Fetal Therapy

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The ultimate goal for prenatal diagnosis is treatment of the affected fetus to correct the defect. For many disorders it is unlikely that effective corrective or preventative therapy will be developed in the foreseeable future. Furthermore, in at least some metabolic disorders, irreversible fetal damage may have occurred by the time the prenatal diagnosis is made. It is possible, however, to outline therapeutic alternatives for the management of a number of fetal disorders that can be recognized in utero.

Most correctable malformations that can be diagnosed in utero are best managed by appropriate medical or surgical therapy after delivery at term. The full-term infant is better able than the prematurely delivered infant to tolerate surgery and anesthesia. Prenatal diagnosis may be important because many anomalies are associated with an excess of amniotic fluid, which may initiate premature labor. Therapy for the excess amniotic fluid or premature labor may allow the fetus to remain in utero longer and be born at term. Additionally, the delivery can be planned so that the necessary neonatologists, anesthesiologists, and pediatric surgeons are available.

There is a subset of fetal anomalies that requires correction ex utero as soon as possible after the diagnosis is made. For these, the risk of prematurity must be weighed against the risk of continued gestation. The principle in each case is that continued gestation would have progressive ill effects on the fetus.

Another subset of fetal disorders may influence the mode of delivery and require that a cesarean section be performed. One indication for cesarean delivery is an anomaly such that the fetus could not fit through the maternal pelvis during vaginal delivery. Occasionally, an elective cesarean section may be indicated for a malformation requiring immediate surgical correction in a sterile environment. Occasionally, infants are delivered who are at risk for a severe immunodeficiency state that would cause them to be unable to withstand infections. Such infants have been delivered by elective cesarean section to protect their sterility.

IN UTERO INTERVENTION

There is a subset of fetal deficiency states that may be alleviated by in utero treatment. These are conditions in which something vital to fetal well-being is not
present in sufficient quantity, and supplementation of the missing element would constitute medical therapy. The simplest method of supplying the fetus is to give the missing element to the mother and allow it to be transported across the placenta to the fetus. Two fetuses have been diagnosed in utero as having vitamin-dependent enzyme deficiencies and have been treated before birth. The first had a vitamin-B_{12}-responsive enzyme disorder (methylmalonic acidemia) (1), and the second had a biotin-dependent disorder (multiple carboxylase deficiency) (2). Each was treated by giving the mother massive doses of the required vitamin. Both of these children are developing normally, albeit taking huge daily supplements of the necessary vitamin. Another example of medicating the fetus via the mother has been the successful treatment of fetal heart rhythm irregularities by giving the mother digitalis. The digitalis crosses the placenta to the fetus and has returned the fetal heart rate to a normal pattern.

The list of substances that will be given therapeutically to the fetus in utero is certain to grow. For example, it may be possible to treat intrauterine growth retardation, in which a normal fetus is not receiving sufficient nutrition, by instilling nutrients into the amniotic sac. Scientists are investigating enzyme therapy for enzyme deficient children. If such techniques can be developed, supplying the missing enzyme to the fetus in utero would represent only one further technical step, and might prevent an irreversible collection and storage of the enzyme substrate.

SURGICAL FETAL THERAPY

The complement of medical therapy is, of course, surgical therapy. Correcting an anatomic malformation will be more difficult than providing a missing substrate, hormone, or medication to the fetus. The prenatally diagnosable anatomic malformations that warrant consideration for surgical therapy are those that interfere with fetal organ development and, if alleviated, would allow normal fetal development to proceed. The first malformations that I shall consider are (a) hydronephrosis secondary to an obstruction, (b) diaphragmatic hernia, and (c) hydrocephalus.

URINARY TRACT OBSTRUCTION

Obstructive fetal urinary tract malformations are being recognized with increasing frequency because fluid-filled masses are particularly easy to detect by sonography. Retained fetal urine may cause a large distended bladder (megacystis), fluid-filled ureters (hydroureters), and fluid accumulation in the kidneys (hydronephrosis). The increased fluid and back pressure interfere with fetal kidney development and may cause sufficient kidney damage to be incompatible with postnatal life. The lack of fetal urine excretion secondarily causes a decrease in the volume of amniotic fluid. The decreased amniotic fluid is associated with underdevelopment of the lungs. The severity of the damage depends on the degree and duration of the urinary outflow obstruction.
It has been observed that failure to take action often leads to the delivery at term of an infant who has neither sufficient functioning kidney tissue or lung capacity to survive. Therefore, the philosophy has developed that it may be advisable to relieve the obstruction at the earliest possible time (3). The concept is that continued obstruction will result in a kidney with such impaired development that survival is impossible, whereas relief of the obstruction may allow sufficient development to support postnatal life and allow “catch-up” development during early childhood.

