Diagnosis and Management of Fetal Hydrocephalus

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The incidence of congenital hydrocephalus is estimated at between 0.5 and 1.5 per 1,000 live births. It is thus less common than some malformations such as congenital heart disease or intrauterine growth retardation, but because it is associated with neurologic disability and may result in prolonged survival of a severely handicapped individual, there is considerable incentive for prenatal diagnosis and, in a few cases, treatment of the condition in utero. As this symposium indicates, the concept of the fetus as a patient has undergone rapid evolution over the past few years. Before 1980 the only fetal condition that was directly treated prior to birth was anemia due to severe maternal blood group isoimmunization. In that era great advances were made in lowering the perinatal mortality and morbidity rates by the application of two principles of fetal care. The first principle was that improved medical care of the pregnant woman would result in a better fetal environment for healthy growth and development. An example of the success of this approach is the improvement in the pregnancy prognosis for diabetic women. This was achieved largely by meticulous care of the mother’s disease. The second principle was careful attention to fetal well-being and timely delivery to avoid both fetal death and iatrogenic prematurity: in effect, rescuing the fetus from a hostile environment.

Fetal transfusion for erythroblastosis represented a completely different approach to the fetus. The fetal condition, anemia due to hemolysis, is directly treated by transfusion of packed red blood cells. Aside from its importance in the management of Rhesus disease, fetal transfusion is a model for direct fetal treatment in general and as such illustrates several important principles. The pathophysiology of the condition to be treated must be understood. Its natural history must be known, and the diagnosis reliably established at a time in pregnancy when treat-

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ment can be effective and yet too early in gestation for safe preterm delivery. The condition must be progressive so that if treatment is delayed until after delivery, it is likely to result in fetal death or severe damage. In this article we consider the application of these principles to the diagnosis and management of fetal hydrocephalus.

Pathophysiology

Relative enlargement of the cerebral ventricular system can be due to two broad categories of disease: increase in pressure within the head and subsequent compression or destruction of brain tissue, or primary loss of brain substance with normal or low intraventricular pressure. Since surgical treatment of hydrocephalus consists of establishing a drain to remove excess ventricular fluid and relieve intracranial pressure, such treatment will be of no benefit if the pressure is low. Elevation of intracranial pressure can be due to obstruction of the usual routes of fluid flow and absorption or in rare cases to increased rate of fluid production, as occurs with choroid plexus papilloma. While a choroid plexus adenoma has not, as yet, been reported in a fetus, it seems likely that they do occur and will eventually be found.

Fetal ventriculomegaly is usually due to obstruction to the flow of fluid through and then out of the ventricular system. The potential sites of this obstruction include the cerebral aqueduct between the third and fourth ventricles, the outlet from the fourth ventricle, and within the subarachnoid space. Different disease processes have the potential to cause obstruction at each of these points.3–6 A small minority of cases (2%) are inherited as X-linked aqueductal stenosis. Since the recurrence risk in male siblings of males with aqueductal stenosis is 12%, up to 25% of aqueductal stenosis in males may be inherited in this fashion.7 Intrataminal viral infection may cause scarring and obstruction of the cerebral aqueduct or at the subarachnoid granulations. It can also cause primary destruction of brain tissue. Chromosomal anomalies may cause brain malformation with obstruction at the cerebral aqueduct or the fourth ventricle. Dandy–Walker malformation and Arnold–Chiari myelodysplasia cause obstruction at the level of the fourth ventricle. Spina bifida is regularly accompanied by Arnold–Chiari malformation and obstruction at the fourth ventricle leading to hydrocephalus in 80% of cases.

Elevation of intraventricular pressure results in compression of the brain tissue. Initially, this is at least partially reversible as demonstrated by the rapid reexpansion of cerebral tissue when the pressure is relieved. With sustained elevation of the pressure, there is disruption of the ependyma, edema of the white matter, and periventricular gliosis and demyelination. If severe and continued long enough, intraventricular hypertension can result in nearly complete destruction of the cerebral hemispheres. The aim of surgical treatment is to relieve this pressure and thus prevent brain damage. The benefit of such treatment is well established in infants and adults with acquired hydrocephalus.5

Natural History

In the infant or child with hydrocephalus, the natural history is often one of gradual progression, resulting in enlargement of the head and loss of functioning brain tissue. This progression is relatively easy to detect by the excessively rapid increase in the head circumference and, in the newborn, bulging of the fontanelles. Occasionally in infants initial progression of the hydrocephalus spontaneously arrests. They either achieve a new steady state at a higher intracranial pressure or reestablish normal intracranial fluid dynamics by overcoming the obstruction or developing alternative channels for disposal of excess ventricular fluid. The number of fetuses with ventriculomegaly who will have an ar-
rest of the process is not known, but such arrest clearly occurs.\textsuperscript{8,9} The situation is complicated by the relative inaccessibility of the fetus and by our lack of a precise causative diagnosis in many cases.

