

The Smallest Patient: Foundations in Fetal Medicine

A CME Issue: Introduction

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Until the latter part of the twentieth century, the fetus was hidden from outside scrutiny and little could be predicted about gestation. Within decades, fetal diagnosis became a reality, largely (but not solely) due to the advent of ultrasonography. Thus, a new specialty was born, as normal and abnormal fetal development could be followed, and more and more accurate diagnosis of fetal conditions could be made. Advance knowledge of fetal diseases led to the quest for fetal treatment, which today ranges from counseling of future parents and alterations in mode or place of delivery to more or less invasive procedures on the fetus himself.

The first invasive fetal intervention was performed in 1963 by Liley, in New Zealand. His intrauterine transfusion of a fetus with rhesus isoimmunization is generally considered to mark the beginnings of fetal medicine. That same year, Karliss Adamsons performed the very first (although unsuccessful) open fetal operation, for the same condition. Dr. Adamsons went on to become the first chairman of Obstetrics and Gynecology in the Brown University Program in Medicine. Almost forty years later, fetal medicine has come of age, and Brown Medical School is one of the first medical schools in the country to have a Program in Fetal Medicine. This program, and the Multidisciplinary Antenatal Diagnosis And Management conferences (affectionately dubbed MADAM) on which it is based, emphasize how fetal medicine has evolved in this relatively short time: whereas care of the pregnancy was traditionally assumed by the obstetrician alone, management of the fetus as a patient has become the responsibility of a large group of health professionals, including maternal-fetal medicine specialists, neonatologists, pediatric surgical and medical

specialists, geneticists and genetic counselors, radiologists and perinatal pathologists.

The present issue on fetal medicine highlights this multidisciplinary approach, as a wide array of fetal conditions and their treatment are discussed. The articles reflect the expertise of these and other members of the Brown Program in Fetal Medicine, and are published in parallel with a state-of-the-art conference ("The Smallest Patient: Foundations in Fetal Medicine") organized on the Brown University campus. Together, these initiatives highlight the spirit of collaboration and the high level of expertise present in Rhode Island.

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Rhesus Isoimmunization

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Rhesus(Rh) isoimmunization is the development of maternal IgG antibodies against fetal Rh red blood cell (RBC) antigens. Transplacental passage of maternal Rh antibody (IgG anti-D) may result in **hemolytic disease of the newborn (HDN)**, a condition characterized by hemolysis, severe fetal anemia and generalized fetal edema (hydrops fetalis). Although other red cell antigens may elicit a maternal immune response resulting in HDN, the Rh blood group system is the most common and important.

INCIDENCE OF RH ISOIMMUNIZATION

The Rh system is comprised of 5 antigens: D, C, c, E, e. The presence of D confers Rh positivity while its absence signifies Rh negativity. Approximately 15% of whites are Rh negative compared with 6% of blacks and 1% of Asians.¹ Rh isoimmunization occurs when Rh-positive fetal RBCs gain access to the maternal circulation and trigger antibody production. Without prophylaxis, nearly 17% of Rh-negative women become immunized as a result of their first ABO-compatible, Rh-positive pregnancy.² The

risk of immunization decreases to 1-2% with ABO-incompatibility.³ Spontaneous **fetomaternal hemorrhage (FMH)** is the most common cause of Rh isoimmunization. The rate of FMH increases with gestational age occurring in 6.7%, 15.9% and 28.9% in the first, second and third trimesters, respectively, and in 50% of pregnancies at delivery.⁴ The incidence of Rh isoimmunization increases with the volume of FMH. Three percent of patients become immunized if the volume of FMH is less than 0.1 ml; 14% and 22% become immunized with FMH volumes of greater than 0.1 ml and 0.4

Table 1. Outcome based on Δ OD 450 Liley graph zone location

Zone	Disease Severity	Fetal/Neonatal Status
1	Mild or no hemolytic disease	10% probability neonatal exchange transfusion required
2	Intermediate disease	disease severity increased as the Δ OD 450 readings approached zone 3
3	Severe hemolytic disease	Severe anemia; hydrops fetalis; fetal death probably within 7 -10 days

Modified from Liley AW. Liquor amnii analysis in management of pregnancy complicated by Rhesus immunization. *Am J Obstet Gynecol* 1961;82:1359-70.

ml, respectively.⁵ The incidence of FMH is 2.5% following amniocentesis, 5% after spontaneous abortion and up to 20-25% after an induced abortion.⁶

PATHOGENESIS OF HEMOLYTIC DISEASE OF THE NEWBORN

The primary maternal immune response to a challenge by fetal RBC antigens tends to develop slowly, is characterized by low avidity and is mostly IgM, which does not cross the placenta. For these reasons and the fact that most cases of isoimmunization occur at birth, the index pregnancy is usually unaffected. The secondary antibody response is usually IgG which readily crosses the placenta. Subsequent maternal exposure to Rh-positive blood is characterized by rapid development and increased avidity of the IgG antibodies. Once in the fetal circulation, maternal anti-D antibodies bind fetal RBC surface antigens and are sequestered and destroyed in the fetal spleen. This leads to fetal anemia, which stimulates erythropoietin production. When RBC destruction exceeds marrow production, extramedullary sites, such as the liver and spleen, are recruited for RBC production. Hepatomegaly and hepatocellular damage result in portal hypertension and hypoalbuminemia which if sufficiently severe, may result in fetal ascites, fetal pericardial and pleural effusions, and fetal skin edema or placental thickening.⁶

SEVERITY OF HEMOLYTIC DISEASE OF THE NEWBORN

Bowman defined 3 categories based on severity of disease.⁶ Approximately 50% of affected newborns have mild disease and do not require treatment. In newborns with mild disease, hemoglobin levels remain above 11 g/dl and serum indirect bilirubin levels do not exceed 20 mg/dl. Moderate disease is noted in 25-30% of affected neonates.

Without treatment after birth, these newborns become severely jaundiced and are at risk of developing kernicterus or bilirubin encephalopathy. Severe disease, characterized by hydrops fetalis, occurs in 20-25% of affected fetuses. Nearly 50% develop hydrops prior to 34 weeks of gestation.

ANTENATAL MANAGEMENT

The Rh-negative woman with a negative antibody screen

A blood type and antibody screen must be obtained at the first prenatal visit of every pregnant patient. Among Rh-negative mothers, the paternal ABO group and Rh status, including zygosity in the case of Rh positivity, should be determined. If the partner is Rh positive, then a maternal antibody screen is repeated at 28 weeks and anti-D immune globulin is administered if the antibody screen is negative. Serial screening has been recommended every 6 weeks from 20 weeks until delivery by some.⁶ In order to prevent isoimmunization, **American College of Obstetricians and Gynecologists (ACOG)** recommends the administration of anti-D immune globulin to Rh-negative, unimmunized women at 28 weeks of gestation and within 72 hours of delivery (of an Rh-positive baby) and other potentially sensitizing events (e.g. amniocentesis, threatened abortion, abruptio placenta and abdominal trauma).⁷ Postpartum anti-D immune globulin prophylaxis has

reduced the alloimmunization rate by 90%.⁸

The Rh-negative woman with a positive antibody screen

The severity of Rh hemolytic disease may be assessed in the immunized patient by several different means which include: past obstetric history, maternal antibody titer, **amniotic fluid (AF)** bilirubin quantification, ultrasonography and percutaneous umbilical blood sampling. A past history of hydrops fetalis, fetal demise, intrauterine transfusion or neonatal exchange transfusion implies that the present pregnancy is or will be severely affected because Rh disease effects on the fetus generally recur or present progressively earlier or more severely with each successive Rh positive pregnancy. Obstetric history does not pertain to the first sensitized pregnancy in which the risk of hydrops is 8-10%.

The maternal antibody titer should be evaluated at the first prenatal visit in Rh-sensitized gravidae, at 16-18 weeks and then every 2-4 weeks.^{6,9} The fetus is not at significant risk for severe disease as long as the titer remains < 1:16.⁹ A titer of 1:16 requires further evaluation because the risk of hydrops increases with Rh antibody titers. Once the critical titer is achieved or hydrops occurs the utility of the antibody titer in managing subsequent pregnancies is low.

Bilirubin, a product of hemolysis, is excreted into the AF by the fetus. The rela-

Table 2. Management based on Δ OD 450 Liley graph zone location

Zone	Timing of subsequent intervention
1	Repeat amniocentesis in 3-4 weeks
2	Repeat amniocentesis in 1-2 weeks; increased frequency as values rise; fetal blood sampling if value falls in upper 65% of modified zone 2
3	Immediate fetal blood sampling

Modified from Grannum P, Copel JA. Prevention of Rh isoimmunization and treatment of the compromised fetus. *Semin Perinatol* 1988;12:324-35.

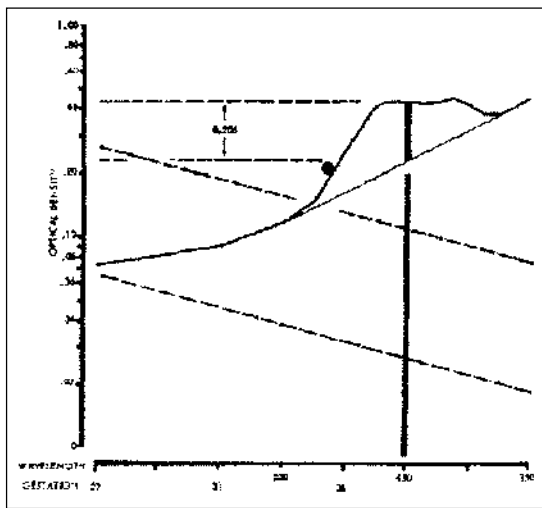


Figure 1.⁶

tive concentration of bilirubin in the AF can be quantified by spectrophotometry. **Optical density (OD)** readings, obtained over the 700 to 350 nm wavelength range, are plotted on semilog paper with wavelength on the horizontal axis and OD on the vertical axis. The readings at 550 nm and 365 nm are connected by a line. The deviation from linearity of the OD reading at 450 nm (the OD 450 value) is the measurement from the actual reading at 450 nm to where the connecting line intersects 450 nm (Figure 1). The OD 450 value is then plotted on a graph with gestational age as the linear coordinate (Figure 2). Liley¹⁰ examined amniotic fluid within a week of birth from 101 Rh immunized pregnancies at 28 weeks of gestation. The OD 450 was correlated with cord hemoglobin and the degree of HDN. Liley described three zones (Table 1 and Figure 2).

The timing of the first amniocentesis is based on the maternal antibody titer or the past obstetric history. The initial amniocentesis for OD 450 evaluation may occur as early as 18 weeks of gestation if a prior pregnancy was complicated by hydrops, stillbirth or neonatal exchange transfusion. Subsequent amniocenteses are planned based on the prior

zone 3 obtained prior to 26 weeks of gestation.⁵ The risks of amniocentesis include: miscarriage, FMH, membrane rupture, preterm labor and infection. Fetomaternal hemorrhage is minimized by performing amniocentesis under ultrasound guidance to avoid transplacental access. According to the ACOG, the midtrimester "risk of abortion secondary to amniocentesis is 1 in 200 or less."¹²

Ultrasonography provides a noninvasive means of diagnosing fetal hydrops and assessing fetal well being. Sonographic attributes claimed to have a clinical association with severe fetal anemia prior to the onset of fetal hydrops include: increased umbilical vein diameter, placental thickness, bowel wall visualization, pericardial effusion, enlarged fetal heart, enlarged liver and spleen, decreased head circumference to abdominal circumference ratio and increased amniotic fluid volume. However, none of these observations, alone or in combination, are as accurate predicting hydrops as serial amniotic fluid OD 450 measurements.¹³ More recently, fetal **middle cerebral artery peak systolic velocities (MCA-PSV)** determined by Doppler flow studies have been found to estimate the degree of fetal anemia in Rh disease. Mari and colleagues utilized MCA-PSV to

OD 450 values. Table 2 provides a general guideline for timing of interventions.

The predictive value of OD 450 measurements for severe disease obtained after 27 weeks of gestation is approximately 95%.¹¹ A OD 450 value may not be as predictive of severe disease when obtained prior to 26 weeks. According to Bowman, fetal blood sampling with direct fetal hemoglobin determination is recommended for OD 450 values in upper zone 2 or

prospectively evaluate 111 fetuses at risk for anemia. An elevated MCA-PSV was defined as a value **1.50 multiples of the median (MoM)** for gestational age. The sensitivity of an increased MCA-PSV for the prediction of moderate or severe anemia was 100% in the absence or presence of hydrops accepting a false positive rate of 12%.¹⁴ Moderate anemia was defined as a hemoglobin concentration from less than 0.65 to 0.55 times the median for gestational age and severe anemia as a hemoglobin less than 0.55 times the median. These data suggest that MCA-PSV measurements, while non-invasive, provide an accurate means of determining the degree of fetal anemia in pregnancies complicated by Rh isoimmunization.

