...
the hallmarks of the fetus with SCT.\textsuperscript{5–7,22} The cardiovascular findings we observed during surgery reflect the summation of the effects of surgery, tocolytics, and anesthesia on the fetus, as well as any change in the primary lesion as a consequence of the operation.

Marked changes were seen in the MMC group, fetuses with a normal cardiovascular system. Heart rate increased and CCO decreased at fetal incision, which suggests diminished stroke volume. Depressed systolic ventricular function and atrioventricular valve insufficiency develop...
oped at fetal incision, with improvement after surgery. Although mild TR can normally be seen in the fetus, mitral regurgitation is not a normal finding.23 In the MMC group, both TR and mitral regurgitation developed during surgery.

These findings suggest impaired myocardial performance during the process of fetal surgery. Inhalational anesthesia provided to the mother is a likely cause. Relatively high levels of isoflurane or Desflurane at MAC=2.0 are necessary to provide an appropriate degree of uterine relaxation. At these levels, maternal CO can drop, with diminution in uterine blood flow of up to 30%.24 Diminished uterine blood flow results in decreased oxygen delivery to the utero-placental unit and subsequent fetal hypoxia.25 In the acutely instrumented fetal sheep, halothane has been shown to increase placental and total vascular resistance, potentially limiting gas exchange and adding undue afterload on the fetal heart.26 Owing to altered characteristics of myocardial compliance, the fetal heart tolerates an acute increase in afterload poorly compared with the postnatal heart.27 Hence, fetal hypoxia, altered afterload, or perhaps a direct anesthetic myocardial depressant effect can all contribute to the decrease in CO, altered systolic function, and valvar dysfunction identified. Unfortunately, these explanations are only speculative, because most of the investigational work done to date has been in the animal model, with little done in the human fetus.

Rudolph28 demonstrated that the fetal response to hypoxia is bradycardia. Although an increase in heart rate was typically seen at fetal incision in the present study, periodic episodes of profound bradycardia were identified in each group, even those undergoing MMC repair. In addition to the physiological effects of the agents administered, mechanical compression of the umbilical cord or uterine vasculature may also be the cause.29 Tension applied to the fetus through a small operative-field incision in the uterus can result in umbilical cord compression, leading to hypoxia. When bradycardia is identified in our MMC cases, we temporarily cease manipulation in the operative field, change umbilical cord position, and increase uterine fluid replacement via level I, with a resultant increase in heart rate.

The cardiovascular findings identified in the non-MMC fetuses in the present study reflect a combination of effects. Fetuses with ITM were the sickest of all the groups at the time of surgery. Hydrops was present with diminution of uterine blood flow of up to 30%.24 Diminished uterine blood flow results in decreased oxygen delivery to the utero-placental unit and subsequent fetal hypoxia.25 In the acutely instrumented fetal sheep, halothane has been shown to increase placental and total vascular resistance, potentially limiting gas exchange and adding undue afterload on the fetal heart.26 Owing to altered characteristics of myocardial compliance, the fetal heart tolerates an acute increase in afterload poorly compared with the postnatal heart.27 Hence, fetal hypoxia, altered afterload, or perhaps a direct anesthetic myocardial depressant effect can all contribute to the decrease in CO, altered systolic function, and valvar dysfunction identified. Unfortunately, these explanations are only speculative, because most of the investigational work done to date has been in the animal model, with little done in the human fetus.

Figure 5. Autopsy specimen of heart of fetus delivered prematurely 4 days after fetal surgical resection of giant SCT. Transection cut is through ventricles. Before surgery, fetus had dilated ventricular cavities with marked cardiomegaly. Note abnormal geometry of thickened ventricular walls and small cavity volume, as a consequence of acute volume reduction.
This is because left ventricular filling volume is diminished in the fetus with CDH owing to compression of the left ventricle, impaired right-to-left shunting at the atrial level, and limited pulmonary venous return as a consequence of pulmonary hypoplasia. Fetuses with SCT exhibit unique physiological changes at the time of surgery. Before surgery, the fetal heart is faced with the consequences of a giant arteriovenous malformation: increased preload and afterload that encompasses the combined vascular resistances of the fetal body, placenta, and low resistance mass. As a result, the heart attempts to compensate by ventricular dilation and hypertrophy. At the time of fetal resection, new conditions are imposed, with an acute reduction in preload and a massive increase in afterload as the low-resistance tumor is eliminated from the vascular circuit. As myocardial mass remains acutely unchanged, an alteration in ventricular geometry with reduction in cavity size and increase in myocardial wall thickness takes place (Figure 5). This geometry can lead acutely to diastolic dysfunction, which may resolve with time as remodeling takes place.

Ductal constriction is seen intraoperatively in all groups. Often, acute progressive reduction in ductal caliber and an increase in velocity were directly visualized during the course of the operation. Ductal constriction was most commonly seen intraoperatively, even though indomethacin treatment continued for 2 days after surgery. Intraoperative administration of indomethacin in combination with supplemental oxygen, both of which are potent constrictors of the ductus arteriosus, may contribute to this phenomenon. It is also conceivable that operative stressors or the anesthetic agents used may act as potentiators of the constrictive effects of indomethacin during surgery. No relationship was identified between the frequency of ductal constriction and the presence, or severity, of TR either during or after surgery.

In summary, echocardiographic monitoring of the heart during fetal surgery demonstrates that important hemodynamic derangements are common. If not looked for, these findings are missed. Cardiovascular phenomena during surgery may need to be considered as a variable when one examines studies of long-term outcome in these patients. In our experience, this level of echocardiographic surveillance impacts greatly on intraoperative management and can potentially contribute to improved overall outcome. As the field continues to advance, our understanding of the effects of stress and anesthetics during fetal surgery in the human will lead to improved techniques and reduced cardiovascular morbidity. Much of what is learned from these noncardiac anomalies may ultimately be applied to fetal interventions for congenital heart anomalies in the future.

References
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