As noted previously, obstructive hydrocephalus can be caused by lesions at several different sites. The obstruction is not usually a disease itself but rather a consequence of a disease process. In the newborn, that disease process is often readily apparent, as in congenital viral infection or spina bifida. Identifying the cause of ventriculomegaly in a fetus in utero requires a meticulous search for possible causes and even then is often unsuccessful. Without a causative diagnosis, it is extremely difficult to predict the outcome. When the cause is known, the lack of experience with the natural history of most such diseases identified in the second trimester of pregnancy makes prediction and counseling patients very difficult. In general, prognosis depends more strongly on the underlying disease process than on the extent of ventriculomegaly at the time of diagnosis.

\textbf{Diagnosis}

With the development of high-resolution real-time ultrasound, one of the first features of internal fetal anatomy studied was the cerebral ventricular system and abnormalities of ventricular size. As diagnostic criteria were refined, several important points about both normal and abnormal fetal cerebral anatomy and development were recognized. First, the size of the fetal ventricles changes rapidly with gestational age. At 16 weeks' gestation, the choroid plexus is very large and relatively echogenic and occupies almost the entire lateral ventricle. If one measures the lateral-ventricular-width-to-hemisphere-width (LVW/HW) ratio as described by Johnson et al., the ratio can be as high as 0.7 in the normal fetus at 16 weeks.\textsuperscript{10} The mean for that gestation is 0.55. From 16 to 22 weeks the LVW/HW ratio declines rapidly to a mean of 0.33 with an upper limit of normal of 0.45. The ratio then stays relatively constant throughout the remainder of gestation. Other investigators have used different methods of measurement, but all have made the same general observation; the ventricles are relatively large at 16 weeks and decrease in relative size with advancing gestation.\textsuperscript{11-13} In hydrocephalus the ventricles increase in size relative to the fetal head before there is an increase in the biparietal diameter. Since decisions about management will be based on the rate of progression of ventriculomegaly, it is essential that the relative size of the ventricles be measured in a consistent and reproducible manner.

In addition to relatively increased ventricular size, failure of the choroid plexus to fill the lateral ventricle is suggestive of ventriculomegaly. With enlargement of the ventricles, the midline echoes, composed of the medial walls of the anterior horns of the lateral ventricles and the midline of the hemispheres, become compressed into a single echogenic line.\textsuperscript{11} This can be seen to undulate in response to ballottement of the fetal head during ultrasound examination. It should also be noted that the posterior horn of the lateral ventricle is the first portion to dilate in obstructive hydrocephalus. Therefore, even though it is often difficult to measure precisely in the normal fetus, its size should be noted in any fetus suspected of having ventriculomegaly. In ventriculomegaly due to obstruction of the cerebral aqueduct, the third ventricle is often enlarged.

Fetal ventriculomegaly is a feature of many diseases, and therefore an attempt must be made to identify the specific diagnosis in all cases. It is a frequent concomitant of neural tube defect (80%), and a meticulous search must be made for spina bifida in all cases of ventricular enlargement. In a postnatal population, Lorber found spina bifida in association with
20–30% of cases of hydrocephalus. Since many of these diagnoses involve malformations in other organ systems, the entire fetus must be examined in detail. Fetal karyotype should be determined and amniotic fluid or fetal blood cultured for viral infection. In general, the prognosis depends more on the specific diagnosis than on the degree of ventricular enlargement.

Experience has shown that the course of fetal ventriculomegaly is highly variable. Some fetuses have massive ventricular enlargement when first encountered. Others have equivocal findings and may or may not show progression of the ventricular enlargement. Some individuals will have relatively enlarged ventricles at the first examination and then either return to normal size or continue to be abnormally large but decline in parallel with the normal zone. In early infancy some of these babies appear to be developing normally, but the long-term prognosis in terms of intellectual development for these children is unknown.