A thorough ultrasonographic evaluation is the key factor in the management of fetal urinary obstruction. Identification of fetal urinary tract dilatation is not uncommon, especially prior to 24 weeks of gestation. However, this dilatation does not, by itself, reflect an obstruction compromising renal function. It is important to separate these entities from each other. The amount of amniotic fluid is very important. If an adequate amount of amniotic fluid is evident on ultrasound, it signifies reasonable fetal renal function and usually assures adequate pulmonary development. Oligohydramnios, on the other hand, signifies fetal urinary tract obstruction. It is imperative that a thorough sonographic evaluation be performed to rule out any additional significant anomaly or disease. A fetal karyotype should be done, because chromosomal abnormalities have been associated with urinary tract abnormalities and obstruction (4).

FETAL RENAL ASSESSMENT

In utero decompression of fetal hydronephrosis or early delivery for ex utero decompression is only beneficial for fetuses whose kidneys have not already suffered irreversible damage. Appropriate counseling and management, therefore, require accurate assessment of renal function, to allow selection of pregnancies likely to benefit from therapeutic intervention.

Renal dysplasia, defined as abnormal parenchymal development secondary to anomalous differentiation of mesonephric tissue, implies irreversible renal damage (5). The functional capacity of an affected kidney depends upon the extent and severity of the dysplasia. Cortical cysts are often, but not necessarily, present. Extensive cortical dysplasia makes unlikely any beneficial effect of decompression of urinary tract obstruction.

SONOGRAPHIC EVALUATION OF RENAL DYSPLASIA

Dysplastic kidneys are associated with renal cortical cysts and increased echogenicity. In our experience (6), visible cortical cysts have a sensitivity of 44% and specificity of 100% in predicting renal dysplasia. Increased echogenicity has a sensitivity of 57% and specificity of 89%. The severity of hydronephrosis is least predictive, with a sensitivity of 35% and specificity of 78%. The demonstration of renal cortical cysts has the highest predictive value for dysplasia among fetuses with obstructive uropathy. Among 34 kidneys with dysplasia, all 15 with sonographically
TABLE 1. Prognostic criteria for fetal bilateral urinary tract obstruction

<table>
<thead>
<tr>
<th>Predicted function</th>
<th>Sonographic appearance of kidneys</th>
<th>Initial amniotic fluid status</th>
<th>Fetal urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>Echogenic/cystic</td>
<td>Moderate to severely decreased</td>
<td>Na (mEq/ml) &gt;100  Cl (mEq/ml) &gt;90  Osmolarity (mosm/l) &gt;210</td>
</tr>
<tr>
<td>Good</td>
<td>Normal/echogenic</td>
<td>Normal to moderately decreased</td>
<td>&lt;100  &lt;90  &lt;210</td>
</tr>
</tbody>
</table>

visible cortical cysts were also highly echogenic. Ten other kidneys were echogenic without demonstrable cysts, however, and an additional nine dysplastic kidneys had neither sonographically visible cysts nor increased echogenicity. Thus, visualization of a kidney without demonstrable cysts or increased echogenicity does not exclude dysplasia.

BIOCHEMICAL AND PHYSIOLOGICAL EVALUATION

Because sonography is not able to identify all dysplastic kidneys and therefore cannot distinguish accurately those fetuses with bilateral urinary tract obstruction that can benefit from decompression from those that cannot, biochemical studies have been considered. Fetal urine is produced by the 13th gestational week and is an ultrafiltrate of fetal serum made hypotonic by selective tubular absorption of Na and Cl (7). In our retrospective experience (8) fetuses with hypotonic urine were later found to have good renal function, whereas those with isotonic urine were found to have poor function. Based on these results, prognostic criteria for identifying the fetuses with good function or with poor function have been generated (Table 1).