The most accurate means of determining fetal hemoglobin concentration requires **percutaneous umbilical blood sampling (PUBS)**. During the PUBS procedure, a needle is inserted into the lumen of the umbilical vein under ultrasound guidance. Once access is obtained, the fetal hemoglobin concentration can be determined and packed red blood cells transfused if necessary. Potential candidates for this procedure include patients with OD 450 measurements in high zone 2 or zone 3, sonographic evidence of fetal hydrops or MCA-PSV ≥ 1.50 MoM. The risks associated with PUBS are listed in Table 3. The procedure-related pregnancy loss rate is approximately 1-1.4%.^{15,16}

MANAGEMENT OF DELIVERY

Among fetuses with Δ OD 450 measurements at or below the middle of zone 2 and normal sonography labor and deliver at term may be anticipated. Alternatively, labor may be induced with documentation of fetal lung maturity and a favorable cervix. The management of the severely affected fetus depends on the gestational age at the time of diagnosis. If severe disease occurs after 34 weeks,

Table 3. Complications of PUBS

	Complications				
	Cord hemorrhage	Cord hematoma	Fetal bradycardia	Infection	Preterm Delivery
Rate	23-53%	17%	3-12%	1%	5-6%

Modified from Ghidini A, Sepulveda W, Lockwood CJ, Romero R. Complications of fetal blood sampling. *Am J Obstet Gynecol* 1993;168:1339-44.

Table 4. Complications of intrauterine transfusion

Maternal	Fetal	Fetomaternal
Preterm membrane rupture	Overtransfusion	Transplacental hemorrhage
Infection	Exsanguination	
Placental abruption	Cord hematoma	
Preterm labor	Bradycardia	
Emergency cesarean section	Fetal injury or demise	

Modified from Bowman JM. Hemolytic disease (erythroblastosis fetalis). In: Creasy RK, Resnik R, eds. *Maternal-fetal medicine*. 4th ed. Philadelphia: Saunders, 1999:736-67.

then delivery is indicated. Prior to 34 weeks, in utero red cell transfusion is recommended. Fetal blood transfusion may occur through the **intrapertoneal (IP)** or direct **intravascular (IV)** routes. Compared to the IP route, direct IV transfusion is preferred because of a significantly improved survival rate (76% vs 88%) and lower complication rate (3.5% vs 0.8%).^{5,17} Complications of in utero transfusion are listed in Table 4. Short and long-term neurologic and physical development among those who have had in utero transfusions appears to be comparable to non-anemic, birth age-matched controls.^{6,18} Major CNS sequelae occur in 4%, of which 25% is secondary to prematurity and 75% attributed to HDN.¹⁸

SUMMARY

Rh isoimmunization is a potentially preventable condition that occasionally is associated with significant perinatal morbidity or mortality. Disease severity may be assessed using the modalities described above and frequently, invasive techniques are required to determine the risk of severe disease. Doppler flow studies appear to offer accurate, noninvasive means of evaluating fetal risk, which may allow for a decrease in invasive diagnostic procedures. The Rh isoimmunized patient, managed by an experienced team, can anticipate a favorable pregnancy outcome.

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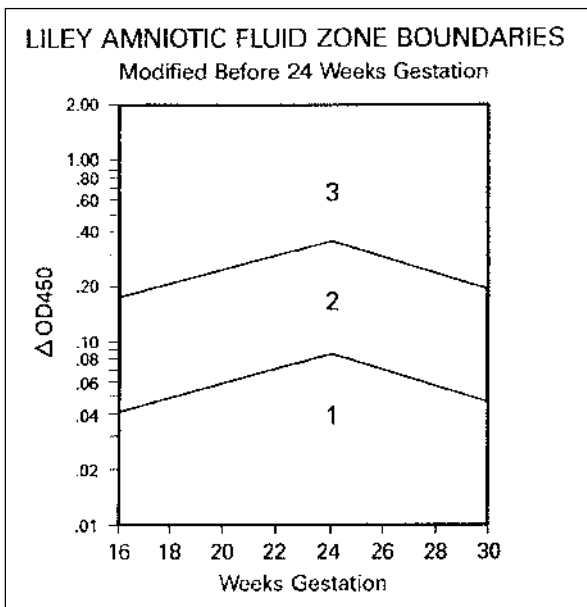


Figure 2. Modified from Liley Δ OD450 reading zone boundaries before 24 weeks of gestation. From Bowman J. Rhesus hemolytic disease. In Wald NJ ed. *Antenatal Screening, 2nd ed*. Oxford, Oxford University Press. By permission.

Alpha-thalassemia Major: Antenatal Diagnosis and Management

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The thalassemias are among the most common single gene disorders in humans. Their high frequency in specific populations appears to be a result of selection by resistance to malaria.¹ Thalassemias result from inefficient synthesis of α -globin (α -thalassemia), β -globin (β -thalassemia) or, more rarely, β - and δ -globin chains ($\delta\beta$ -thalassemia).

Without medical intervention, the lethal form of α -thalassemia, homozygous α -thalassemia major or hemoglobin Bart's disease, is not compatible with intrauterine survival through the third trimester. This disorder is a frequent cause of perinatal deaths and the principal cause of fetal hydrops in South China, Thailand, Vietnam, Laos, Cambodia, Malaysia, the Philippines and other parts of Southeast Asia.^{2,3} During the past several decades, increased emigration from Asian regions where α -thalassemia-1 is prevalent has heightened awareness of this disorder in the United States. An estimated 5-6% of persons of Southeast Asian origin living in the United States carry an α -thalassemia deletion, and carriage rates in specific Asian ethnic groups may be much higher.^{4,5}

DEVELOPMENTAL ASPECTS OF HEMOGLOBIN SYNTHESIS: THE THALASSEMIAS

The timing of onset and clinical course of α -thalassemia major follows from the normal developmental programming of hemoglobin chain synthesis. Each tetrameric hemoglobin molecule consists of two different globin chain pairs, each containing one heme molecule. Balanced expression of α -globin and non- α -globin chains is necessary for normal hemoglobin synthesis and red cell function. The duplicated α -globin genes lie in close proximity (~3.7 kilobases [kb] apart) on chromosome 16p13.3. The α -globin gene cluster spans 30 kb and consists of one embryonic ζ -globin gene (ζ_2), two α -globin genes (α_2 and α_1) and four pseudogenes. Thus, each diploid cell contains four α -globin gene copies. Deletion of two α -globin

chains can either occur on the same chromosome (cis type) or as two single gene deletions, one on each chromosome (trans type). Cis-type α -thalassemia trait (α -thalassemia-1, α^0 -thalassemia) is most frequent in individuals of East Asian descent (and in some Mediterranean populations) and carries the risk for fetal disease, while the *trans*-type deletions are more common in individuals of African descent.

During the first 6 to 7 weeks of embryogenesis, zeta (ζ) chains are transiently expressed from the α -globin gene cluster in preference to α -globin chains. Thereafter, one of the hemoglobin chain types always is an α -globin chain. (see Table). During development, α -globin chains are incorporated into fetal hemoglobin (Hb) F (α_2/γ_2) and embryonic Hb Gower 2 (α_2/ϵ_2). Normally, 12 to 16 weeks after birth the postnatal globin chain switch takes place from δ to β resulting in a shift to the predominant adult Hb, Hb A (α_2/β_2). This phenomenon of postnatal hemoglobin switching precludes appearance of β -thalassemias before or at the time of birth.

β -Thalassemia also is commonly caused by point mutations of the β -globin gene whereas α -thalassemias usually result from deletions of one or more α -globin genes. The α -thalassemia silent carrier state has the genotype of three normal genes ($-\alpha/\alpha\alpha$). α -Thalassemia trait results from two normal genes in cis ($-\alpha/\alpha\alpha$) or trans orientation ($-\alpha/-\alpha$). In Hb H disease, which is characterized by a microcytic hemolytic anemia, there is one normal gene ($-\alpha/-\alpha$). No normal α -globin genes ($---$) cause homozygous α -thalassemia major, or Hb Bart's hydrops fetalis. In α -thalassemia major, the absence of α -globin chain production leads

to excess γ chain synthesis and formation of the unstable and physiologically ineffective Hb Bart's (γ_4).

HB BART'S HYDROPS FETALIS: CARRIER DIAGNOSIS AND SCOPE OF THE PROBLEM

A diagnosis of α -thalassemia-1 should be considered whenever a woman of East Asian, Southeast Asian or Filipina background has microcytosis (MCV <80 fL, frequently <75 fL [nl 80-100]), which sometimes is accompanied by erythrocytosis and a mild hypochromic anemia. Other causes of anemia such as iron deficiency, chronic blood loss and β -thalassemia may co-exist with α -thalassemia and should be evaluated. Other laboratory findings in the α -thalassemia-1 carrier state are hypochromia (MCH <27 pg [nl 27-34]), a normal Hb electrophoresis (i.e., normal or low Hb A₂ level), and presence of precipitated Hb H (β_4) inclusions after supravital staining with the redox reagent brilliant cresyl blue. Adult carriers of the dual α -globin deletion ($---^{SEA}$, see below) have minute amounts of persistent embryonic ζ -globin chains incorporated into Hb. Detection by immunocytological staining of peripheral blood smears with anti-human ζ -globin antibodies has high positive predictive value.⁶

When both prospective parents have microcytosis, identification of the α -globin cluster genotypes by DNA testing becomes important for genetic counseling and prenatal diagnosis. If both parents are heterozygous for the cis-type α -globin gene deletion, each pregnancy carries a 25% risk for Bart's hemoglobinopathy. In Southeast Asia, the common α -thalassemia mutation is a 20.5 kb deletion of both α -globin genes, sparing the

Table: Ontogeny of Human Hemoglobin Synthesis

Embryo	Fetus	Adult
ζ_2/ϵ_2 (Hb Gower 1)		α_2/β_2 (Hb A)
ζ_2/γ_2 (Hb Portland 1)	α_2/γ_2 (Hb F)	α_2/δ_2 (Hb A ₂)
α_2/ϵ_2 (Hb Gower 2)		

embryonic ζ -globin gene ($--^{SEA}$). Individuals of Filipino or Thai ancestry may carry more extensive α -globin gene cluster deletions ($--^{SEA}$, $--^{FIL}$) that also involve loss of the ζ -globin gene. In these instances, the absence of functional embryonic hemoglobins in homozygous null fetuses probably induces early pregnancy loss, before onset of the hydrops syndrome would occur.

A second indication for genetic testing in a risk population is a previous obstetric history of either fetal losses or hydrops. Given the molecular heterogeneity of α -thalassemia mutations, Asian-Americans may carry one or more different mutations. Optimal genetic testing and counseling for individuals at risk for α -thalassemia, therefore, require knowledge of the frequencies of different mutations and the specificity of specific testing methods to detect these mutations. Although more than 20 types of α -globin gene deletions have been described, three mutations ($--^{SEA}$, $-\alpha^{3,7}$, and $--^{FIL}$) account for most mutant alleles present in North Americans of mixed Southeast Asian ancestry.⁵ DNA hybridization probes have been designed to detect α -globin and γ -globin deletions and the two large deletions ($--^{THAI}$, $--^{FIL}$) that remove the entire ζ - α -globin gene complex. Genotypes are assigned by comparing the observed restriction fragment length patterns on genomic Southern blots to previously defined patterns of α -globin gene deletions. **Polymerase chain reaction (PCR)**-based diagnosis for homozygotes has been limited by technical and interpretive concerns stemming from high **guanine/cytosine (GC)** content and extensive α -globin cluster sequence homology. Recently, however, development of multiplex-PCR assays capable of detecting the common α -globin gene cluster deletions has resolved some of these issues.

Hb BART'S HYDROPS FETALIS: ANTENATAL DIAGNOSIS AND MANAGEMENT

Early in pregnancy, production of ζ -globin and ϵ -globin chains results in synthesis of embryonic Hb Gower 1 (ζ_2/ϵ_2) and Hb Portland 1 (ζ_2/γ_2), which permit oxygen dissociation to the developing fetus. Later in the first trimester,

when the fetus with α -thalassemia major switches from ζ - to α -globin chain expression, Hb Bart's (γ_4) predominates in the fetal circulation. Hb Bart's has an abnormally high oxygen affinity and no Bohr effect and cannot deliver oxygen taken up in the placenta to fetal tissues. The relatively unstable Hb Bart's molecules also can precipitate and shorten red cell survival. Hypoxia and anemia (6-8 g Hb/dl at 12-13 weeks⁷) lead to excess extramedullary erythropoiesis, high output cardiac failure, impaired hepatic synthetic function, hepatic blood flow obstruction and, inevitably, fetal hydrops. Half of fetuses with Bart's hemoglobinopathy die between 23 and 28 weeks gestation, and live-born infants usually die soon after birth, despite aggressive resuscitative efforts.⁸ Hb Bart's hydrops fetalis also significantly increases maternal risk for preeclampsia, polyhydramnios, placental retention and postpartum bleeding, the last complication probably related to placental hypertrophy.^{2,9}

For these reasons, prenatal diagnosis of Bart's hemoglobinopathy in the first trimester is often undertaken to allow pregnancy termination. The fetal diagnosis can be made by DNA analysis of chorionic villi or amniocytes obtained by chorionic villus biopsy or amniocentesis or by Hb studies obtained by cordocentesis. This is the principal indication for cordocentesis in Southeast Asia.¹⁰ The large number of affected pregnancies that present to perinatal centers in Hong Kong and Thailand also has aided early sonographic diagnosis of evolving Bart's hydrops fetalis. In high-risk pregnancies at 10-14 weeks of gestation, placental thickening¹¹ and elevated fetal cardiothoracic ratio¹² appear to have good positive predictive value.