**Selection for Fetal Treatment**

An international group of physicians and ethicists interested in fetal treatment have agreed that only cases with unequivocal progression of ventriculomegaly should be considered for experimental fetal surgery. The selection of a fetus for such an experiment is a meticulous process. Frigoletto et al. have proposed the following guidelines for patient selection for experimental treatment:

1. The hydrocephalus should be detected sufficiently early that delivery and postnatal shunting are not realistic options.
2. The hydrocephalus should appear as a simple obstructive variety without major dysmorphic brain development.
3. The hydrocephalus should not be associated with other major malformations that are incompatible with survival or that indicate an irremediable malformation syndrome (including positive viral cultures from the amniotic fluid or fetus).
4. Each pregnancy should be evaluated for chromosomal abnormalities and associated neural tube defects during initial workup.
5. The ventricular dilatation should be progressive.
6. Pretreatment evaluation should include a multidisciplinary team's consultation with physicians in perinatology, neonatology, ultrasonography, neurosurgery, and genetics.

Because fetal treatment of hydrocephalus is experimental, it is essential that the parents decide in an appropriate atmosphere to participate in the experiment. All treatment options legally available to them must be presented and fully discussed. These may include pregnancy termination in cases diagnosed sufficiently early. They also include not treating the fetus and then making decisions about management in the third trimester of pregnancy. If the hydrocephalus has been severely progressive with enlargement of the fetal head, management may include cesarian delivery or, to avoid cesarian section and minimize maternal risk, cerebral decompression and vaginal delivery. This approach should never be adopted if there is any intention of neonatal survival.

Because fetal treatment is an experiment on the unconsenting human fetus, most centers have required that the procedure be approved by an ethics or human research committee. At the University of Colorado, each family is interviewed by a subcommittee of the Human Subjects Committee. This is to ensure that the rights of the fetus and the parents have been appropriately considered and that neither the investigators nor the parents have abridged those rights. These rights may include the right to die rather than survive severely handicapped. Since this decision-making process is highly stressful for the parents, appropriate psychosocial counseling and support should be provided both during and after the pregnancy.
Fetal Surgery

Since the benefit of ventricular shunting in infantile hydrocephalus is well established,\textsuperscript{17,18} it seems likely that decompression of the ventricle would be beneficial in some cases of fetal hydrocephalus. This was first attempted by repeated aspiration of ventricular fluid by ultrasound-guided needle puncture.\textsuperscript{18} Because this could provide only intermittent and transient relief from the elevated intracerebral pressure, a procedure involving chronic decompression was developed.\textsuperscript{19}

This procedure involves the ultrasound-guided insertion, under local anesthesia, of a large-bore, thin-walled (13 gauge, 2.44 mm external diameter, 2.01 mm internal diameter) needle into the lateral ventricle of the fetal brain. Before needle placement, the fetus is gently manipulated to bring the head into an appropriate position to allow insertion of the needle through the posterior parietal region of the calvarium. The mother and fetus are sedated to allay maternal anxiety and reduce fetal movement. In the course of the operation the pressure in the amniotic fluid and inside the ventricle is measured with a manometer filled with normal saline. The difference between the ventricular and amniotic fluid pressure represents the transcerebral pressure gradient, which is to be relieved by the shunt. The absence of a significant pressure gradient would suggest "hydrocephalus ex vacuo," and such a condition would not be benefited by shunting. Once the needle is in place, the shunt is passed through the needle and pushed into position with a stylet as the needle is withdrawn.\textsuperscript{19}

The shunt is made of silicone rubber tubing. It contains a valve to limit the rate of drainage of ventricular fluid and prevent the backflow of amniotic fluid into the ventricle. Adjacent to the valve is a pair of rubber flanges that anchors the shunt within the fetal skull. These flanges fold flat along the shunt while it is passing through the needle and then expand to keep it anchored in the fetal skull. The amniotic end has a short collar the same diameter as the valve to prevent the shunt from being pushed or drawn into the fetal head.\textsuperscript{19} Since it was first developed, the shunt has undergone several minor modifications, including a change in valve design and the addition of the anchoring flanges. It has also been made radio-opaque to facilitate locating it if it becomes dislodged.

At the time of operation a 1-ml sample of ventricular fluid is taken for viral cultures. The ventricle is not decompressed at the time of the procedure because rapid ventricular collapse may cause subarachnoid hemorrhage. After shunt placement the ventricular size is followed by ultrasound at frequent intervals. Normal shunt function is confirmed by noting a progressive decrease in the LVW/HW ratio. Shunt failure due to obstruction or dislodgement is diagnosed by noting a rapid increase in the LVW/HW ratio.

