

RECENT ADVANCES IN THE PRENATAL DIAGNOSIS AND SUBSEQUENT MANAGEMENT OF CONGENITAL ANOMALIES

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ABSTRACT

Recent advances in prenatal ultrasound, along with wide application of these services to nearly all pregnancies, have created a separate patient: the fetus. This patient is accessible by a wide array of non-invasive and invasive diagnostic techniques, and even in-utero intervention. While the information gathered from these procedures clearly enhances care, it also serves to increase parental anxiety. While ultrasound has been the mainstay of prenatal diagnosis, Magnetic Resonance Imaging (MRI) has emerged as a superior imaging modality, particularly for CNS malformations.

Improved resolution of MRI images has created the opportunity to correlate prenatal findings with postnatal outcome. We review fetal MRI and focus on recent advances in the management of congenital hydronephrosis and congenital heart disease, two of the most commonly diagnosed prenatal conditions.

INTRODUCTION

The fetus has become a distinct patient, accessible with an ever increasing array of imaging techniques, diagnostic procedures, and even in-utero interventions. Ultrasound (US) has been the mainstay of prenatal imaging since the 1970's when techniques were originally developed for imaging the gravid uterus. Techniques have progressed such

that 3-D imaging, vascular and cardiac Doppler, and ultrasound-guided invasive procedures, are all commonly performed for prenatal diagnosis. We can now identify the majority of congenital anomalies before birth, and this ability has provided valuable insight into the natural history of these defects. This level of information also raises the anxiety level of the expectant parents. Prenatal consultation is valuable to help alleviate this anxiety, and to create plans for the special needs of the baby and mother at birth, including the mode and location of delivery. Neonatal and Pediatric specialists can develop treatment strategies in advance, and review them with the parents. Rarely, an anomaly will even require a prenatal intervention. This rapidly growing field is constantly evolving as increasingly subtle antenatal findings are correlated with post natal outcomes. This review will provide an update on some of these advances. We will explore fetal MRI as a new diagnostic modality. Then, we will discuss recent recommendations about two of the most common prenatal diagnoses, hydronephrosis and congenital heart disease.

FETAL MRI

Even with the tremendous versatility of contemporary prenatal US techniques, there are still some diagnoses that elude delineation by sonography. As

early as the mid 1980's, fetal MRI demonstrated promise in improving anatomic visualization compared to US, but fetal motion and long imaging times limited the diagnostic quality of early studies. Mothers required sedation to quiet the fetus in order to achieve adequate images, severely limiting utilization of MRI. With the development of ultra fast imaging techniques in the mid to late 1990's, however, fetal MRI has grown rapidly. Maternal sedation is no longer necessary for high-quality diagnostic images. Newly developed techniques provide high-resolution anatomical information, and tissue characterization using fat-suppression and diffusion imaging. Moreover, MRI cine techniques can evaluate fetal motion and swallowing.

In general, fetal central nervous system (CNS) abnormalities are the most frequent indications for MR imaging. Ventriculomegaly seen on ultrasound is the most common diagnosis referred for further investigation with MRI. Though many cases turn out to be idiopathic mild ventricular prominence, MRI can demonstrate many etiologies that are more serious, including aqueductal stenosis, CNS malformations, evidence of prenatal infection such as CMV, or evidence of hypoxic/ischemic injury. Other CNS abnormalities that are commonly imaged include enlargement of the cisterna magna and abnormal cystic or sonolucent areas in the brain. MRI can directly visualize the cerebellar vermis, brainstem, and cerebral hemispheres to assess the presence of brain malformation, tissue loss, hemorrhage, or abnormal tissue signal that indicates ischemia or abnormal myelination. Imaging of the spine is also useful for further evaluation of spinal anomalies, but MR is no more accurate than US in determining the level of an anomaly or open defect, and postnatal imaging is still needed for accurate localization.