The most difficult problem in the management of the fetus with urinary tract obstruction has been the selection of the fetus that might benefit from in utero treatment. Study of the natural history of untreated obstruction has shown that the fetus with unilateral obstruction and the fetus with mild bilateral obstruction and normal amniotic fluid volume do not require in utero therapy (9). Also, the fetus that presents with severe oligohydramnios and severe dysplastic kidney changes seen by sonography is unlikely to benefit from in utero therapy (5). Between these extremes there is a gray zone where potentially fatal renal and pulmonary damage may be averted by intervention. Assessment of the functional potential of the obstructed fetal urinary tract has proven difficult. Indirect methods, such as sonographic determination of bladder filling and emptying (10) or stimulation of urine production by furosemide (11) have proven unreliable. The development of the prognostic criteria given above that predict the potential for recovery has greatly simplified counseling of families and the selection of appropriate management.
MANAGEMENT OF FETAL URINARY TRACT OBSTRUCTION

Patients who are referred for evaluation undergo a thorough real-time ultrasound examination. If other life-threatening abnormalities are identified, we counsel the parents about these findings and their significance. Most couples, at this time, elect to proceed with pregnancy termination.

If ultrasonography reveals no evidence of additional anomalies, the amount of amniotic fluid becomes the deciding factor in our management scheme. There are instances of hydramnios and dilated urinary tract systems, most often associated with unilateral obstruction. If the amniotic fluid volume is normal, the nature of the obstruction becomes paramount. Uncomplicated unilateral obstruction with a normal amniotic fluid volume does not warrant interventive decompression (10).

For bilateral urinary tract obstruction with normal amniotic fluid volumes, we do not recommend invasive intervention. If the hydronephrosis is sufficiently severe we accelerate pulmonary maturity with betamethasone and proceed with delivery between 32 and 34 weeks gestation by the vaginal route, unless cesarean section is dictated by other obstetric indications. Of some concern are two neonates who died of pulmonary hypoplasia with associated urinary tract obstruction yet had "adequate" amniotic fluid volumes throughout pregnancy. We have also reported cases in which the obstruction actually resolved with expectant management, and term deliveries resulted with normal neonatal urinary and pulmonary function (9).

Therapy for urinary tract obstruction is reserved for cases that demonstrate isolated bilateral urinary tract obstruction with oligohydramnios. We start with needle aspiration of the fetal bladder to determine the osmolarity of the urine and its Na and Cl concentrations, thus separating dysplastic kidneys from the nondysplastic ones. Patients whose fetuses have severe oligohydramnios and severe renal dysplasia are offered the options of early termination of the pregnancy or nonintervention.

<table>
<thead>
<tr>
<th>Primary diagnosis*</th>
<th>No. of cases</th>
<th>% of total</th>
<th>No. of survivors</th>
<th>% Survival by diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior urethral valve syndrome</td>
<td>25</td>
<td>28.7%</td>
<td>17</td>
<td>68%</td>
</tr>
<tr>
<td>Karyotype abnormality</td>
<td>7</td>
<td>8%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Renal dysplasia by ultrasound</td>
<td>6</td>
<td>6.9%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Urethral atresia</td>
<td>6</td>
<td>6.9%</td>
<td>1</td>
<td>17%</td>
</tr>
<tr>
<td>&quot;Prune belly&quot; syndrome</td>
<td>5</td>
<td>5.7%</td>
<td>1</td>
<td>20%</td>
</tr>
<tr>
<td>Uretero-pelvic obstruction</td>
<td>2</td>
<td>2.3%</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>36</td>
<td>41.3%</td>
<td>11</td>
<td>30.6%</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>100%</td>
<td>32</td>
<td>40.2%</td>
</tr>
</tbody>
</table>

* Primary diagnosis as confirmed by either antenatal or neonatal assessment or autopsy.