Although Hb Bart's disease is almost always fatal *in utero* or shortly after birth, there are rare instances of survival into childhood.¹³⁻¹⁶ These infants were all delivered quite prematurely after exposure to the harmful consequences of Hb Bart's hydrops fetalis. Since **intrauterine transfusion (IUT)** can reverse the hydrops caused by fetal isoimmune hemolytic anemia, we reasoned that IUT might be a successful approach in this disorder as well. Reversal of fetal hydrops, anemia and hypoxia ought to improve fetal de-

velopment and permit delivery of healthier infants at >34 weeks of gestation. The first intrauterine exchange transfusions for salvaging a fetus with Hb Bart's fetal hydrops were performed at Women & Infants Hospital in 1994.⁸ This patient was a Filipina-American woman whose previous pregnancy resulted in intrauterine demise of a hydroptic fetus at 28 weeks. Pathologic and DNA analysis had confirmed α -thalassemia major and Southern blotting revealed both parents to be α -thalassemia carriers with the genotype, $\alpha\alpha/\alpha^{-SEA}$. The parents received genetic counseling and, in the next pregnancy, the mother underwent amniocentesis at 16 weeks, which again confirmed fetal Hb Bart's disease. After considering their options, this couple elected IUT. During a course of three exchange IUTs, fetal ascites resolved and fetal Hb concentrations normalized. A 2.1 kg male was electively delivered at 34 weeks and was begun on a program of hypertransfusion. Since then, Dr. Stephen Carr and the Brown Fetal Medicine Program have similarly managed another Hb Bart's pregnancy. This Cambodian-American couple first presented to medical attention in mid-pregnancy. After IUT, a non-hydroptic male infant was delivered at 35 weeks of gestation. Several other affected couples have chosen pregnancy termination. Since our first case, there have been several additional reports describing successful management of Hb Bart's fetal hydrops by IUT and scheduled delivery.¹⁷⁻¹⁹

The approach taken at Women & Infants Hospital for this disorder begins with genetic counseling (preferably before pregnancy), identification of pregnancies at risk and prenatal diagnosis. The maternal risks of carrying a fetus with Hb Bart's hydrops into the third trimester make medical intervention desirable. In our experience, couples often opt for pregnancy termination, especially when their α -thalassemia carrier status was unknown before pregnancy.

Before a couple chooses pregnancy maintenance with IUTs, they meet with several specialists experienced with this condition. The perinatologist reviews the risks of intrauterine intervention, the neonatologist describes the range of out-

comes and neonatal interventions, and a pediatric hematologist reviews chronic hypertransfusion and **bone marrow transplantation (BMT)**. The **Multidisciplinary Antenatal Diagnosis And Management (MADAM)** program aims for preterm delivery at 33-35 weeks with minimized use of neonatal intensive care. Long-term management, as in β -thalassemia major, requires regular blood transfusions and iron chelation. Transfusion dependency is expensive and carries risks over time of central venous catheter complications and iron accumulation with myocardial, pancreas or liver damage, growth deficiency, hypogonadism, infection, and folic acid deficiency.

For these reasons, when intrauterine therapy is begun, we also begin **human leukocyte antigen (HLA)** typing to search for a matched sibling donor. The first successful HLA-matched allogeneic sibling donor BMT for α -thalassemia major took place in a 21-month-old girl in Hong Kong in 1997.¹⁹ Our first Hb Bart's survivor is an only child, but the second child treated *in utero* has an HLA-identical sibling. In 1999, at age two years, he also underwent successful HLA-identical sibling donor BMT.

In these Hong Kong and Providence cases, liver biopsies before BMT showed iron accumulation and hemosiderosis. After BMT, neither child has required blood transfusions. They also show accelerated developmental catch-up, although their physical growth remains along the 3rd percentile. These HLA-identical BMT recipients show mixed α -globin gene cluster chimerism, but no evidence of **graft-versus-host disease (GVHD)**. Despite the chimerism, peripheral blood cell counts of these two children have remained normal.

Westgren et al²⁰ and Hayward et al²¹ have reported intrauterine stem cell transplantation in two fetuses with Hb Bart's hemoglobinopathy, the former with donor fetal liver cells (a source of extramedullary erythroid precursors), the latter with haploidentical paternal CD34 cells. In each instance, the child's subsequent blood transfusion dependency was not reduced and the donor cells did not show a survival advantage compared with endogenous stem cells. At present, then,

and until the level of donor chimerism can be increased, BMT in early childhood remains the best long-term intervention for survivors with α -thalassemia major when an HLA-identical related donor is available. A second option, BMT from an unrelated partially mismatched donor, may emerge as a feasible alternative for those α -thalassemia major survivors who do not have an HLA-identical sibling. BMT across HLA boundaries has been undertaken for more common hemoglobinopathies, such as β -thalassemia major and clinically severe sickle cell disease.

We previously have raised ethical concerns about embarking on an expensive and technology-intensive therapeutic course for these fetuses.^{8,22} In considering long-term outcomes and quality of life measures, uncertainties have focused on associated congenital anomalies and the potential for developmental compromise from intrauterine hypoxia.

Transverse limb reduction defects have been reported frequently in fetuses affected by Hb Bart's disease and occurred in 8% of cases in one series from Hong Kong.²³ The severity and number of involved limbs varies. Our first patient has a terminal transverse defect with absence of most of the distal left foot. At birth, other limbs showed partial cutaneous syndactyly of several digits. These findings, fortunately, have not led to major motor disability (M. Msall, MD, personal communication). The pathogenesis may be terminal arteriolar occlusion by the abnormally large and poorly deformable red cells which are induced in Hb Bart's fetuses by megaloblastic erythrocytosis. Sonographic diagnosis of major terminal limb defects is sometimes possible at 10-12 weeks of gestation.²⁴ Embryoscopy at the time of cordocentesis and fetal MRI also may have a diagnostic role and assist in parental counseling.

In addition, apparently, all male survivors with homozygous α -thalassemia have hypospadias. Hypospadias, ambiguous genitalia or misassignment of female sex has been common in autopsy or sonographic series of stillborn fetuses with this condition.²² Our two patients have undergone hypospadias repairs with

good results. We have speculated that the hypospadias, like the terminal limb defects, may be due to ischemic tissue disruption, in this instance, at the corpus spongiosum.²² Hb Bart's-associated hypospadias alternatively might be due to *in utero* edema leading to failure of fusion of the urogenital folds²⁵ or to a defect or deletion of another, unidentified gene falling within the α -globin gene cluster.¹⁷

The intrauterine hypoxia has raised concerns about long-term neurodevelopmental outcomes in survivors with homozygous α -thalassemia.^{8,13-15} Fortunately, as more survivors are reported, normal development, at least into school age, appears the most common outcome. Surprisingly, this seems to be true whether or not intrauterine therapy was undertaken.^{14,16,18} These findings are similar to the wider experience with isoimmune hemolytic anemia, the most common indication for IUT in the United States. Isoimmune hemolytic and Hb Bart's fetuses both are affected by severe intrauterine anemia, although the conditions differ in timing of onset of severe disease and degree of tissue hypoxia. Nevertheless, long-term follow-up of children treated with IUT for hemolytic disease also indicates normal developmental outcome can be expected.²⁶

In summary, without medical intervention α -thalassemia major is a uniformly lethal fetal or, occasionally, neonatal disease. Current antenatal management options are pregnancy termination for maternal safety or, in selected instances, IUT and prudent delivery timing. Life-long hypertransfusion for survivors probably carries similar morbidities and lifestyle constraints to those for individuals with β -thalassemia major. HLA-identical related donor BMT during early childhood can cure α -thalassemia major. In the near future, intrauterine stem cell transplantation may emerge as the therapy of choice for this genetic disease.

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Fetal Obstructive Uropathy: Diagnosis and Management

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In recent years fetal ultrasound examination has become a routine part of obstetrical care. In addition, improvements in ultrasound resolution have facilitated diagnosis of fetal anomalies that previously would have gone undetected until postnatal symptomatic presentation. A significant fetal anomaly can be detected in approximately 1% of prenatal ultrasounds, and approximately 20% of these anomalies are genitourinary.¹ Hydronephrosis represents 50% of these prenatally detected genitourinary abnormalities, but only in a minority of cases is it associated with significant obstruction resulting in renal dysplasia and pulmonary hypoplasia. It is important, therefore, to distinguish physiological from pathological hydronephrosis.

Evaluation of fetal renal function as well as surgical intervention for fetal genitourinary obstruction is now possible. Although this technology has made the treatment of fetal obstructive uropathy possible, the results have not been as successful as once hoped. Not only is our understanding of diagnosis and patient selection incomplete, intervention carries a high complication rate and renal and pulmonary sequelae may not be prevented. The purpose of this article is to review the current approaches to the di-

agnosis and management of prenatally detected hydronephrosis and fetal obstructive uropathy.

EMBRYOLOGY

Renal development is a result of the interaction between the ureteral bud and the metanephric blastema. It is initiated in the fifth week by the ureteral bud, which arises from the mesonephric duct and penetrates the metanephric blastema. The ureteral bud then undergoes several divisions and forms the renal collecting system by the 20th week of gestation. Simultaneously, nephron development occurs at an exponential rate. Approximately 80% of nephrons have developed by mid second trimester and nephrogenesis is complete by the 36th week of gestation.

Fetal urine production begins at the eighth week and replaces the placenta as the major source of amniotic fluid by 18 weeks. The developing kidneys maintain appropriate amniotic fluid volume throughout the remainder of gestation but contribute minimally to fetal electrolyte and fluid management. At term, fetal urine production may approach 51 ml/h.²

Adequate amniotic fluid volume leads to normal pulmonary development and function. Lung development begins

at three to four weeks and development of the respiratory structures continues until term. Development of the tubular structures, however, is completed by the 24th week. Low amniotic fluid volume, or oligohydramnios, interferes with normal lung development due to extrinsic compression of the lungs or loss of adequate internal pulmonary stenting.³ The result is pulmonary hypoplasia which is the major cause of neonatal mortality in obstructive uropathy. Severe oligohydramnios also results in compression deformities of the head, thorax, and extremities.

FETAL URINARY TRACT OBSTRUCTION

Fetal urinary tract obstruction often presents as hydronephrosis. The differential diagnosis of fetal hydronephrosis includes multicystic dysplastic kidney, vesicoureteral reflux, duplication anomalies, infravesical obstruction, ureterovesical junction obstruction, or ureteropelvic junction obstruction. Obstruction of both renal units (i.e., posterior urethral valves or bilateral upper tract obstruction) may result in oligohydramnios with its subsequent complications.

Genitourinary obstruction also leads to fetal renal injury and dysplasia. Experimental models have shown that mod-

erate ureteric obstruction leads to a decrease in **renal blood flow (RBF)**, **glomerular filtration rate (GFR)**, and potassium excretion. When the obstruction is relieved, renal function improves but not to baseline. Severe obstruction may produce a rapidly progressive decrease in RBF and GFR, which may not recover.⁴ In 1971, Beck demonstrated that ureteral obstruction in the fetal lamb led to ipsilateral renal fibrosis, focal parenchymal disorganization, and other histologic changes consistent with renal dysplasia.⁵ In the early 1980s, Harrison et al created a model of obstructive fetal uropathy by placing a constricting device around the urethra of fetal lambs. By changing the timing and duration of the insult during gestation, they demonstrated that both the time of the obstruction as well as its duration were key in producing renal dysplasia and greatly influenced its severity. Lesions created early in gestation and maintained for a longer period caused the most severe injury. Furthermore, they demonstrated that genitourinary decompression in the fetal lambs could restore amniotic fluid volume and prevent pulmonary hypoplasia.^{3,6-8}

These experiments suggested that in utero surgical intervention in fetuses with prenatally detected hydronephrosis and oligohydramnios may improve clinical outcome. Although technically feasible, early operative results were not as successful as expected. Often renal insufficiency persisted and intervention did not prevent pulmonary hypoplasia, leading to fetal or early neonatal demise. In one series of 73 fetuses in 1986, 60% of fetuses died despite intervention, implying irreversible fetal renal damage.⁹ This led to the development of prognostic criteria and careful fetal selection for intervention.

ULTRASOUND FINDINGS IN OBSTRUCTIVE UROPATHY

The normal kidneys and bladder can now be evaluated as early as 16 to 17 weeks of gestation, while markedly dilated systems can be seen as early as 12 to 14 weeks.¹⁰ Hydronephrosis is the most common genitourinary abnormality seen on prenatal ultrasound. Often a distended bladder with bilateral ureteral dilation is evident, implying bladder outlet obstruction. The degree of collecting

system dilation seen on ultrasound must be correlated with gestational age, because it can vary during gestation. A minimal degree of hydronephrosis is often physiologic, resulting in a normal neonatal examination, and requires no further intervention. It has therefore become necessary to establish thresholds of renal pelvic diameter that distinguish between physiologic and pathologic hydronephrosis. Currently, a renal pelvic **anteroposterior diameter (APD)** of >6mm at <20wks, >8mm at 20-30 weeks, and >10mm at >30 weeks' gestation is considered significant.⁴ In addition to renal collecting system dilation, the ultrasound should evaluate renal parenchymal appearance for echo density and/or cortical cysts, unilateral or bilateral involvement, amniotic fluid volume, fetal size and weight for age, external genitalia and gender, other organ system abnormalities, and bladder size, thickness, and cycling.

