Review Article

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Ultrasonographic Detection of Fetal Anomalies: Impact, Prognosis and Management

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Abstract

Congenital anomalies are one of the major causes of morbidity and mortality during perinatal and early neonatal period. The overall fetal outcome depends upon the extent, severity, onset and number of organs affected by anomalies. Early detection with ultrasonography helps in establishing prognostic impact of fetus if pregnancy is continued versus timely termination of pregnancy if fetal late viability is questionable or permanent irreversible anomalies detected have high propensity for lifelong physical or mental disability. However, the sensitivity and specificity of ultrasonography for fetal anomaly detection is varied depending upon gestational age, operator training, and definition of malformations and risk of anomalies prevalent in target population. Recent advancements in screening by ultrasonography and maternal serum biochemistry have posed a serious challenge to invasive prenatal testing methods, which still is considered gold standard. End of life decision by parents for detected fetal anomalies by premature termination of pregnancy is emotionally challenging event mixed with moral, legal and ethical dilemma.

Keywords: Congenital Anomalies; Ultrasonography; Fetal Malformations.

Introduction

Congenital malformations occur in 2-4% of all births. Despite their relatively low prevalence, fetal malformations are responsible for approximately 30% of perinatal deaths in addition to considerable infant morbidity in developed countries [1-3]. Major impact of antenatal diagnosis of malformations are related to the severity of the malformations detected. Most severe defects are reportedly detected earlier than minor ones, which is especially relevant in many countries where only before viability is termination of pregnancy authorized by law [4].

The gestational age at which a severe malformation is diagnosed is therefore crucial to further management of the pregnancy With the burgeoning of ultrasound, questions around the appropriate obstetric management in case of sonographically established fetal abnormalities have arisen. Should we apply all means to keep alive a fetus with a very poor prognosis? Do medical professionals in the field of perinatal medicine agree on fetal prognosis after ultrasound diagnosis of fetal abnormality? How should obstetric and neonatal management be attuned? How do parents view end-of-life decisions concerning their unborn infant?

During the last few decades, the use of ultrasonography for the detection of fetal abnormalities has become widespread in many industrialised countries.

This resulted in a shift in timing of the diagnosis of congenital abnormalities in infants from the neonatal period to the prenatal period. This has major implications for both clinicians and the couples involved. In case of ultrasound diagnosis of fetal anomaly there are several options for the obstetric management, ranging from standard care to non-aggressive care to termination of pregnancy. This essay explores the context of both clinical and parental decision-making after ultrasound diagnosis of fetal abnormality

- *Fetal Head, Spine, and Face*

Acrania, Exencephaly, Anencephaly

Anencephaly is the most common anomaly affecting the central nervous system and results from failure of closure of the rostral portion of the neural tube. Typically, there is progression in utero from a relatively normal-appearing brain to an amorphous brain mass to no recognizable brain tissue (which is the usual US appearance of anencephaly in the second and third trimesters). In the first trimester, the brain of affected fetuses may appear relatively normal or may demonstrate varying degrees of distortion and disruption (exencephaly). However, the important US feature is an absent cranium, which allows diagnosis from 11 weeks onward [5]. At 11–14 weeks gestation, the majority of cranial ossification is in the lateral aspects of the frontal bones and lower parietal bones, and no vault ossification is visible in the midline on a perfect midsagittal image. Hence, misdiagnosis may occur if only midsagittal views of the fetus are obtained, such as those for NT measurement and nasal bone assessment. The absence of cranial ossification may not be noted, and the head may appear relatively normal. It is important to look specifically for frontal bone ossification in the axial and coronal planes.

Encephalocele

Encephalocele is characterized as a protrusion of the brain and/or meninges through a defect in the skull that is covered with skin. It is one of the most severe neural tube defects, with a prevalence estimated to be 0.8–5 per 10,000 live births [6]. Prenatal diagnosis of encephalocele is accomplished by maternal screening of serum á-fetoprotein levels and ultrasound (US). With two-dimensional ultrasound (2D US), encephalocele appears as a defect in the calvarium containing a cystic or solid mass with a gyral pattern that is contiguous with the brain [7]. Prenatal 2D US detects approximately 80% of encephaloceles. The diagnosis is easily and confidently made from sonographic findings during the second trimester and can also be made in the first trimester [8]. The prognosis for patients with encephalocele depends on the extent of herniated neural tissue in the sac and on the presence of associated anomalies. In a previous series, 83% of patients with encephaloceles had mental handicap and/or physical impairment [9]. The mortality rate of encephalocele was 29% [10]. Seizure disorders are present in about 20% of infants with congenital encephalocele[11]. Encephaloceles may occur with genetic conditions such as Meckel-Gruber syndrome, an autosomal recessive disorder characterized by renal cystic dysplasia, encephalocele, and polydactyly.