** Elective pregnancy termination.

Data from the International Registry, 1986, by Dr. Frank Manning, Winnipeg, Canada (with permission).
TABLE 3. Presentation, open surgery management, and outcome of pregnancies with fetal obstructive uropathy

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Maternal history</th>
<th>Ultrasound findings</th>
<th>Urine Na, Cl, Osm/Chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 y o, G-1, P-0 Oligohydramnios persisted 15 wk., Presented at 19 wk. C/S at 35 wk.</td>
<td>Bilateral fetal hydronephrosis. Megacystis, dilated bladder neck; renal parenchyma: increased echogenicity</td>
<td>Na 99 mEq/l Cl 84 mEq/l Osm 235 46,XY</td>
</tr>
<tr>
<td>2</td>
<td>31 y o, G-1, P-0 Oligohydramnios pt normal for 9 wk.</td>
<td>Bilateral fetal hydronephrosis. Megacystis, dilated bladder neck</td>
<td>Na 88 mEq/l Cl 83 mEq/l Osm 255</td>
</tr>
<tr>
<td>3</td>
<td>19 y o, G-1, P-0 Oligohydramnios AF normal for 11 wk. Presented at 22 wk.</td>
<td>Bilateral fetal hydronephrosis. Megacystis; renal parenchyma: normal</td>
<td>Na 79 mEq/l Cl 71 mEq/l Osm 160 46,XX</td>
</tr>
<tr>
<td>4</td>
<td>35 y o, G-1, P-0 Oligohydramnios AF normal for 14 wk. Presented at 18 wk.</td>
<td>Bilateral fetal hydronephrosis. Megacystis; renal parenchyma: normal</td>
<td>Na 100 mEq/l Cl 91 mEq/l Osm 221 46,XX</td>
</tr>
<tr>
<td>5</td>
<td>28 y o, G-4, P-3 Oligohydramnios AF normal for 10 wk. Presented at 22 wk. C/S at 32 wk.</td>
<td>Bilateral fetal hydronephrosis. Megacystis; thorax bell-shaped, renal parenchyma: increased echogenicity</td>
<td>Na 100 mEq/l Cl 92 mEq/l Osm 215 46,XY</td>
</tr>
<tr>
<td>6</td>
<td>25 y o, G-1, P-0 Oligohydramnios Presented at 23.5 wk. C/S at 25.5 wk.</td>
<td>Bilateral fetal hydronephrosis. Megacystis; kidneys: unilateral small cysts</td>
<td>Na 74 mEq/l Cl 71 mEq/l Osm 165 46,XX</td>
</tr>
</tbody>
</table>

The outcome of these pregnancies, in our experience, has been very poor with no survivors (9). If the menstrual age is less than 32 weeks, amniotic fluid volume is decreased, and adequate renal function is present, then the UCSF team offers vesico-amniotic shunting. Each mother is sedated with intravenous diazepam prior to infiltration of her skin with lidocaine for placement of a needle and a catheter into the fetal bladder. Uterine activity is monitored and ritodrine hydrochloride given if significant uterine contractions occur. The placement of a permanent, double pigtailed fetal bladder catheter allows shunting of fetal urine into the amniotic cavity and prevents pulmonary hypoplasia (8). Data are sent to the Fetal Surgery Registry where 87 cases of fetal obstructive uropathy treated by in utero placement of a chronic vesico-amniotic shunt have been registered (12). Thirty-five out of the 87 treated fetuses survived (40.2%). In 13 cases (14.9%) pregnancy was electively terminated after shunt placement (Table 2). Seven of these 13 cases (8%) showed an abnormal karyotype subsequent to treatment. Of the remaining 74 pregnancies that were allowed to continue, 35 infants survived (47.3%). As vesico-amniotic catheters are often displaced or blocked, requiring in utero replacement of the catheter, patients at UCSF of less than 28 menstrual weeks are offered open fetal surgery under general anesthesia. The uterus is opened in an area...
FETAL THERAPY