Renal parenchymal appearance on prenatal ultrasound does not always correlate with renal function. Nevertheless, the presence of cortical cysts and hyperechoic parenchyma is a sign of renal dysplasia. In one study the presence of renal cortical cysts had a 100% specificity for renal dysplasia but it had a low sensitivity of 60%.¹¹ Thus the absence of cortical cysts does not ensure the absence of dysplasia. When evaluated separately, increased echogenicity of the renal cortex was less sensitive and specific than the presence of cortical cysts.¹² These sonographic findings are, therefore, only useful when present and their absence provides no prognostic information regarding renal function. Similarly, amniotic fluid volume is only prognostic at the extremes.¹³ Thus a more sensitive means of assessing fetal renal function is necessary to facilitate appropriate selection of fetuses with obstructive uropathy for prenatal treatment.

EVALUATION OF FETAL RENAL FUNCTION

Fetal renal function can be evaluated by studying the fetal urine biochemistry and the rate of bladder filling after ultrasound guided vesicocentesis. The healthy fetus makes hypotonic urine. As renal injury progresses, proximal tubular function declines and the urine be-

comes isotonic. Fetuses in whom there is an elevation in urinary sodium concentration to greater than 100mEq/L, chloride concentration greater than 90mEq/L, and urine osmolality greater than 210mOsm/L are at high risk of irreversible renal dysplasia and poor postnatal renal function, even with intervention. Urinary calcium concentration greater than 8mg/dl is the most sensitive indicator of dysplasia. Total protein greater than 20mg/dl and PO₄ greater than 2mMol/L also correlate with renal injury.¹⁴ In addition, elevated fetal urinary levels of β 2-microglobulin to greater than 2mg/L may reflect proximal renal tubular dysfunction. β 2-microglobulin is a low molecular weight protein that is filtered through the glomerular basement membrane and is almost entirely resorbed in the proximal renal tubule.¹⁵ β 2-microglobulin may be elevated in spite of normal urine electrolytes in fetuses with normal amniotic fluid volume. This finding has been shown to correlate with worse postnatal renal function at one year of age when compared to similar fetuses with low urinary β 2-microglobulin levels.¹⁶

Individual urinary parameters are not very accurate in predicting presence or absence of renal dysplasia. However, when used in combination, these parameters greatly improve sensitivity and specificity in diagnosing underlying renal damage. Due to normal deviation in renal function, urinary electrolytes can vary resulting in inaccurate prediction of fetal renal function. Furthermore, a single sampling from stagnant urine in an obstructed system may be inaccurate as osmotic gradients and urothelial secretions may change its composition. The first sampled urine may, indeed, be isotonic leading to a misdiagnosis of severe renal dysplasia. However, sequential vesicocentesis which shows progressively hypotonic urine in combination with sub-threshold last urine values improves diagnostic precision and indicates a reversible renal injury.¹⁷

SELECTION CRITERIA FOR FETAL INTERVENTION

Survival for fetuses with unilateral renal obstruction is almost 100% as the contralateral kidney compensates for the loss. Bilateral hydronephrosis, however, represents a potentially more serious situation,

and it may be due to infravesical obstruction. It may lead to oligohydramnios, which is potentially life threatening and is a strong predictor of an adverse outcome. Therefore, fetuses with unilateral hydronephrosis are excluded from in utero intervention.¹⁴

Fetal intervention aims to relieve urinary obstruction (preserve renal function) and to restore normal amniotic fluid volume (prevent pulmonary hypoplasia). If renal injury is severe and irreversible at time of diagnosis, surgical intervention is likely to be unsuccessful as oligohydramnios will persist with resultant pulmonary hypoplasia and probably fatal neonatal respiratory failure. Therefore, criteria for in utero intervention in obstructive uropathy indicative of adequate renal function have been used as selection criteria for further evaluation and intervention. These criteria are summarized in Table 1.

APPROACH TO THE FETUS WITH HYDRONEPHROSIS

Using the selection criteria above, fetuses with hydronephrosis can be grouped into three categories: 1) fetuses with severe irreversible renal injury unlikely to benefit from intervention, 2) fetuses with adequate renal function to benefit from prenatal genitourinary decompression, and 3) fetuses with good prognoses without intervention to avoid unnecessary and risky intervention. An algorithm suggesting management of the fetus with antenatally detected hydronephrosis is presented in Figure 1.¹⁸

Fetuses with bilateral hydronephrosis, oligohydramnios, and poor renal function that fail to improve on serial vesicocentesis fall into Category 1 and likely will not improve after prenatal in-

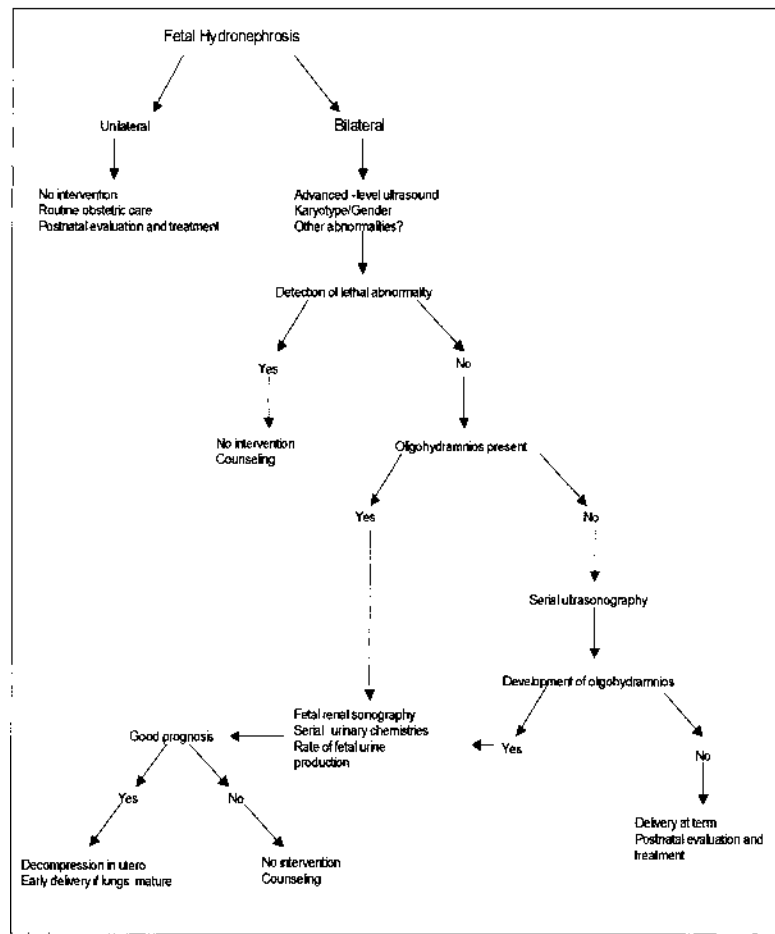


Figure 1. Algorithm for management of fetal hydronephrosis. (From Gloor JM¹⁸)

tervention. Fetuses with bilateral hydronephrosis in whom assessment demonstrates good renal function based on sonographic findings, urinary biochemistry and post-vesicocentesis bladder filling fall into Category 2 and should be considered for decompression. Fetuses with bilateral hydronephrosis and adequate amniotic fluid volume throughout gestation fall into Category 3 and are unlikely to benefit from in utero inter-

vention. Their pulmonary development should not be compromised and their genitourinary abnormalities are best addressed postnatally.

FETAL INTERVENTION

Percutaneous vesicoamniotic shunt placement, open fetal surgery, and fetoscopic surgery have been reported as approaches to decompress the obstructed fetal genitourinary system. Ultrasound guided percutaneous shunt placement is the most widely used technique to date and several series of prenatal shunt placement have been reported. The results, however, have been mixed and difficult to interpret due to wide variations in patient selection, operative technique, and outcome measurement. In a recent report, Freedman et al, reviewed the records of 55 consecutive patients presenting between 1987 and 1994 using the selection criteria described above.¹⁹ They concluded that when evaluated by specific diagnosis, intervention appeared to provide outcomes in these high-risk fetuses that were

Table 1. Criteria for prenatal intervention

<i>Ultrasound Findings</i>	Bilateral Hydronephrosis No renal cortical cysts Normal renal parenchymal echogenicity Adequate bladder filling after vesicocentesis Oligohydramnios
<i>Urine Biochemistry</i>	
Na	<100 mEq/L
Cl	<90 mEq/L
Osm	<210 mOsm/L
Ca	<8 mg/dl
PO ₄	<2 mMol/L
Total Protein	<20 mg/dl
β ₂ -microglobulin	<2 mg/L

comparable to those for disease detected postnatally. However, the study failed to answer whether these comparable outcomes were due to shunting or the natural history of the obstructive disease process that did not necessarily need intervention. Strictly speaking, therefore, the benefit of prenatal genitourinary decompression remains questionable. The use of vesicoamniotic shunting must also be tempered by a 45% complication rate.²⁰ This includes inadequate shunt drainage or shunt migration, premature labor, urinary ascites, chorioamnionitis, and iatrogenic gastroschisis.¹⁴ Nevertheless, it may be reasonable to assume that some benefit may be gained by prenatal intervention in this high-risk population.

Open surgical decompression of the fetal bladder had been suggested in fetuses less than 24 weeks' gestation as shunt placement is technically most difficult in early gestation fetuses with severe oligohydramnios. Bilateral cutaneous uterostomies were first reported in a 21-week fetus in 1981.²¹ Although technically successful, the fetus died at birth due to pulmonary hypoplasia. There are several other reports in the literature of open surgical decompression, but the results have not been better than percutaneous shunting.¹⁴ Further, open procedures are riskier with complications including infection, premature labor, fetal death, and surgical failure. The mother receives no direct benefit but assumes the inherent risk of general anesthesia, laparotomy, and hysterotomy.

Fetoscopic surgery is the newest approach to decompression of the fetal genitourinary tract. A cutaneous vesicostomy using an argon laser has been reported in a 17-week fetus.²² It requires no hysterotomy as fetal cystoscopy is technically possible through a 0.7mm fiberoptic endoscope. As technology improves, endoscopic intervention holds promise for the future.

Termination of the pregnancy may be considered in fetuses with severe renal dysplasia and oligohydramnios that cannot be reversed by intervention. These fetuses have a uniformly poor outcome and most die at birth or soon thereafter. Termination may also be considered if other organ systems are affected or there are karyotypic abnormalities.

Early delivery may be helpful if there is new onset third trimester oligohydramnios (28 to 32 weeks). The fetal lungs can be induced to mature with steroids and lung maturity can be assessed by measuring the amniotic lecithin-sphingomyelin ratio. There is a high risk of perinatal respiratory distress. After 35 to 36 weeks' gestation delivery can be induced in the fetus with oligohydramnios with little pulmonary risk. There are, however, currently no studies documenting improved outcomes after early delivery.²³

CONCLUSION

The advent of routine prenatal ultrasound examination has resulted in an increase in the detection of fetal hydronephrosis. Although fetal hydronephrosis is not synonymous with urinary obstruction, findings on ultrasound and fetal urinalysis can suggest obstructive uropathy. Intervention should be limited to chromosomally normal fetuses with bilateral hydronephrosis, oligohydramnios, and adequate renal function.

The basic structure of the kidneys and lungs is complete by 12 weeks. The diagnosis of obstructive uropathy, however, often is not made until well into the second trimester when injury may already be irreversible. Thus it is understandable why the results of fetal intervention have not been uniformly successful. As the surgical and diagnostic technology improves, successful intervention earlier in gestation may become feasible with better neonatal outcomes.

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The Fetus With an Abdominal Wall Defect

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Antenatal detection of abdominal wall defects has impacted the perinatal care of both the expectant mother and of the fetus. Prenatal referral to tertiary care centers that can provide for the surgical needs of the infant has also allowed for focused management from the obstetric perspective to identify the unique problems associated with these pregnancies. With advances in maternal-fetal medicine, obstetrics and neonatal surgery and the increasing availability of in utero interventions it is essential to determine which current therapeutic interventions result in optimized outcomes and where future investigational efforts should be directed. In this age of information technology we need to provide expectant parents with reliable and useful information.

Although not specifically elucidated, the etiologies of omphalocele and gastroschisis are likely widely discrepant, based not only on the spectrum of associated anomalies in the fetus but also the differing demographics of the maternal populations. This dichotomy extends to the postnatal period in terms of operative management and morbidity and mortality. Vital to appropriate counseling and stratification of risk therefore, is the ability to make a specific diagnosis for a fetus with an abdominal wall defect.

On sonogram, the presence of a defect to the right of the umbilicus, with eviscerated bowel that is not contained within a membrane is consistent with gastroschisis. The fetus with omphalocele has an absent abdominal wall subjacent to the cord insertion site with a membrane usually containing the protuberant liver and eviscerated intestine. Localization of the defect is helpful particularly to avoid diagnostic errors associated with the rare ruptured omphalocele that masquerades as gastroschisis.

OMPHALOCELE

Approximately 20% of anterior abdominal wall defects are omphaloceles (abdominal wall defects at the level of the umbilicus, usually covered by a mem-

brane) Antenatal evaluation of the fetus with omphalocele focuses on the associated conditions. These may include lethal chromosomal anomalies (particularly trisomy 13 and 18), congenital cardiac defects, other upper midline/thoracic defects such as in the Pentalogy of Cantrell (sternal, diaphragmatic, pericardial defects with ectopia cordis and omphalocele) or the lower midline OEIS complex (omphalocele, exstrophy, imperforate anus, spinal defect). Other associated conditions include Beckwith-Wiedeman syndrome, cleft lip/palate and cryptorchidism. The incidence of associated anomalies (excluding intestinal malrotation, which is uniformly present in those with large defects) is reported as high as 69%.¹

In a recent study of 23 fetuses or infants with the pre or postnatal diagnosis of omphalocele, 21 fetuses had an antenatal diagnosis made by 18 weeks gestation.² In 18 pregnancies, the diagnosis was correct. (two false positives, and 3 false negatives). Associated anomalies were correctly identified in 12 but incorrectly reported in 8. There were 13 terminations including 2 trisomy 18s and one trisomy 13. Two fetal deaths followed amniocentesis. Of the 10 live births, 9 had their ventral defect repaired with a one-year survival rate of 89%.