Fetal MR imaging is also valuable in evaluating many congenital anomalies outside the CNS. Fetuses with a variety of chest malformations are often referred for further investigation. Imaging is then performed in multiple planes, allowing excellent visualization of the diaphragm and improved differentiation between types of soft tissues. Suspected congenital diaphragmatic hernia is better evaluated with MRI, which can determine which structures are herniated into the chest, and how much lung tissue is present. Lung volume calculations can help predict the likelihood of respiratory compromise at birth, and the need for more advanced modalities such as extracorporeal membrane oxygenation (ECMO).

Other diagnoses that often prompt referral for fetal MRI include pulmonary sequestration and cystic adenomatoid malformation of the lung, neck masses and airway abnormalities, renal agenesis, cloacal and genitourinary sinus anomalies, cystic hygroma and other neck masses, and cystic abdominal masses.

The superior tissue characterization capability of MRI and the excellent spatial resolution enable accurate diagnoses in the majority of fetuses over 20 weeks gestation. In fetuses less than 20 weeks gestation, resolution can be limited, although most studies will still provide valuable diagnostic information. The increased proportion of amniotic fluid in relation to size of the fetus early in the second trimester provides greater space for fetal movement and can therefore limit the resolution of the MRI images. As the proportion of fluid decreases with increasing gestational age, MRI imaging improves. Visualization in fetuses with reduced amniotic fluid can be quite good, providing another advantage over US, where reduced amniotic fluid impairs the acoustic window.

Magnetic Resonance Imaging does not involve ionizing radiation and so safety concerns during imaging are primarily limited to maternal oxygenation and tissue heating. Maternal oxygenation is monitored with pulse oximetry during scanning because both the gravid uterus and the imaging coil placed over the uterus limit diaphragmatic excursion, and hence respiration. Oxygen is administered if needed. Tissue heating is avoided by advance estimates of energy deposition calculated by the scanner prior to each imaging sequence based on maternal weight and specific imaging parameters. Tissue heating is limited to less than one degree. The International Society for Magnetic Resonance Imaging in Medicine does not recommend elective MRI in the first trimester due to the theoretical increased sensitivity of fetuses to any exposure early in development. Experience with fetal exposure to MRI is much less than with US, but no adverse outcomes have been reported thus far from fetal exposure to MRI in the second and third trimesters.

FETAL HYDRONEPHROSIS

Urological abnormalities, specifically hydronephrosis, are commonly discovered during routine fetal ultrasound. It is estimated that 1 of every 100 fetal sonograms will demonstrate some degree of hydronephrosis. Over the last 25 years, there has been much emphasis on the postnatal evaluation of these patients, with the ultimate intent of preventing renal deterioration in the

postnatal period which could result from obstruction or infection of the affected kidneys. Consequently, many patients have received antibiotic prophylaxis, with the premise that this would prevent urinary tract infections (UTI) and renal injury in the growing infant kidney. The usual approach in the past has been to start the neonate on antibiotic prophylaxis, usually amoxicillin, and then obtain a postnatal ultrasound and a voiding cystourethrogram (VCUG) looking for vesicoureteral reflux (VUR), a condition that has been associated with UTI and renal damage. It is estimated that 50% of children who experience a febrile UTI are found to have reflux, and when children with prenatal hydronephrosis are evaluated postnatally, reflux can be detected in 7 to 35% of patients (average: 16%).

In recent years, there has been increasing emphasis upon correlating postnatal pathology with prenatal findings. It is well accepted, for example, that a male fetus with bilateral hydronephrosis and a thickened, enlarged bladder, is likely to have posterior urethral valves, and this patient should be fully evaluated at birth. It is less certain to what degree fetal hydronephrosis predicts post-natal VUR, a diagnosis that requires a postnatal VCUG and prophylactic antibiotics. Currently, there does not appear to be any correlation between the degree of hydronephrosis seen on fetal ultrasound and the likelihood of reflux. Therefore, measuring the degree of pre-natal dilatation of the renal pelvis is not a reliable means of predicting the severity of postnatal reflux.