outcome in six fetuses with bilateral hydronephrosis

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Neonatal outcome</th>
<th>Long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral ureterostomies at 20 wk.</td>
<td>Neonatal death. Pulmonary hypoplasia; Renal dysplasia</td>
<td></td>
</tr>
<tr>
<td>Fetal bladder marsupialization at 24 wk.</td>
<td>Live-born. Good pulmonary function</td>
<td>Alive. 3 years old; Renal insufficiency</td>
</tr>
<tr>
<td>Fetal bladder marsupialization at 23 wk.</td>
<td>Live-born. Good pulmonary function; Normal renal function</td>
<td>Died unrelated causes 9 months old.</td>
</tr>
<tr>
<td>Fetal bladder marsupialization at 18 wk.</td>
<td>Live-born. Good pulmonary function</td>
<td>Alive. 2 years old; Normal renal function</td>
</tr>
<tr>
<td>Fetal bladder marsupialization at 22 wk.</td>
<td>Neonatal death. Pulmonary hypoplasia; Renal dysplasia</td>
<td></td>
</tr>
<tr>
<td>Fetal bladder marsupialization at 24 wk. Abnormalities: hypoplastic lungs, renal dysplasia</td>
<td>Neonatal death at 25.5 wk with multiple congenital anomalies</td>
<td></td>
</tr>
</tbody>
</table>

AF, amniotic fluid; C/S, cesarean section.

chosen by sonographic evaluation, the lower abdominal wall of the fetus is exposed, and the fetal bladder is marsupialized. The UCSF experience with the first six such open human fetal procedures is summarized in Table 3.

One fetus underwent bilateral ureterostomies and the other five had bladder marsupializations. Five pregnancies proceeded to cesarean delivery at 32 to 35 menstrual weeks. Neither intraoperative complications nor long-term maternal morbidity occurred. Three of these pregnancies had normal amniotic fluid volumes after intervention and had normal pulmonary function at birth. The outcome varied in the three surviving children: one died of unrelated reasons at 9 months of age with normal renal function, one has normal renal function at 22 months, and the third started manifesting renal failure at 2 years of age and required renal transplantation at 4 years.

The three neonatal deaths were all due to pulmonary hypoplasia and renal dysplasia. On sonography, all three had increased renal parenchymal echogenicity. One pregnancy never had a normal amniotic fluid volume after decompression and a second showed a deformed tiny chest cavity due to the long period of oligohydramnios before decompression. Pregnancy number 6 was terminated at 26 weeks when recurrence of oligohydramnios and a dilated bladder made a second intervention...
necessary. When fetal exploration showed anal atresia and a cloacal abnormality in this female fetus, the mother wished to terminate the pregnancy. Autopsy findings included lung immaturity, renal dysplasia, and multiple abnormalities.

Our current selection criteria, including favorable fetal urine electrolytes and osmolarity, sonographically normal renal parenchyma and oligohydramnios, would have excluded from treatment the three fetuses who died as neonates and the fetus who later developed renal failure.

**DIAPHRAGMATIC HERNIA**

Congenital diaphragmatic hernia is usually an isolated anomaly in an otherwise normal full-term infant. The abnormality is a failure of the diaphragm to form and to separate the abdominal wall and chest cavities. The bowel and other abdominal contents herniate into the chest. Surgical correction consists of placing the herniated bowel back in the abdomen and closing the defect in the diaphragm. However, approximately 80% of these infants die of lung underdevelopment caused by lung compression during the last half of gestation (13). The incidence of congenital diaphragmatic hernia is between 1:2,500 and 1:5,000 newborns, so that 700 to 1,400 affected children are born annually in the United States. Despite marked advances in neonatal anesthetic, surgical, and respiratory care over the last two decades, the mortality rate of this anomaly has not changed.

A study of Adzick et al. (14) surveyed collaborative results of 94 fetuses diagnosed with congenital diaphragmatic hernias. Prenatal diagnosis was made in 88 of the cases and retrospectively appreciated in six cases. In 66% of these cases, the mother was referred for an ultrasound examination for uterine size larger than dates, and polyhydramnios was noted in conjunction with congenital diaphragmatic hernia. Approximately 20% were diagnosed at the time of a routine obstetric ultrasound evaluation. In 97% of the cases, the diagnosis could be made with ultrasound alone or in conjunction with an amniogram or single section computerized tomography scan (14 cases). Polyhydramnios was present in 76% of the cases.