When providing antenatal counseling to parents, this information needs to be relayed within the appropriate context. Those liveborn infants with an omphalocele and without additional life-threatening anomalies have a lesion that is amenable to surgical therapy with good outcomes.

SURGICAL CONSIDERATIONS

Repair of the omphalocele provides specific challenges to the infant and surgeon, but in over 50% cases, a primary repair can be achieved. The spectrum of defects ranges from the "hernia of the cord," which could potentially be reduced and closed at the bedside, to omphalocele minor with a fascial defect

of up to 4cm and to omphalocele major typically with defects from 4 cm to 8 cm. Given the closed nature of the defect, with liver and intestines enclosed in peritoneum and amnion, postnatal management can initially focus on the potentially lethal malformations. Once these have been identified and addressed, usually within 24-48 hours, decisions can be made regarding surgical closure. In contrast to gastroschisis, the intestinal tract is usually normal, but the size of the defect and the liver may provide major impediments to complete fascial approximation. Viscero-abdominal disproportion refers to the discrepancy between the current abdominal capacity and the extra-abdominal volume of eviscerated organs. Aggressive reduction into the abdomen may result in compromised hepatic or visceral perfusion requiring urgent decompression. Infants with very large defects may require staged closure to allow for gradual expansion of the abdominal wall. This may involve: 1) primary coverage with skin flaps with subsequent ventral hernia repair, 2) staged closure using a silo, with or without excision of the sac or 3) topical treatment may induce sufficient wound contraction with epithelialization to achieve closure for subsequent ventral hernia repair. Infants with lethal cardiac or chromosomal disorders can be managed nonoperatively with topical therapy.

Extended hospital courses and complications are primarily limited to those with defects measuring greater than 8 cm in diameter. Even in this group the surgical mortality was only 8%.¹ In the absence of associated severe anomalies these infants can have an uncomplicated course with a normal long-term quality of life. Less optimal outcomes are determined primarily by the nature of the chromosomal defect and the complexity of associated cardiac and other organ system defects. With improvements in the reconstruction of these complex anomalies, this will further reduce mortality and improve quality of life. As such, the an-

tenatal assessment by a multidisciplinary team including perinatologists, neonatologists, geneticists, cardiologists and surgeons will have critical impact on the decision to continue the pregnancy.

GASTROSCHISIS

In a gastroschisis, the defect is always to the side (and almost always to the right) of the umbilicus, which is normal. A gastroschisis is never covered by a membrane. The perinatal management of infants with gastroschisis is distinct from those with omphalocele. Whereas the size of the ventral defect and associated anomalies dictate prognosis in omphalocele, the relevant parameters in the infant with gastroschisis are related to the condition of the newborn and the intestine. Short bowel syndrome with its attendant risks remains one of the significant complications of the diagnosis of gastroschisis.

Fetuses with gastroschisis tend to be small for gestational age and are born to young primiparous women, often after preterm labor. Although the specific factors leading to this congenital malformation have not been elucidated, the focus has rested on environmental and potentially nutritional factors. Studies from the California birth defects monitoring program have proposed that a low prepregnancy body mass may represent a risk factor for offspring with gastroschisis.³ These investigators suggest that abnormal levels of 3 nutrients (low alpha carotene, low total glutathione and high nitrosoamines) are potential candidates for further investigation.⁴ Much of the clinical and basic science investigation into gastroschisis has tried to identify factors that contribute to the intestinal wall thickening and formation of a peel over the serosal surface, the findings that most impede reduction of the intestine into the abdominal cavity and that are thought to contribute to the dysmotility encountered postoperatively. Conventional wisdom attributes these changes to exposure to amniotic fluid, although not all infants with gastroschisis exhibit the serosal peel. A recent animal study has sought to differentiate between urinary and gastrointestinal waste products in amniotic fluid, and has implicated components of meconium as

the more significant sources of inflammation.⁵ Saline amnioinfusion performed both in an animal model and in a small cohort of patients with gastroschisis and severe oligohydramnios was found to be associated with less inflammatory peel as compared to non-amnioinfused infants with gastroschisis.^{6,7,8} These concerns have been the premise for advocating early delivery of these infants, particularly when visceral distension is noted to be progressive, suggesting an underlying intestinal obstruction. Vascular etiologies of the intestinal atresias and of the inflammatory changes have been proposed and may be related to constriction of the mesentery by the approximating fascial edges as evidenced in fetuses born with antenatal detection of gastroschisis and consequent jejunal atresia or congenital **short bowel syndrome (SBS)** without abdominal wall defect. Based on the premise that the amniotic insult to the intestine is cumulative and a function of time, preterm induction of labor was considered prudent so as to enhance the ability to achieve primary closure. In the current literature, no randomized prospective series exists to support this intervention and preliminary evidence from our series of inborn patients in whom no attempt was made to induce early labor suggests that there is no beneficial effect to early delivery and that term infants recover as well if not better than their preterm counterparts. Premature labor however, remains a feature associated with gastroschisis and may not be an avoidable event in approximately 30% of patients.⁹ Debate in the perinatal management of gastroschisis has also revolved around the mode of delivery with Cesarean section advocated by multiple centers. Vaginal delivery, however, has been shown to be safe in multiple recent studies and general consensus would indicate that a trial of labor is appropriate and that Cesarean section should be reserved for obstetric indications only.^{10,11,12}

OPERATIVE MANAGEMENT

Antenatal counseling by a pediatric surgeon will focus on the immediate surgical care to be delivered to an infant with exposed viscera that are at risk for further vascular compromise. The options

for acute management range from operative intervention either in the delivery room or in the operating room. The exposed intestine has a variable degree of inflammatory peel. When extensive, this may prohibit identification of an intestinal atresia. In virtually all cases, the bowel length appears shortened, with a thickened mesentery. Sedation and paralysis with expansion of the lateral abdominal wall may enable complete reduction of the viscera and permit fascial closure. If not feasible then a silo, typically spring-loaded and no longer requiring fascial sutures, can be inserted. This can also be accomplished at the bedside with minimal sedation. A recent prospective trial of routine insertion of a silo as compared to emergency operating room closure provided favorable results for the routine insertion of the silo with reduced number of days of extubation, to full feeds and to home discharge.¹³ The postoperative course of these infants is typically marked by a prolonged ileus, during which they rely on parenteral nutrition support. When intestinal continuity has not become evident after several weeks, contrast studies are performed to delineate the anatomy and to exclude the possibility of an occult atresia. By this time much of the inflammatory peel, which may have been present initially, will have resolved and now allows for intestinal resection and anastomosis to establish continuity. Short bowel syndrome may occur as a consequence of atresias or after postnatal hypoperfusion insults to the intestine or even florid necrotizing enterocolitis. With appropriate nutritional management focusing on measures to avoid cholestasis, these infants can be transitioned to full enteral feedings.

The use of promotility agents has not been shown to be useful in expediting normal motility.¹² Motility agents and acid suppression therapy however may play a role in a significant number of infants who have evident gastroesophageal reflux.¹⁴ Although both omphalocele and gastroschisis are associated with intestinal malrotation, the occurrence of gastroesophageal reflux during the first year of life is reported to be higher in omphalocele than gastroschisis.

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Fetal Cardiac Arrhythmias: Diagnosis and Management

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In the last two decades, the subspecialty of fetal cardiology has grown dramatically. Prenatal diagnosis and management have evolved from basic descriptive reports to more invasive and experimental therapeutics. The management of fetal arrhythmias has seen the greatest opportunity for *in utero* therapy. This paper will review current diagnostic and management strategies for the fetus with a cardiac arrhythmia. Optimal outcome relies on a well integrated team approach to the maternal-fetal patient set. Careful consideration of the risk-benefit ratio of any therapy as it relates to both expectant mother and fetus must be discussed. Accurate diagnosis of fetal arrhythmias requires knowledge of, and experience with, highly specialized ultrasonographic techniques, and is crucial prior to consideration of fetal therapy. Any attempt at developing a rational treatment plan requires a working knowledge of the likely electrophysiologic principles of the suspected arrhythmia, the pharmacology of the pertinent antiarrhythmic agents, as well as their pharmacokinetics when utilized in the pregnant patient.

DEFINITION, INCIDENCE & ETIOLOGY

One may define a fetal arrhythmia as any irregular rhythm, or any sustained regular rhythm whose rate falls outside the normal fetal range of 120-160 bpm. This excludes the well-characterized abnormalities of fetal heart rate seen in the course of labor and delivery, as well as those associated with fetal distress for other reasons. It has been estimated that a cardiac arrhythmia is detected in approximately 1-4% of fetuses,¹ of which roughly 10% are considered potentially serious.² Table 1 lists the more common indications for fetal arrhythmia evaluation.

Cardiac arrhythmias may be grouped into three main categories: isolated extrasystoles, tachyarrhythmias,

(sustained fetal heart rate greater than 160-180 beats per minute) and bradyarrhythmias (sustained fetal heart rates below 110-120 beats per minute). The critical initial step in the management of the fetus with a suspected arrhythmia is accurate diagnosis.

DIAGNOSTIC TECHNIQUES

Cremer³ first described the fetal electrocardiogram (ECG) in 1906. Although technically feasible, the quality and integrity of the signal obtained has prevented its routine application in clinical practice. Indirect methods presume the electrical activity of the heart by evaluation of the physical consequences of atrial and ventricular contraction. By their inferential nature these techniques are obviously more prone to errors in diagnosis.

Table 1. Indications for Fetal Arrhythmia Evaluation

Suspected arrhythmia
Non-immune hydrops fetalis
Structural congenital heart disease (esp heterotaxy syndromes, corrected transposition)
Fetal cardiac tumors
Maternal collagen vascular disease
Maternal medications/toxins that may predispose fetus to arrhythmia

Atrial systole (and the inferred atrial depolarization, or p wave on the ECG) may be detected by evaluation of **atrio-ventricular (AV)** valve motion or atrial wall directly. Ventricular wall motion (or opening of the semilunar valves) are mechanical events that indirectly represent ventricular depolarization (the QRS complex of the ECG). By careful analysis of this association, one can deduce the specific arrhythmia in a manner similar to that used with a surface ECG. Similarly, Doppler interrogation of blood flow serves as a reliable recorded physical consequence of chamber depolarization. Evidence of atrial depolarization may be determined when assessing the flow pattern across either of the AV valves. Doppler evaluation in either of the great arteries will represent ventricular depolarization. Simultaneous recording of velocities in the pulmonary artery and pulmonary vein can also determine fetal rhythm.

ISOLATED EXTRASYSTOLES

The vast majority of fetal arrhythmias noted in routine obstetric care are benign extrasystoles; isolated atrial or ventricular premature contractions that if infrequent, have no physiologic significance for the developing fetus or newborn. Isolated extrasystoles generally comprise about 80%-90% of suspected arrhythmias for which fetuses are referred to tertiary centers for evaluation.⁶ These extrasystoles typically are perceived as pauses or 'dropped beats' noted during routine auscultation of fetal heart rate. Determination of the origin of the premature beat may be difficult. If incessant, or if occurring in a recognizable recurring pattern, premature extrasystoles may rarely be indicative of more significant pathology and complete fetal echocardiography is indicated.

Sustained arrhythmias may be classified into two groups (Table 2) based on the observed **fetal heart rate (FHR)**: tachyarrhythmias, are those in which the FHR is greater than 160 bpm, or bradyarrhythmias, in which the FHR is less than 120 bpm. Any fetus with a sustained arrhythmia should have a complete level II ultrasound including a fetal echocardiogram to detect any potential associated defects.

TACHYARRHYTHMIAS

These are by far the most common of the sustained arrhythmias seen in the practice of fetal cardiology, and are made up of a wide-ranging group of distinct diagnoses, listed in Table 2. The etiology of fetal tachyarrhythmias generally mirrors that seen in the newborn infant, with some important differences. As a general rule, sinus tachycardia is not a pathological diagnosis in and of itself, but rather the physiologic consequence of another pathologic process affecting the fetus such as anemia, thyrotoxicosis or infection. At higher rates (200-230 bpm) it may be difficult to differentiate between sinus tachycardia and some of the other relatively "slower" (and less common) supraventricular tachycardias such as ectopic focus atrial tachycardia, or junctional ectopic tachycardia. Most pathologic arrhythmias, (ie not sinus tachycardia) will begin and end abruptly, while sinus tachycardia occurs more gradually. This may be observed while performing a vagal maneuver, such as exerting moderate head pressure.

REENTRANT SUPRAVENTRICULAR TACHYCARDIA

The most common type of tachyarrhythmia seen in clinical practice is reentrant, or reciprocating **supraventricular tachycardia (SVT)**, which makes up approximately 65-85% of all sustained fetal tachycardias.⁷ Reentrant SVT is rarely associated with structural heart disease. As their names imply, both forms of reentrant tachycardia require a one-to-one relationship of atrial and ventricular depolarization, and this should be carefully sought when attempting to make either of these diagnoses in utero. Rates may range from 220 bpm to as high as 300 bpm; the more typical rate observed has been 240-250 bpm.