The current guidelines for the use of antibiotic prophylaxis and VCUG based on the findings of prenatal ultrasound are well established. The prenatal sonographic findings of an abnormal bladder, unilateral or bilateral ureteral dilatation, ureterocele, and high grades of hydronephrosis (Society for Fetal Urology (SFU) grades III and IV: moderate to severe pelvicaliectasis) should raise the suspicion of significant VUR, and should prompt referral to a pediatric urologist for prenatal counseling. During that visit, plans can be made to start antibiotic prophylaxis in the newborn period, followed by a renal and bladder ultrasound and VCUG 2 to 3 weeks after birth. Similarly, any child with known prenatal hydronephrosis who experiences a febrile UTI should be placed on prophylactic antibiotics after treatment of the infection, while awaiting VCUG. The antenatal finding of mild or moderate hydronephrosis alone (SFU grade I or II), either unilateral or bilateral, is not predictive of postnatal VUR. In fact, only 16% of these patients will have reflux, and

84% would have a negative postnatal VCUG. There does not seem to be any improvement in outcome with immediate postnatal diagnosis in this group of patients, and VCUG is not indicated soon after birth in these patients with isolated hydronephrosis.

The selection of the antibiotic agent is also important. The ideal prophylactic agent should be well tolerated, have a favorable risk profile, be excreted preferentially in the urine, and have minimal effect on the gastrointestinal bacterial flora. Of the various antibiotics available, trimethoprim appears to be the ideal urinary tract prophylactic agent. The recommended dose for prophylaxis is 2 m/kg/day. This antibiotic should not be used in cases of neonatal jaundice.

CONGENITAL HEART DISEASE

Cardiac surgery outcomes in infants and children with congenital heart disease (CHD) have improved dramatically over the last 20 years. For example, the mortality after surgery for transposition of the great arteries (TGA) has decreased from 10-20% in infants after an atrial switch procedures in the early 1970s to <3% for infants with TGA after an arterial switch operation by the late '90s. Recent evidence suggests that earlier diagnosis of CHD leads to improved outcomes. Since most congenital heart defects present antenatally, a multidisciplinary approach is critical. The perinatologist/obstetrician, the neonatologists, and the cardiac team (cardiologists, surgeons, and anesthesiologists) collaborate to ensure accurate diagnosis and optimal perinatal management of the fetus with CHD. Preparations can be made in advance to provide the newborn with the appropriate level of care and support, to ensure that the baby is the best surgical candidate possible. In addition, this approach allows the parents to become better informed about the disease and the treatments that will be needed.

The first step in the evaluation of suspected CHD is a fetal echocardiogram. The American Institute of Ultrasound recommends referral for a fetal echocardiogram at 18-22 weeks. Transvaginal fetal echo may be done as early as 12 weeks. The most common indications for referral are: a family history of CHD, maternal diabetes mellitus, suspicion of CHD on obstetrical ultrasound, arrhythmia, extracardiac congenital abnormalities such as congenital diaphragmatic hernia, systemic lupus erythematosus, chromosomal anomaly, or exposure to teratogens such as alcohol.

CHD can be divided into three broad categories: left to right shunts, obstructive lesions, and cyanotic

lesions. The typical left-to-right shunt lesion diagnosed antenatally is a ventricular septal defect (VSD), which is the most common congenital heart defect overall. Standard 2D echo is very useful in diagnosing most VSDs. Since fetal right sided ventricular pressures are equal to left sided ventricular pressures, the shunting across a large VSD should be bidirectional on Doppler imaging. Large perimembranous VSDs are generally treated with surgical closure on cardiac bypass, while muscular defects may now be closed by an interventional cardiologist with a transcatheter device postnatally.

Atrial septal defects (ASDs) are difficult to diagnose in utero. Since a patent foramen ovale (PFO) is normal in a fetus, it is difficult to differentiate from a true ASD. Similarly, a PDA is a normal in utero structure, and only becomes abnormal if it persists after birth.