The survival results in these infants were discouraging. Ninety percent of the cases had optimal perinatal care, including maternal transport, planned delivery, immediate resuscitation, pediatric surgical consultation, etc. However, only 20% of these infants survived, and three of these developed severe bronchopulmonary dysplasia requiring prolonged postoperative respiratory support. The need for a thorough prenatal evaluation was evidenced by a 16% rate of lethal associated anomalies, mostly cardiac, chromosomal, or CNS. The presence of late gestation polyhydramnios was found to be a prognostic indicator. The survival rate for infants with polyhydramnios was 11% and for those without polyhydramnios, a more encouraging 55%.

To date, in utero correction of a diaphragmatic hernia has been attempted on a few fetuses referred to the University of California, San Francisco, Fetal Treatment Program. Upon referral, extensive counseling was performed and most couples have not requested a surgical attempt at closure. The first two that have been attempted
were evaluated and neither of these fetuses were found to have coexisting anomalies, and both had normal karyotypes. At the time of surgery, both fetuses were found to have the entire liver in the chest cavity, and attempts to replace the liver into the abdomen proved fatal. These were felt to have been inoperable, postnatally. Additional experience is still at an early stage but has now produced the first surviving neonates.

FETAL VENTRICULOMEGALY

Hydrocephalus of prenatal origin occurs in 0.2% of all deliveries. It represents a failure of normal cerebrospinal fluid dynamics so that this fluid accumulates in the ventricles, causing them to enlarge and cause pressure atrophy of the brain (15). The diagnosis of ventriculomegaly has been made by ultrasound as early as the 13th menstrual week (16). The choroid plexus fills the ventricles until 20 weeks so that excess fluid is usually apparent. After 20 weeks, the most frequently used measure of ventriculomegaly is the LVW/HW ratio, which is the ratio of the displacement of the lateral wall of the ventricle (LVW) to the hemispheric width (HW). Filly and Callen have suggested a more sensitive measure: that of the displacement of the medial wall of the lateral ventricle toward the midline (17).

Trials using ventriculo-amniotic (V-A) shunts in human pregnancies by Clewell et al. (18) or multiple aspiration by Frigoletto et al. (19) were fraught with complications such as blockage and infection. A review in 1986 by Manning et al. (12) showed that 34 out of 39 fetuses shunted for hydrocephalus survived, but 22 of these had varying degrees of deficit.

Because there is no clear benefit to intrauterine shunting for hydrocephalus at the present time, operative candidates must be carefully selected. Detailed ultrasonography should be performed to look for associated anomalies. Karyotyping should be performed and amniotic fluid alpha-fetoprotein should be assessed to aid in the diagnosis of neural tube defects. A careful history should be taken from the mother and testing performed to rule out infections such as congenital rubella, toxoplasmosis, cytomegalovirus, and syphilis. Because progression of ventricular enlargement is unusual, stable ventriculomegaly should be followed to term. Progressive lesions in extremely premature fetuses might be considered for intrauterine treatment. However, experience thus far seems to indicate that although V-A shunting may improve survival, especially in cases of aqueductal stenosis, the shunts are subject to frequent mishaps without clear benefit to cerebral function. Until there are better diagnostic criteria for selecting the at-risk fetus who could be helped by shunting, there is a self-imposed moratorium on ventricular shunting.

COMMENTARY

The potential for in utero correction of some birth defects gives added significance to the rapidly expanding field of prenatal diagnosis. Therapeutic decisions will require
a thorough evaluation of the fetus beyond accurate anatomic definition of any malformation being considered for therapy. Because it is known that malformations often occur as part of a syndrome, a search for associated abnormalities is necessary to avoid delivering a neonate with one corrected anomaly, but other unrecognized disabling or lethal abnormalities.

A major issue has been whether it would be possible to open the uterus and operate upon the fetus without jeopardizing the mother and/or fetus. The threat of precipitating preterm labor and abortion remain the principal barriers to such fetal surgery. Limited experience with surgical exposure of the human fetus for even a minor procedure in the 1960s was so unfavorable that the procedure was abandoned. Over the last few years extensive research on fetal surgery in models, particularly monkeys, has resulted in improved techniques of anesthesia, surgery, and labor inhibition. These advances have now been employed in performing the first successful in utero fetal surgical procedures, and a milestone has been passed.