ATRIAL FLUTTER/ATRIAL FIBRILLATION

Atrial flutter and atrial fibrillation are relatively uncommon, comprising approximately 10-15% in many series. Like reentrant SVT, they are not usually associated with any specific form of structural heart disease, though any condition that results in dilated atria predisposes the fetus to development of atrial arrhyth-

mia. The atrial flutter rate is typically in the range of 400-600 bpm and is associated with some degree of AV block and lower ventricular rates. For example, an atrial rate of 500 bpm with accompanying 2:1 AV block would result in a ventricular rate of 250 bpm. The degree of AV block may be variable, resulting in an irregular ventricular response. The extremely high atrial rates make accurate recording with either Doppler or m-mode techniques far more challenging. Atrial fibrillation is exceedingly rare, and is characterized by a paucity of organized atrial depolarization or contraction and is always associated with a variable and irregular ventricular response.

VENTRICULAR TACHYCARDIA

Ventricular tachycardia (VT) is very rare in the prenatal setting, accounting for less than 3-5% of all sustained tachyarrhythmias. The electrophysiologic mechanism usually involves an irritable ventricular focus related to ischemia, cardiomyopathy, myocarditis, maternal drug use or electrolyte abnormality. The focus may be associated with cardiac rhabdomyoma seen in tuberous sclerosis, but is not usually associated with any specific form of structural heart disease. The rates encountered have been widely variable (180-400 bpm). The hallmark of diagnosis is the presence of atrioventricular dissociation, where the ventricular rate exceeds the atrial rate, with no clear relationship between ventricular and atrial depolarization/contraction.

BRADYARRHYTHMIAS

The causes for sustained bradyarrhythmias include sinus bradycardia and high grade (second or third degree) heart block. (Table 2) As noted earlier for sinus tachycardia, sinus bradycardia is rarely a pathologic process in and of itself, but is more likely a physiologic response to some other process, most commonly increased vagal tone from a variety of causes. Postnatal experience has shown that newborns may tolerate sinus rates in the 50-70 bpm range with no untoward effects.

Congenital heart block is usually noted on routine prenatal screening as an unusually low heart rate, generally in the 60-80 bpm range. Evaluation finds

the atrial rate to be normal (120-160 bpm) accompanied by a slower ventricular rate. Congenital heart block may either be second degree or (more commonly) third degree, which is also termed complete heart block. Second degree heart block is defined as the intermittent loss of normal atrioventricular (AV) conduction. Complete or third degree heart block is the more commonly encountered form of sustained bradycardia, where there is no conduction whatsoever of any electrical impulse from the atria to the ventricles. It is useful to point out the difference between complete AV block, where the atrial rate is always greater than the ventricular rate, and AV dissociation, (seen with ventricular tachycardia) where the ventricular rate is faster than the atrial rate.

Both second and third degree AV block may be broadly grouped into two categories: those with and those without associated structural heart disease. Approximately half of all cases of complete heart block are associated with structural heart disease,⁸ and include those defects with atrial isomerism (heterotaxy syndromes), AV septal defects or L-transposition of the great arteries (ventricular inversion) as part of their cardiac malformation. The other group, those with grossly normal cardiac anatomy are almost invariably associated with maternal collagen vascular disease. The mother may be asymptomatic at the time fetal heart block is diagnosed. Prognosis is significantly worse in fetal heart block when associated with structural heart disease, hydrops fetalis or very low ventricular escape rate (<50 bpm).

Therapy

The decision to treat the fetus with a cardiac arrhythmia is a difficult one based on many factors. Initially, one must decide whether the arrhythmia is associated with poor outcome, which is generally manifested by the development of fetal hydrops and its associated high mortality. If the fetus is hydropic at presentation, there is general agreement that antiarrhythmic therapy is warranted, though optimal route of administration is highly variable among practitioners (oral vs. intravenous vs. transumbilical). In general, sustained arrhythmias are far

more likely to progress to fetal hydrops, though the duration of the arrhythmia after which hydrops is likely to develop is unknown for any given arrhythmia at any given rate. As with non-sustained arrhythmias, it is not known what percentage of normal sinus rhythm in a 24-hour period is required to prevent the development of hydrops. One must consider the likelihood that the arrhythmia in question will respond to the proposed therapy, based on past experience and reports in the literature from many centers. Potential maternal morbidity related to proposed therapy *must* enter into the decision before attempting transplacental therapy. A thorough understanding of the proarrhythmic and myocardial depressant effects of nearly all antiarrhythmic drugs for both the mother and fetus is essential.

Maternal monitoring during the initiation phase of therapy should, at a minimum, include daily and/or continuous electrocardiographic monitoring for potential proarrhythmic effects, as well as surveillance specifically tailored to the agent used. Route of administration must also be considered. If transplacental therapy is reasonable, the maternal intravenous route is generally chosen for the initial (loading) phase, with change to oral therapy once the arrhythmia has been controlled. Alternatively, direct fetal therapy via cordocentesis is feasible, and may be indicated if severe hydrops is present, or if placental edema is thought to interfere with transplacental therapy. Parental concerns, social circumstances and informed consent as to the parents' understanding of the potential risks and benefits must also be determined. It is important to remember that if fetal lung maturity can be documented, or facilitated by the administration of antenatal steroids, delivery of the baby is usually the therapy of choice, since treatment of the arrhythmia is much safer and more reliable when administered to the

infant directly. If transplacental or transumbilical therapy has been unsuccessful, and/or maternal morbidity precludes continuation of antiarrhythmic therapy, knowledge of institutional outcome statistics for various birthweights will be of great importance in decision making. The myriad factors at play again highlight the optimum outcome achieved by a coordinated multidisciplinary fetal team.

ISOLATED EXTRASYSTOLES

As mentioned above, isolated atrial or ventricular premature contractions are benign and require no therapy save for watchful observation for the unlikely association with a sustained tachyarrhythmia.

TACHYARRHYTHMIAS

Supraventricular tachycardia

When considering therapy for sustained SVT, thought should be given to the likely electrophysiologic mechanism. Treatment is generally directed at slowing conduction in one or both of the available pathways (AV node or accessory connection) in the reentrant circuit, thereby "breaking the electrical loop." Additional efficacy may be gained by choosing an antiarrhythmic drug that also suppresses atrial extrasystoles.

Digoxin has been the first line therapy of choice for many years. It acts primarily by slowing conduction at the AV node, but also reduces the frequency of atrial extrasystoles. It is also the only antiarrhythmic agent without any negative inotropic effects. Generally, initia-

Table 2. Sustained Arrhythmias

Tachyarrhythmias

- Sinus tachycardia
- Supraventricular tachycardia
 - AV (atrioventricular) reentrant tachycardia (AVRT) (eg WPW syndrome)
 - AV Node reentrant tachycardia (AVNRT)
 - Atrial flutter/fibrillation
 - Junctional tachycardia
- Ventricular tachycardia

Bradyarrhythmias

- Sinus bradycardia
- High grade (2nd or 3rd degree) AV block
 - Maternal collagen vascular disease
 - Structural congenital heart disease

tion of digoxin therapy is accomplished by intravenous loading or "digitalization" consisting of 1.5 - 2.0 mg in the first 24-36 hours of therapy. Maternal digoxin toxicity (nausea, vomiting, malaise, blurry vision, arrhythmia, etc.) can be minimized by close attention to maternal renal function, serum potassium concentration and common drug interactions. Maintenance dosing should be based on maternal trough digoxin levels, therapeutic effect, and toxicity, but commonly fall in the range of 0.5-1.5 mg per day due to the high maternal glomerular filtration rate seen during pregnancy. Dosing will be guided by daily trough drug level as transplacental digoxin pharmacokinetics are highly variable. The goal of therapy is to achieve a maternal serum concentration near the toxic range of 2.0-2.3 ng/ml if well tolerated by the mother.

If digoxin fails to achieve conversion to sinus rhythm, a second drug may be added to the regimen. The most commonly utilized classes of drugs have been the class IA agents (procainamide) and class IC agents (flecainide). Amiodarone (mixed class II and class III action) and sotalol have also been used with efficacy. Calcium channel blockers are generally contraindicated. Each of these medications has its own list of potential risks the full review of which is beyond the scope of this paper. Perhaps the most important factor in guiding the use of second line antiarrhythmics in this situation is personal physician experience. The most effective agent to add to or substitute for digoxin when it alone fails has not yet been established.

Intrauterine treatment of atrial flutter or fibrillation is aimed at control of ventricular response rate. Again, digoxin has the broadest experience as first line therapy, with second line drugs used as in reentrant SVT. Atrial flutter may be particularly resistant to pharmacotherapy, prompting important consideration for early delivery and electrical cardioversion.

VT is much less common in the fetus than are other tachyarrhythmias, and requires the documentation of AV dissociation for its diagnosis. Unlike the supraventricular arrhythmias however, digoxin is not the drug of first choice, and in fact may aggravate the ventricular

tachycardia by precipitating ventricular fibrillation, a frequently lethal event. Drugs of first choice in this scenario would be those in class IB, such as lidocaine or mexilitene. Alternatives include procainamide and amiodarone.

Complete heart block

The fetus with CCHB on the basis of maternal connective tissue disease without hydrops does not require therapy, but should be followed closely for the development of hydrops. The bradycardic fetus with hydrops is at extremely high risk for fetal or neonatal demise regardless of the presence of associated structural heart disease and thus warrants attempts at *in utero* therapy or early delivery. Plasmapheresis and steroid administration have been variably successful. The fetus with structural heart disease and heart block is at high risk of developing hydrops, and must be closely observed. Theoretically, fetal ventricular (or even sequential atrioventricular) pacing would seem the logical treatment of choice. Both techniques have been accomplished via maternal hysterotomy and fetal sternotomy in the fetal lamb, but have not yet been successfully applied to the human fetus. The future may be in the use of fetal thoracoscopy to reduce the morbidity associated with exteriorizing the fetus. Early delivery may be the treatment of choice even if the fetus is preterm, if other therapeutic options have been exhausted.

SUMMARY

The diagnosis and management of fetal cardiac arrhythmias requires complex skills and knowledge, and has had a great impact on the care of infants with congenital heart disease and their families. Optimal benefits will be derived from a thoughtful team approach, with skillful internal communication, and especially when parental involvement is encouraged in the decision making process.

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Contemporary Evaluation and Management of Twin-Twin Transfusion Syndrome

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Twinning rates vary by twin type and location throughout the world. The rate of monozygotic twinning is quite constant worldwide at 3.5/1000 deliveries while dizygotic twinning rates range from 49/1000 deliveries in Nigerian populations to 1.3/1000 deliveries in Japanese populations. Thirty per cent of monozygotic twins result from division of the embryo within the first 72 hours after fertilization and result in monochorionic-diamniotic twins. These are the twins that are at risk for twin-twin transfusion syndrome. Twin pregnancies evidence greater morbidity and mortality than do singleton pregnancies, and among twin pregnan-

cies monozygotic twins have greater morbidity and mortality than do dizygotic twins. The morbidities seen more commonly in monochorionic twins include structural defects and twin-twin transfusion. **Twin-twin transfusion syndrome (TTTS)** is the consequence of unbalanced blood flow from one twin (the donor) to the other (the recipient) across transplacental vascular communications and results in the polyhydramnios/oligohydramnios sequence and can include growth discordance. These vascular communications (of which there are four types) are present in nearly 100% of monochorionic twins but occur only rarely in dichorionic twins.^{1,2}

60-70%. Even more troubling is the increased incidence of cerebral palsy and other cerebral impairment (from 20-40%) in the surviving co-twin when one of a set of monochorionic twins dies in utero.^{4,5}

Several treatment modalities have been used to treat TTTS. Those receiving the most attention include serial amnioreduction, septostomy, and **fetoscopic laser ablation of chorioangiopagus vessels (FLOC)**.

AMNIOREDUCTION

Amnioreduction is the removal of large quantities of amniotic fluid from the polyhydramniotic sac of the recipient twin. This is accomplished using an 18 or 20 gauge needle under ultrasound guidance and is performed from one to several times. Although amnioreduction does not address the postulated cause of TTTS, it is postulated to result in decreased pressure on the transplacental vascular anastomoses, which increases placental compliance, thus reducing the preload and afterload in the hearts of both twins.⁶ The reduction in intrauterine volume also appears to decrease the incidence of preterm labor, a major contributor to the morbidity of TTTS. Proponents of amnioreduction point to its simplicity and success rates; one recent trial of aggressive amnioreduction reported 57% survival of both twins at 24 months of age and 70% survival at 24 months of age of at least one twin.⁷ Preterm premature rupture of membranes complicates 8% of pregnancies treated with serial amnioreduction.⁸

The diagnosis of TTTS has in the past been based on neonatal findings, but these findings are unreliable for the prenatal detection of the syndrome. Current strategies use ultrasound to determine both the presence and severity of prenatally diagnosed TTTS. Table 1 lists the salient points in ultrasound diagnosis of TTTS.