Obstructive lesions that typically present in utero are valvular pulmonic stenosis, and aortic valve stenosis. An important finding in severe pulmonic stenosis, which decreases pulmonary artery pressure, is reversal of flow in the PDA. Left to right flow (rather than the usual right to left) supplies some pulmonary blood flow from the left ventricle and aorta. This is a sign of severe obstruction and a prostaglandin infusion (PGE1) should be initiated at birth to maintain ductal patency and pulmonary blood flow. Valvular pulmonic stenosis is amenable to balloon dilatation by an interventional cardiologist.

Severe aortic stenosis may present with a stenotic valve and a dilated or hypertrophied left ventricle. These valves may also be amenable to balloon dilation postnatally. In contrast, hypoplastic left heart syndrome presents with hypoplastic mitral and aortic valves and left ventricle. In these patients, flow through the PFO is usually left-to-right due to obstruction at the mitral valve, diverting all blood flow through the right ventricle, so it is important to check the degree of obstruction at the PFO because a restrictive PFO negatively affects prognosis. Repair of these defects is complicated, often requiring several surgical procedures during the first years of life. Referral to an experienced cardiac center greatly improves outcomes.

Cyanotic CHD lesions include TGA and, less commonly, Tetralogy of Fallot (TOF). During routine fetal heart screening with US, a normal four chamber view alone does not exclude these defects, and it is important to visualize the origin of the great vessels. Patients with TGA need prostaglandin E1 (PGE1) infusion at birth to maintain patency of the PDA and promote mixing of oxygenated and deoxygenated

blood. Patients with TOF may require PGE1 infusion at birth depending on how severe the right ventricular outflow tract obstruction is.

In cases of complex CHD where there is a poor prognosis with standard therapy, fetal intervention may be considered. For example, there have been reports of fetal balloon septostomy to open a restrictive interatrial septum in a fetus with hypoplastic left heart syndrome. These procedures are done in a few specialty centers in the United States. While technically the procedure can be done successfully, only 1/2 of these infants survive past infancy. Very rarely, the aortic valve can be ballooned in utero with very limited success.

The most common prenatal arrhythmias referred to a pediatric cardiologist are premature atrial contractions. They are considered benign in the absence of a structural heart defect. We recommend fetal monitoring every 2 weeks because of a low risk (1/2-1%) of supraventricular tachycardia (SVT). If the heart rate is over 180 bpm, fetal SVT is likely and referral should be made to a cardiologist. Fetal SVT is usually very responsive to maternal digoxin unless the mother is full term and then delivery is indicated. Premature ventricular contractions (PVCs) are less common, as is ventricular tachycardia. Fetal magnetocardiography (fMCG) is a new technology that enables characterization of the electrophysiological patterns of arrhythmias including SVT in the fetus.

Many fetuses with uncomplicated CHD can be safely delivered vaginally at a community hospital that has a Neonatal ICU capable of establishing umbilical arterial and venous access, starting a PGE1 infusion, and performing tracheal intubation. In this scenario, the mother can be cared for by her perinatologist and obstetrician throughout the pregnancy and delivery. Once the baby is stabilized, he or she can safely be transferred to a Pediatric Cardiac Center. Babies with more complex lesions should be born at a regional hospital with high-risk obstetric expertise and a level III NICU, in proximity to the cardiac center. Rarely, a baby with CHD will need to be born at the Pediatric Cardiac Center for immediate post-natal intervention, such as a fetus with hypoplastic left heart syndrome and a restrictive ASD.

SUMMARY

Recent advances in prenatal diagnostic techniques have yielded enormous benefits. Congenital anomalies are diagnosed with increasing accuracy and resolution during pregnancy. Much is being

learned about the natural history of these anomalies, and about how they impact postnatal outcomes. This information allows Perinatologists, in collaboration with various pediatric specialists, to make plans for delivery and treatment, and to help allay parental anxiety. MRI is being used increasingly to improve diagnostic accuracy, particularly for CNS

abnormalities. Better understanding of the relationship between fetal hydronephrosis and postnatal VUR has helped to clarify treatment strategies. Earlier diagnosis of CHD has allowed babies with even the most complex anomalies to receive prompt, coordinated care in Pediatric Cardiac Centers, and has helped dramatically improve postnatal outcomes.

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