Results

Since the first shunt operation for fetal ventriculomegaly in April 1981, 43 patients have been referred to the University of Colorado Program in Fetal Medicine and Surgery specifically for a diagnosis of fetal hydrocephalus. Twenty-five of these were excluded from consideration for intrauterine treatment. The reasons for their exclusion are listed in Table 1. After their initial evaluation, 18 patients met our cri-

\textbf{TABLE 1.} Reasons for Exclusion from Experimental Procedure

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td>Gestational age at referral &gt; 30 wk</td>
<td>7</td>
</tr>
<tr>
<td>Associated neural tube defect</td>
<td>5</td>
</tr>
<tr>
<td>Other CNS anomalies</td>
<td>2</td>
</tr>
<tr>
<td>Anomalies in other systems</td>
<td>8</td>
</tr>
<tr>
<td>Twin gestation</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
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</tbody>
</table>
TABLE 2. Outcome, Treatment of Fetal Hydrocephalus

<table>
<thead>
<tr>
<th></th>
<th>Fetal Shunt</th>
<th>No Shunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective abortion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Infant death</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Alive</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Normal development</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mild handicap</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Severe handicap</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

teria for fetal treatment. Thirteen of these families declined fetal treatment. Five chose to have a fetal shunt placed. The outcome for these 18 patients is summarized in Table 2. Six of these patients (33%), including one in the shunted group, had in addition to hydrocephalus major malformations that were not identified before delivery.20 One of the shunted infants had an eventration of the diaphragm. Two unshunted infants had alobar holoprosencephaly, one had esophageal atresia and a cerebellar cyst, one had an arteriovenous malformation of the thalamus, and one had polymicrogyria.

One of the families who had consented to participate in the experimental treatment terminated the pregnancy. At the time of the shunt operation, no pressure gradient was found between the ventricle and the amnion, and in view of this, no shunt was placed. With this finding and the uncertainty of its implication, the family decided to terminate the pregnancy at 23 weeks, 5 days. The legal limit for elective pregnancy termination is 24 weeks in Colorado.

The neurologic development of the shunted and unshunted patients is of paramount importance. Two of the four survivors in the shunted group are severely handicapped. One had a family history consistent with X-linked hydrocephalus: a male sibling had been born with severe hydrocephaly and expired shortly after birth, and a maternal uncle had died at birth with congenital hydrocephalus. The fetus's ventricles appeared to be well decompressed in utero until shortly before delivery. He had a ventriculoperitoneal shunt placed on the first day after birth and had an uneventful neonatal course. At 4 years he has a Developmental Quotient of less than 50. The other child had a diaphragmatic eventration that was not recognized before birth. He suffered severe neonatal asphyxia, and this may account in part for his poor neurologic development. His hydrocephalus appeared to have been well controlled in utero and remains under control with a ventriculoperitoneal shunt. Two of the survivors are showing nearly normal development. One had his shunt placed at 23 weeks’ gestation, but an amniotic fluid leak was noted a few days later. He was delivered at 27 weeks when it was thought that amnionitis was developing. His shunt was in place and functioning at birth and was replaced with a ventriculoperitoneal shunt. Whether the 3 weeks of intraventricular shunt treatment contributed to his outcome is uncertain. The last child had his shunt placed at 24 weeks’ gestation. At 27 weeks his ventricles had enlarged and the shunt could not be seen on ultrasound. He had a second shunt inserted at that time. He was delivered at 32 weeks’ gestation because of spontaneous rupture of membranes, and his shunt was again out of his head. At 4 years of age he is developing normally and has a ventriculoperitoneal shunt in place.

Two of the three survivors in the unshunted group have shown nearly normal development to date. They were both delivered prematurely by cesarian section and had ventriculoperitoneal shunts placed after birth. The third survivor did not require immediate shunt treatment but at 6 months was noted to have mild developmental delay and enlarging ventricles. He had a shunt placed at that time. These two groups do not represent a controlled study.
In 1982 at a workshop on fetal treatment a registry was established to record all cases of direct fetal treatment. The registry is located in the Department of Obstetrics and Gynecology at the University of Manitoba and is directed by Dr. Frank Manning (see Manning in this symposium). As of June 1985, 39 cases of fetal hydrocephalus treatment were reported to the registry. (These results were reported at the meeting of the Fetal Medicine and Surgery Society, June 8, 1985.) Three additional operations were performed by Luciano Bovicelli of Bologna, Italy (reported at Bologna, September 1985). The outcome of these cases is summarized in Table 3. The 85% survival rate is similar to that in the University of Colorado series. The developmental outcome is also similar: 40% of survivors “normal,” 8.5% mildly handicapped, and 51.5% severely handicapped.