MANAGEMENT OF TTTS

Once diagnosed, untreated TTTS results in morbidity and mortality that exceeds 70%.³ Despite enthusiasm for different modalities, treatment of TTTS is associated with survival rates of only

Table 1. Ultrasound diagnosis of twin-twin transfusion syndrome (TTTS)

- A. Monochorionic twin gestation
 - 1. Twins of same gender
 - 2. Thin inter-twin membrane
 - 3. Single placenta
- B. Discordance in amniotic fluid volume
 - 1. "Donor" twin with decreased fluid (deepest vertical pocket < 2.0 cm is consistent with severe TTTS).
 - 2. "Recipient" twin with increased amniotic fluid volume (deepest vertical pocket > 8.0 cm is consistent with severe TTTS).
- C. Other ultrasound findings
 - 1. Appearance of a "stuck" twin that does not change intrauterine position regardless of maternal position.
 - 2. Small or non-visualized bladder in the "donor" twin
 - 3. Large bladder in the recipient twin
 - 4. Abnormal Doppler findings
 - a. pulsatile umbilical venous blood flow
 - b. absent or reversed end-diastolic umbilical arterial blood flow
 - c. tricuspid valve regurgitation.
 - 5. Hydrops: ascites, pleural or epicardial effusions

Table 2. Comparison of FLOC and amnioreduction

	FLOC	Serial amnioreduction
2 survivors	42%	42%
≥ 1 survivor	79%*	61%*
SAb	12%	7%
Double fetal loss	3%*	19%*
Neonatal deaths	6%	14%
Abnormal brain scan survivor(s)	6%*	18%*
Birth weight (donor)	1750 grams*	1145 grams*
Birth weight (recipient)	2000 grams	1560 grams

*p<0.05

a 20 or 22 gauge needle is introduced to the uterine cavity using ultrasound guidance in such a way as to deliberately breach the amniotic membrane overlying the smaller oligohydramniotic sac. A recent study of 12 patients with severe TTTS treated with intentional septostomy yielded 75% survival of both twins to delivery and 92% survival of at least one twin.⁹ The authors, and others, postulate that deliberate septostomy results in an equilibration of amniotic fluid volumes around both twins as a result of hydrostatic pressure differences between the sacs that may be too small to measure. As in amnioreduction this technique does not directly address the postulated cause of TTTS, the transplacental vascular anastomoses, but offers temporizing measures in an attempt to prolong the pregnancy to the point where survival ex utero is possible.

FETOSCOPIC LASER ABLATION OF CHORIOANGIOPUS VESSELS

Fetoscopic laser ablation of chorioangiopagus vessels (FLOC) is the only proposed intervention for TTTS that directly addresses the postulated etiology of TTTS, that is, the

transplacental vascular communications. This technique, first described by De Lia et al,¹⁰ uses a fetoscopically-directed neodymium-YAG laser to photocoagulate those transplacental vascular communications felt to be contributing to the TTTS. Initial use of this technology involved ablation of all vessels crossing the vascular equator of the placenta, but more recently there has been more selective ablation involving only those vessels thought to be contributing to the TTTS. Data from recent series indicate 69% survival of both twins, 82% survival of at least one twin, and 4.3% significant handicap in survivors of an in-utero demise.¹¹

CHOICE OF TREATMENT

Direct comparison of the efficacy of the different available interventions has not been accomplished. Comparisons extant in the TTTS literature typically compare case series using one intervention with case series using a different intervention. One such recent comparison¹² compared outcomes in 73 cases of severe TTTS treated with FLOC in one center with 43 cases of severe TTTS treated with serial amnioreduction in another center.

(Table 2; * denotes p < 0.05)

There are currently two randomized trials underway in attempts to determine the most effective intervention for treatment of TTTS. The EUROFOETUS consortium (<http://www.eurofoetus.org>) randomizes cases diagnosed with severe TTTS between serial amnioreduction and FLOC. At the University of North Carolina¹³ the trial is randomizing between serial amnioreduction and septostomy. The relatively infrequent nature of severe TTTS cases near any one center, and the (usually) strongly held opinions of a given treatment team has rendered recruitment into these trials more time-consuming than might have been originally anticipated.

Timing the intervention is of paramount importance in the treatment of TTTS. As in any medical procedure, the risks of the procedure itself must be weighed against the risk of the disease that is being treated. The known risks of any of the interventions for TTTS (preterm premature rupture of membranes, infection, preterm labor, placental abruption, hemorrhage and fetal death) must be acknowledged in deciding when to intervene. Quintero et al¹⁴ presented a classification schema based on their experience (Table 3). The group recently published their results following FLOC using their staging schema¹⁵ (Table 4).

COMPLICATION OF TTTS

Consideration of the morbidity following diagnosis and treatment of TTTS is of equal importance to survival. In cases of TTTS treated with serial amnioreduction that are complicated by in-utero demise of one twin,

Table 3. Staging of severe TTTS according to Quintero RA

Stage I:	MVP > 8 cm in recipient and < 2 cm in donor
Stage II:	stage I and bladder not seen in the donor twin
Stage III:	stage II and critically abnormal Doppler findings (absent or reversed end-diastolic flow in the umbilical artery, pulsatile umbilical venous flow, reverse ductus venosus flow)
Stage IV:	stage III and hydrops
Stage V:	stage IV and demise

Table 4. Survival by stage of severe TTTS (Quintero RA et al)

Stage	No Survivors	> 1 Survivor	Total
I	3/19 (15.8%)	16/19 (84.2%)	19
II	4/24 (16.7%)	20/24 (83.3%)	24
III	4/23 (17.4%)	19/23 (82.6%)	23
IV	0/4 (0.0%)	4/4 (100.0%)	4
Total	11/70 (15.7%)	59/70 (84.3%)	70

Table 5. Ischemic complications of severe TTTS

	EGA (wk) at onset	EGA (wk)at intervention	intervention	lesion	outcome
Scott 1995	24	24, 25, 26	amnio x 3	gangrene L leg	2 live
Hecher 1994	22	22	FLOC	gangrene L foot	1 live (recipient)
Margono 1992	28	none	none	gangrene R foot	1 live (recipient)
Dawkins 1995	23	23-32	amnio x 6	gangrene L leg	2 live
Lundvall 1999	17+	17+	FLOC	gangrene R leg	TOP
Arul 2001	19	19	FLOC	ileal atresia	1 live (recipient)
	20	20	FLOC	ileal atresia	1 live (recipient)
Van allen 1992	12	none	none	CL/CP, L hand, both feet	1 live
	18	none	none	L hand, L toe	1 live
current	14	14 - 23s	amnio x 7; FLOC	gangrene L leg	2 live

neurological handicap is seen in approximately 30% of survivors.¹⁶ Cases of TTTS treated with FLOC that are complicated by in-utero demise of one twin experience neurological handicap in 4.2%¹⁷ (compared with the 18% incidence of neurological handicap seen in singleton survivors following serial amnioreduction.¹² Taken at face value, these data suggest that while overall survival appears to differ little between the different interventions, there is a lesser risk of neurologic morbidity in survivors following FLOC than in survivors following serial amnioreduction.

There have also been reports of limb reduction anomalies and intestinal atresia associated with TTTS. Table 5 summarizes published cases of structural anomalies associated with monochorionic twinning. The etiology of these defects remains unclear. Hecher et al¹⁸ suggested that polycythemia and an arterial steal syndrome were the probable etiology of necrotic toes detected prior to FLOC for severe TTTS. Margono et al¹⁹ suggested that their findings of thrombosis of the transplacental vascular connections and necrosis of the right foot of the surviving twin were consistent with a thromboembolic phenomenon. Lundvall et al²⁰ found necrosis in the right lower leg of the recipient twin 27 days after FLOC. Post mortem examination found a thrombus in the right common iliac artery, "presumably the result of polycythemia." Scott and Evans²¹ documented a case of severe TTTS managed with serial amnioreduction that resulted in 2 live

twins. At time of delivery the recipient twin was found to have left lower leg necrosis that was associated with polycythemia (Hb 26.8 g/dL, Ht 89%). The authors concluded that the necrosis was the result of hyperviscosity due to polycythemia. Dawkins et al⁶ reported a pregnancy with severe TTTS managed with amnioreduction x 6 over a nine week period. Delivery was at 32 weeks. The recipient twin was born with Hb 25.9 g/dL, Ht 72% and gangrene of the left lower leg. Arul et al²² presented two cases of severe TTTS treated with FLOC. In both cases there was demise of the donor twin and in both survivors ileal atresia was noted after birth. The authors suggest three possible etiologies for these findings: hypoperfusion or hyperviscosity associated with TTTS could cause mesenteric ischemia; death of the donor could affect the hemodynamics of the survivor, causing mesenteric hypoperfusion; a shower of emboli or thromboplastins could be released into the fetal circulation. Van Allen et al²³ described two sets of monochorionic twins. The first case documented a singleton demise at 12 weeks EGA. At birth the surviving twin had cleft lip and palate and terminal limb reduction with ring constrictions of the left hand and both feet. In the other case singleton demise was documented at 18 weeks EGA. At birth the survivor was found to have ring constrictions of the left hand digits and left big toe. There was no evidence of amniotic bands in either case. The authors suggest that these findings were the result of vascular disruption in the co-twin. In our

case TTTS was first diagnosed at 14 weeks and was treated with serial amnioreduction x 7. FLOC was performed at 23+ weeks EGA. Preterm premature rupture of membranes occurred at 26+ weeks EGA and cesarean delivery was at 28+ weeks. At time of delivery necrosis of the left lower extremity of the recipient was seen. The toe-heel length of the necrotic limb of 3.2 cm is consistent with 19 weeks 4 days gestation, which is prior to either the FLOC or the amnioreductions. Polycythemia was not universally seen in these cases, but is the most common finding among these pregnancies with severe TTTS affected with structural anomalies. Polycythemia could result from the elevated atrial natriuretic protein found in recipient twins and the resulting diuresis, and would lead to hyperviscosity. This hyperviscosity would result in greater incidence of thrombosis. It remains unclear why the lower extremities are more affected by such a thrombotic diathesis.

CONCLUSION

Monochorionic twins present unique challenges above and beyond those associated with multiple gestation. There have been several developments in the evaluation and treatment of twin-twin transfusion syndrome, but these twins remain at high risk. In spite of these advances, these twins are at continued risk for anomalies that appear to result from hypoperfusion. These anomalies have been seen in monochorionic twins that have undergone serial amnioreductions, FLOC or no intervention at all. This suggests

that the tendency towards these defects is intrinsic to monochorionic twins suffering from TTTS, and is not related to the interventions that have been used in attempts to mitigate the impact of TTTS. The care of monoamniotic twins affected by TTTS continues to require coordinated care by a team of highly trained individuals.

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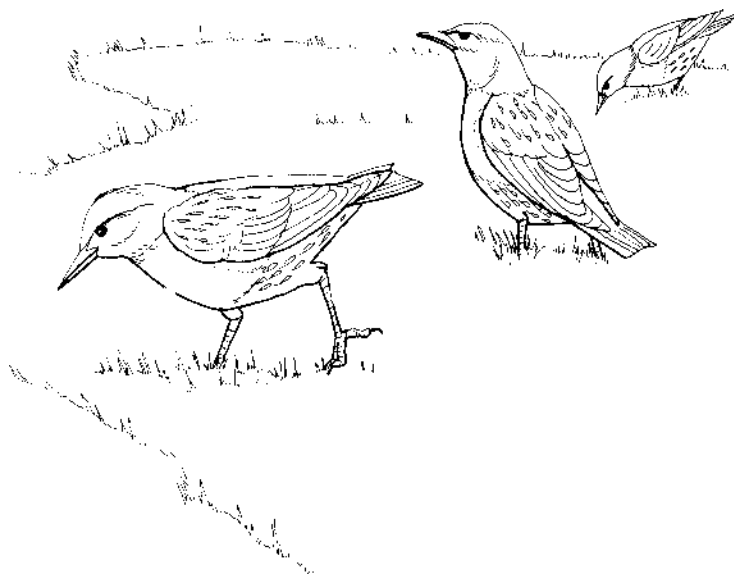
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Fetal Surgery

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In the last five decades, increased knowledge of fetal physiology and ever-improving diagnostic capabilities have paved the way for fetal medicine. As more conditions are discovered in utero, the possibility of intervening before birth has become real. For most fetal conditions, however, the best approach is still postnatal intervention. Exceptionally, a structural condition may deteriorate through late gestation and place the fetus's survival at risk. In these, even the earliest postnatal treatment may come too late. It is for these rare conditions that fetal surgery may be considered.

The first recorded operative intervention on a human fetus was reported in 1963,¹ the same year that Liley, considered the father of modern fetal therapy, performed his first percutaneous intrauterine transfusion. Reports of fetal surgery were few and unsuccessful until the late 1980s when Michael Harrison and his team at University of California San Francisco applied their experience with animal models to clinical situations.^{2,3}

Fetal surgery is a formidable undertaking, and should be reserved for a select group of conditions. Several criteria must be fulfilled before surgical intervention can be considered: 1) accurate diagnosis should be possible, and 2) the condition should be differentiated from other, non-surgical diseases; 3) the natural history of the condition should be predictable with reasonable accuracy, so that no fetuses are needlessly operated; 4) the condition should be lethal or severely debilitating if left untreated, justifying this very aggressive form of treatment; and 5) surgical correction of the condition should be technically feasible.⁴ This further implies that fetal surgery should only be performed at a few specialized centers where multidisciplinary expertise is available.