The benefits and risks of fetal diagnosis and therapy will have to be carefully evaluated and weighed, keeping in mind that two patients are being treated. Assessment for the fetus will be relatively straightforward: the risk of the procedure and/or medication versus the benefit of correction or amelioration of the deleterious condition. This last factor will depend on the severity of the condition and its predictable consequences on survival and quality of life. Assessment for the mother will be more difficult. Her health usually will not be affected by the fetal disorder, but she will have to bear some risk from the therapy attempt.

Our ability to diagnose fetal birth defects has achieved considerable sophistication. Treatment of several fetal conditions has now proven to be feasible, and treatment of more complicated defects will expand as techniques for fetal intervention improve. The concept that the fetus is a patient, an individual whose disorders are a proper subject for medical therapy, has been established.

REFERENCES

FETAL THERAPY


DISCUSSION

**Dr. Pollak:** I was very interested in the results of your diaphragmatic hernia babies. You pointed out that one of the major problems is hypoplasia of the lung. What happened to your patients’ lungs after surgery?

**Dr. Golbus:** Diaphragmatic hernia occurs very early in development at a time when the number of bronchial branches is determined. Even if the intrathoracic mass is removed, it is too late for any growth of new bronchial branches. However, the lung is capable of developing more villi off each of the existing branches, and in as little as 5 to 6 weeks there is enough catch-up in lung growth for the fetus to be able to breathe.

**Dr. Marini:** Would you comment about amniotic pressure and lung hypoplasia. We usually assume that there is high amniotic fluid pressure in these cases, but recently Nicolini in England (1) showed that there is low pressure in some of these cases. Could we treat very early during pregnancy by giving infusions into the amniotic cavity?

**Dr. Golbus:** I do not think amniotic infusions would be likely to help in cases where there is a mass in the chest, but certainly in cases of oligohydramnios of unknown etiology we will end up with hypoplastic lungs if we do nothing. We have tried infusions and have had some successes and some failures. On balance we feel such treatment is worth trying in oligohydramnios of unknown etiology.

**Dr. Gold:** One of the biggest problems in open fetal surgery is that it requires a corporeal cesarean section. This is a big decision for the mother to take. Can you comment on this? I have heard and read that results with congenital diaphragmatic hernia are disappointing, so the question of the operation on the uterus needs careful examination.

**Dr. Golbus:** With regard to the operation, we tell the patients that since they are going to have a classical incision they will need to have a cesarean in every future pregnancy. We counsel very strongly that we are not just talking about one operation but three or four or as many as there will be children. I agree that open surgery involves a whole new consideration because risk to the mother is involved, not just to the fetus. The majority of patients we counsel decide not to proceed. With regard to prognosis, we have performed eight in utero
diaphragmatic hernia repairs. The first four died, and of the second four, three were delivered alive but one subsequently died of an unrelated cause.

Dr. Guesry: What is the optimal time for surgery?

Dr. Golbus: The optimal time is different for different conditions. For bladder obstruction, operation can take place as early as 18 weeks, since the procedure is very brief and well tolerated. Diaphragmatic hernia surgery cannot be done until about 24 weeks since before that time the fetus cannot tolerate the procedure, which lasts for an hour at least even with practice.

Dr. Van Geijn: How would you compare intrauterine surgery at 24 to 25 weeks with early delivery and neonatal surgery, with life support by ECMO or ventilation?

Dr. Golbus: I am not an expert on ECMO but the Boston group looked at their diaphragmatic hernia neonates with and without ECMO and did not find it very helpful. We have ECMO and we use it, but I don’t think we know yet how helpful it is going to be. With regard to other prenatally diagnosed conditions in utero transplantation may offer some hope of success. We and others have been able to do successful in utero transplants in a mouse model and our group has also published results of successful rhesus monkey allogenic transplantation. In the successful rhesus model there was a range of 5–10% of donor cells in the recipient’s peripheral circulation after birth, in all cell lines. Although this may be sufficient to correct an enzymopathy, it is not sufficient to correct a hemoglobinopathy. However, clinically we are going to be transplanting in a situation in which there is a disease, and this may give the donor cells a competitive advantage and increase their engraftment. We need to be transplanting at the time when the fetus is seeding the marrow, about 20 weeks. If we seed our donor cells later than this it will probably be too late both for immunologic (rejection) and hematopoietic reasons.

REFERENCE