Discussion

Fetal ventriculomegaly is readily identifiable by real-time ultrasound in the second trimester of pregnancy. The cause, however, is not so easy to establish in most cases. Without a specific cause, it is very difficult to make statements about natural history or prognosis. Even in cases in which the diagnosis is known, the natural history of ventriculomegaly found in the second trimester of pregnancy is usually not known. This lack of specific diagnosis and knowledge of natural history is the major defect in the surgical approach to fetal hydrocephalus.

The coexistence of non–central nervous system malformations in fetuses with ventriculomegaly makes patient selection for aggressive treatment difficult. In the Colorado series, one of the treated fetuses had an evertedation of the diaphragm that was not recognized before delivery. In retrospect, it could have been suspected on some of the ultrasound studies, but not all of them. In the unshunted group, 5 out of 13 had unrecognized anomalies. Whether these would have been recognized with additional ultrasound examinations is uncertain. All of these diagnoses have been made by ultrasound, but whether they can always be made is unknown. Glick et al.9 also found a high incidence of unrecognized anomalies in other organ systems in fetuses with ventriculomegaly.

From our experience at the University of Colorado School of Medicine, we cannot state whether treating fetal ventriculomegaly improves the outcome of the affected fetus. It does appear to increase the proportion of survivors, but that reflects in part the fact that the treated fetuses were delivered by cesarian section while 4 of the 13 untreated fetuses were delivered vaginally after cerebral decompression and were stillborn. Had they been delivered by cesarian, they also may have survived. Glick et al. noted that out of 24 fetuses with ventriculomegaly, 13 had either elective termination of pregnancy or cerebral decompression and vaginal delivery. Ten of the remaining 11 survived. Six of these appear to have normal development.9 The difference in survival rate thus reflects partly parental and physician attitude toward the pregnancy and partly the condition of the fetus.

The developmental outcome difference between the two groups suggests that intrauterine treatment increases the number of handicapped survivors, not the number of

| TABLE 3. Outcome of Fetal Hydrocephalus Treatment (Report of Fetal Treatment Registry) |
|---------------------------------|-------|
| Cases reported                | 42    |
| Shunt in utero                | 40    |
| Serial ventriculocentesis     | 2     |
| Fetal or neonatal death       | 7     |
| Cause of death                |       |
| Treatment complications       | 4     |
| Associated anomalies          | 2     |
| Unexplained                   | 1     |
| Development of survivors      |       |
| Normal                        | 14    |
| Mild handicap                 | 3     |
| Severe handicap               | 18    |
normal survivors. The figures reported from the Fetal Surgery Registry lead to the same conclusion. Comparison of these results with published figures for development in babies with congenital hydrocephalus diagnosed near term or after delivery also fails to show an advantage to fetal shunt operations. Neither of these, however, represents a controlled study. Obviously both the fetal treatment group and perinatally diagnosed group have been subjected to selection. Fetuses treated in utero have had clearly progressive ventricular enlargement and thus represent very severely affected cases. Many severely affected fetuses at term would be managed by cerebral decompression and vaginal delivery, while less severely affected cases would be managed more conservatively. While the question of efficacy of fetal treatment could be answered by a carefully constructed, prospective, randomized trial, it seems unlikely that a sufficient number of patients would consent to participate. The process of selection and introduction of bias begins as soon as a fetal anomaly is suspected.

With all these uncertainties of treatment, benefit, and difficulties of accurate prenatal diagnosis, it is clear that prenatal treatment of fetal ventriculomegaly remains highly experimental. The current operation of needle placement of shunt catheters has serious problems with maintaining shunt patency and stability. The anomaly, however, is relatively common, and both patients and physicians will be faced with difficult choices for pregnancy management. Placement of a fetal ventriculoamniotic shunt provides a third option between pregnancy termination and inaction in the mid trimester of pregnancy. Even without a prospective, controlled study of the procedure it is essential that as much information as possible be gathered from any procedures done. All children must be meticulously evaluated for their development. Any fetal or neonatal deaths must be subjected to postmortem examination. Finally, all results must be communicated to the scientific community.

References