With such stringent conditions, few diseases have been considered surgically correctable before birth, and some indications have since been abandoned. An

early example was obstructive hydrocephalus not associated with chromosomal or other systemic conditions. It is possible to place a ventriculoamniotic shunt, in an attempt to relieve intracranial pressure caused by aqueductal stenosis.⁵ Unfortunately, the technical feasibility of the procedure was offset by the frequent finding that the fetus would pull out the shunt. Moreover, increased survival of fetuses with ventriculoamniotic shunt resulted in a higher rate of neurologic sequelae in this group than in the untreated fetuses, many of whom would die before term. This prompted a moratorium on this type of procedures.

Bilateral urinary tract obstruction, most often caused by posterior urethral valves in male fetuses, appeared to be a promising indication. Extensive experimentation in the fetal lamb established the feasibility of vesical decompression, by percutaneous cystostomy or operative vesicostomy. Thus, the onset of hydronephrosis, renal dysplasia and renal failure could be averted, and sufficient amniotic fluid could be restored to avoid pulmonary hypoplasia and neonatal death. Unfortunately, patient selection proved to be difficult.⁶ Establishing renal function is still frustratingly unreliable, and even successfully shunted fetuses often go on to develop end-stage renal failure in infancy or early childhood. Consequently, few fetuses undergo shunting of the bladder as a means to salvage renal function.

Certain thoracic lesions, such as **congenital cystic adenomatoid malformations (CCAM)** of the lung and sequestrations, can sometimes cause massive compression of the ipsi- and contralateral lungs, jeopardizing pulmonary function at birth. Rarely, these fetuses may even develop hydrops secondary to mediastinal shift and impairment of venous return. Operative intervention has had some success in the hands of fetal surgeons in San Francisco and, more recently, Philadelphia. Through an hysterotomy, the fetal chest is incised and

the affected lobe resected.⁷ Fortunately, only a minority of fetuses will require antenatal intervention, because up to 85% of these lesions spontaneously regress later in gestation.⁸

Congenital diaphragmatic hernia (CDH) is probably the most publicized indication for fetal surgery. When it occurs early in gestation, herniation of abdominal viscera into the chest causes compression of the lung, leading to pulmonary hypoplasia and immaturity at birth. Although repair of the hernia is relatively straightforward, as many as 40% of infants born with this condition die in the neonatal period, most commonly from refractory pulmonary hypertension. Extensive experimentation with various animal models has greatly increased our knowledge of normal and abnormal lung development. Thus, several investigators have demonstrated that reduction of the viscera before birth could allow catch-up growth of the lung and normalization of lung function at birth.⁹ However, positive results in fetal lambs and nonhuman primates could not be translated into clinical successes: Open fetal surgery proved to be much too stressful and invasive, as the gravid uterus is exquisitely sensitive to surgical trauma. In addition, reducing the liver often caused acute kinking of the ductus venosus and interruption of placental blood flow.¹⁰ Furthermore, the small abdominal cavity could often not accommodate this sudden increase in content, necessitating the placement of a temporary silo. As a result, more than 60% of fetuses operated for diaphragmatic hernia died intraoperatively or secondary to premature labor and pulmonary insufficiency.

In addition to the poor results with open fetal surgery, antenatal intervention for diaphragmatic hernia was becoming more difficult to justify as postnatal results improved. The use of **extracorporeal membrane oxygenation (ECMO)** and novel ventilatory strategies has greatly increased survival, which is now upward

Table 1. Results of fetal surgery for congenital diaphragmatic hernia (University of California, San Francisco and Children's Hospital of Philadelphia)

	Date	N	Survival (%)	Comment
Open fetal surgery ("classic" repair) ¹⁰	1993/97	18	7 (39)	1 late neonatal death
Open fetal surgery (tracheal clip):				
San Francisco	1998	28	6 (21)	1 died in infancy
Philadelphia ¹⁶	2000	15	5 (33)	
Endoscopic tracheal clip	1998	16	11 (69)	3 vocal cord damages

of 70% in some centers. Thus, the bar has been raised for fetal surgery.

Two developments, in the last decade, have given new hope to the future of fetal surgery. First, the popularization of laparoscopy and other minimally invasive procedures paved the way for endoscopic fetal surgery.^{11,12} This approach to the fetus, which is kept in utero during the operation, proved to be much less aggressive to the uterus as well.^{13,14} Techniques are still being refined, and miniaturization has allowed the use of telescopes and instruments of 2 mm diameter and less. One of the most common applications of this new technology is laser ablation of placental vessels in twin-to-twin transfusion syndrome.

Second, a little-known phenomenon was applied to the treatment of diaphragmatic hernia in utero: when the trachea of the fetus is occluded, lung fluid is trapped and lung growth is accelerated. Thus, elegant experiments in fetal lambs with diaphragmatic defects showed how tracheal occlusion caused gradual pulmonary hyperplasia, which reduced the viscera into the abdomen.¹⁵ At birth, the animals had normal respiratory function. Clinical application soon followed, with mixed results. Fetal tracheal occlusion via the open surgical technique yielded a 33% survival rate,¹⁶ but endoscopic fetal surgery appears less traumatic (up to 75% survival). The optimal technique of tracheal occlusion is still a matter of debate, as it must be complete, atraumatic and reversible at birth. The exact timing and duration of tracheal occlusion is likely to be important, to minimize exaggerated growth (which can lead to hydrops) and avoid the side effects of accelerated lung growth. Indeed, several investigators have demonstrated that prolonged tracheal occlusion causes severe surfactant defi-

ciency.¹⁷⁻¹⁹

Finally, the technique of tracheal occlusion has been refined as well. With the use of endoscopic surgery, it is now possible to place a tracheal clip or, better yet, to perform endotracheal occlusion by means of fetal bronchoscopy.²⁰ Thus, a condition that previously required a generous hysterotomy, exteriorization of the fetus, fetal laparotomy and thoracotomy, may be replaced with an endoscopic procedure performed through a single, 3 mm port into the gravid uterus. Early results are encouraging, and appear to compare favorably with open fetal surgery for diaphragmatic hernia (Table 1). It is important to realize that this subgroup of patients has a much worse prognosis than most infants born with CDH. Nevertheless, postnatal results are improving steadily, and prognostic indicators are still not optimal. Therefore, fetal surgery for diaphragmatic hernia, and for most other surgical conditions of the fetus, remains a semi-experimental undertaking. As technology improves and our understanding of fetal conditions grows, it is likely that more fetal conditions will be amenable to in utero interventions.

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CME OBJECTIVES

After completing this CME activity, the primary care physician will be able to meet the following objectives:

1. Describe the management of the fetus with anemia.
2. Describe the work-up and treatment of the fetus with a urinary tract anomaly.
3. Describe the role of prenatal counseling in the management of abdominal wall defects.
4. Understand the treatment principles of fetal cardiac anomalies.
5. Describe the role of invasive fetal intervention in twin-twin transfusion syndrome, and other surgical conditions of the fetus.

NEEDS ASSESSMENT

Traditionally the purview of obstetricians, fetal medicine today is multi-disciplinary: ob/gyn, pediatrics, surgery and their subspecialties all participate in the care of the unborn patient. These papers are intended for residents, fellows and attending physicians in obstetrics and gynecology, perinatology and maternal-fetal medicine, neonatology and pediatrics, pediatric surgical specialties, genetics, and for medical students, genetic counselors, midwives, obstetrical nurses and clinical social workers, to present up-to-date information on fetal medicine.

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	Poor			Excellent	
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3. Format	1	2	3	4	5
4. Faculty	1	2	3	4	5
5. Achievement of educational objectives					
* Describe the management of the fetus with anemia.	1	2	3	4	5
* Describe the work-up and treatment of the fetus with a urinary tract anomaly.	1	2	3	4	5
* Describe the role of prenatal counseling in the management of abdominal wall defects.	1	2	3	4	5
* Understand the treatment principles of fetal cardiac anomalies.	1	2	3	4	5
* Describe the role of invasive fetal intervention in twin-twin transfusion syndrome, and other surgical conditions of the fetus.	1	2	3	4	5
6. This material was presented without evidence of commercial bias.		yes		no	

Please comment on the impact that this CME activity might have on your practice of medicine.

FETAL MEDICINE CME QUESTIONS — CIRCLE THE CORRECT ANSWER.

- Which of the following criteria is NOT routinely used to diagnose severe twin-twin transfusion syndrome (TTTS) in utero?
 - Polyhydramnios in one twin and oligohydramnios in the other
 - A difference in hematocrit between the twins of more than 20%
 - Inability to visualize the bladder in the donor twin
 - Tricuspid valve regurgitation in the recipient twin
 - Same gender in both twins
- Compared with serial amniocentesis, fetoscopic laser occlusion of chorioangiopathic vessels ("FLOC") to treat twin-twin transfusion syndrome:
 - Significantly increases the survival of both twins
 - Significantly increases the survival of the donor twin
 - Significantly decreases the risk of prematurity
 - Significantly decreases the morbidity of the surviving twin
- Which of the following is NOT a known complication of twin-twin transfusion syndrome?
 - Cerebral palsy
 - Intestinal atresia
 - Limb necrosis
 - Aortic stenosis
 - Ascites
- Fetal surgery for a congenital anomaly can only be justified if:
 - The natural history of the disease, if left untreated, is known
 - Surgical correction *after* birth would subject the child to multiple and/or complex operative interventions
 - It is performed as part of a clinical research study
 - The anomaly can be completely corrected before birth
- Which of these conditions has never been considered an indication for fetal surgery?
 - Congenital diaphragmatic hernia
 - Esophageal atresia
 - Posterior urethral valves
 - Congenital cystic adenomatoid malformation of the lung
 - Aqueductal stenosis
- Which of the following fetal urine samples is a predictor of poor renal function at birth?
 - Osmolarity 180 mOsm/L, Na 100 mEq/L
 - Na 80 mEq/L, Cl 70 mEq/L
 - Cl 90 mEq/L, β_2 -microglobulin 4 mg/L
 - β_2 -microglobulin 2 mg/L, osmolarity 210 mOsm/L
- Which fetus might be a candidate for in utero bladder decompression (vesicoamniotic shunting)?
 - A 33-week-old fetus with hydronephrosis and normal amniotic fluid volume
 - A 27-week-old fetus with hydronephrosis, oligohydramnios and isotonic urine
 - A 29-week-old fetus with bladder distension, oligohydramnios and normal fetal urinary electrolytes
 - A 30-week-old fetus with bladder distension, oligohydramnios and an abnormal karyotype
- Currently, the best available treatment for alpha-thalassemia major (hemoglobin Bart's disease) is:
 - Intrauterine stem cell transplantation
 - Intrauterine blood transfusions followed by bone marrow transplantation in early childhood
 - Frequent postnatal blood transfusions and chelating agents
 - There is no treatment available; the disease is uniformly fatal
- Which statement about alpha-thalassemia is correct?
 - If two parents each are heterozygous for a *cis*-type -globin gene deletion, the risk of an offspring with -thalassemia major (Hb Bart's disease) is 25%
 - If two parents each are heterozygous for a *trans*-type -globin gene deletion, the risk of an offspring with -thalassemia major (Hb Bart's disease) is 50%
 - A fetus with -thalassemia major (Hb Bart's disease) usually develops hydrops and dies early in the first trimester
 - alpha-thalassemia major usually manifests itself in utero, since half the globin chains in normal fetal hemoglobin are of the type
- Which statement about digoxin to treat fetal arrhythmias is true?
 - Digoxin is the first-line therapy for ventricular tachycardia (VT)
 - Digoxin is the first-line therapy for supraventricular tachycardia (SVT)
 - Digoxin is the first-line therapy for ventricular extrasystole (VES)
 - Digoxin is the first-line therapy for atrial flutter
 - B and D are both true
- Which of the following is NOT currently a treatment option for fetal arrhythmias?
 - Maternal plasmapheresis
 - Maternal digoxin administration
 - Fetal pacemaker
 - Fetal digoxin administration
 - Early delivery
- Which of the following statements about abdominal wall defects is true?
 - Preterm delivery for gastroschisis prevents edema and thickening of the intestinal wall ("peel") caused by prolonged exposure to amniotic fluid
 - Cesarean section is indicated in gastroschisis to prevent further damage to the exposed intestines
 - Even in the absence of associated anomalies, omphalocele carries a poor prognosis
 - Gastroschisis typically occurs in mothers over 30 years of age
 - None of the above
- Which syndrome is NOT associated with omphalocele?
 - Pentalogy of Cantrell (including pericardial, diaphragmatic, pleural and cardiac defects)
 - OIES complex (including cloacal exstrophy and imperforate anus)
 - VATER association (including vertebral anomalies, tracheo-esophageal fistula and imperforate anus)
 - Beckwith-Wiedemann syndrome (including macroglossia and hypoglycemia)
 - Trisomy 18
- Which of the following may cause rhesus isoimmunization of a Rh-negative mother:
 - Induced abortion
 - Placental abruption
 - Abdominal trauma
 - A and B
 - All of the above
- According to the recommendations of the American College of Obstetrics and Gynecology (ACOG), which of the following patients may require administration of anti-D immune globulin to prevent Rh-isoimmunization:
 - Rh-negative mother with negative Rh-antibody screen and an Rh-negative fetus
 - Rh-negative mother with positive Rh-antibody screen, before amniocentesis
 - Rh-negative mother with negative Rh-antibody screen, within 72 hours of delivery
 - Rh-negative mother with positive Rh-antibody screen, at 28 weeks gestation