Spina Bifida

Spina bifida includes a continuum of anomalies that have in common a defect of closure (dysraphism) of the neural tube. Although many entities are found and different terminologies are used, it is commonly accepted that two main categories exist: open spina bifida (nervous tissue and/or meninges exposed to the environment) and closed spina bifida (skin-closed dysraphism) [12]. Most studies on the prenatal diagnosis of spina bifida have focused upon open spina bifida, which is associated with an increased concentration of alpha-fetoprotein (AFP) in amniotic fluid and maternal serum and with typical cranial signs at the sonographic examination [13-16]. The level of amniotic fluid AFP may assist the distinction between open and closed spina bifida. Increased concentrations of amniotic fluid AFP are almost invariably found with open defect. Distinction between open and closed spina bifida has prognostic implications. While Spina bifida poses a diagnostic and therapeutic challenge, it can be components of more complex syndromes, associations or complexes. For this reason, a key aspect of evaluation of the fetus is to perform a thorough and detailed examination of the entire fetus. Knowledge of what to expect can help increase the detection of associated abnormalities.

Holoprosencephaly

Holoprosencephaly (HP) results from failure of the prosencephalon to differentiate into the cerebral hemispheres and lateral ventricles between the fourth and eighth week of gestation [17-19]. Most cases occur sporadically and have a normal karyotype. However, the disorder can be associated with a variety of chromosomal abnormalities such as trisomy 13, ring chromosomes and deletions.

The prognosis of affected patients depends on the severity of HP. Alobar and semilobar HP have a very poor prognosis, virtually all infants with the more severe form die in the first postpartum year [20]. Some children with semilobar HP may survive into infancy with amentia [21]. Patients with lobar HP have variable degrees of mental impairment and visual and olfactory abnormalities [19], but often a normal life expectancy [21]. Since HP is not compatible with long survival, a specific prenatal diagnosis of the condition may be very influential in the clinical management.

Dandy-Walker Complex

Dandy-Walker complex (Dandy-Walker malformation) consists of a posterior fossa cyst, partial or complete absence of the cerebellar vermis, and in some cases hydrocephalus. The Dandy-Walker malformation has an estimated prevalence of about 1:30,000 live births with a slight female preponderance and is responsible for 4-12% of infantile hydrocephalus [21].

Dandy-Walker malformation is frequently associated with other intracranial anomalies such as agenesis of the corpus callosum, holoprosencephaly, occipital encephaloceles and ocular abnormalities [22]. Extra-cranial anomalies include polycystic kidneys, cardiovascular defects, polydactyly and cleft palate. In the absence of a recognizable syndrome a recurrence risk in subsequent pregnancies of 1-5% is suggested [23].

- *Fetal Neck and NT Screening*

Top of Form

Bottom of Form

Normally, a thin layer of fluid is seen in the posterior nuchal region in the first-trimester fetus. This layer is called the *nuchal translucency*, and its thickness can be measured with US.

Most fetuses with Down syndrome and some normal fetuses show an increased NT (>95th percentile) in the first trimester. Recently, NT measurement in conjunction with maternal age and maternal serum biochemistry has been used to assess the risk for having a baby with Down syndrome. It has been shown that measuring NT thickness between 11–14 weeks gestation and combining it with maternal age allows identification of 75% of fetuses with Down syndrome and approximately 70% of fetuses with other chromosome abnormalities (trisomy 13, trisomy 18, and Turner syndrome) with a false-positive rate of 5% [24]. By using a combination of maternal age, fetal NT thickness, and maternal serum biochemistry (free β–human chorionic gonadotropin and pregnancy-associated plasma protein-A), the detection rate for fetuses with Down syndrome is increased to 89%, with a false-positive rate of 5% [25].

In addition, an increased NT in the presence of a normal karyotype is associated with an increased frequency of many structural abnormalities (including major cardiac defects, skeletal dysplasias, fetal akinesia, diaphragmatic hernia) as well as a variety of genetic syndromes [25,26]. Therefore, an increased NT is an indication for detailed anatomic scanning of the fetus and fetal echocardiography. During the second trimester, this fluid collection often resolves. However, in some cases it evolves into either nuchal fold thickening or cystic hygroma, with or without generalized hydrops .

- *Fetal Heart*

Identification and management of fetal cardiac abnormalities are important because congenital anomalies are the leading cause of infant death and congenital heart disease accounts for 30 to 50 percent of these deaths [27,28]. Prenatal diagnosis of cardiac disease provides parents an opportunity to obtain prognostic information prior to birth, learn about treatment options before and after delivery, reach decisions concerning the management approach that is best for their family (eg, whether to terminate pregnancy or undergo in utero intervention, if available; nonintervention), and plan for specific needs at birth (eg, place of delivery, pediatric and obstetric providers, route of delivery, palliative care). It may also improve neonatal outcome [29]. Prenatal diagnosis of cardiac disease has also been associated with a reduction in neonatal morbidity, including severe acidosis [13]. Infants with congenital heart defects that require patency of the ductus arteriosus for systemic or pulmonary blood flow can benefit by early postnatal intervention (prostaglandin E1) to prevent closure of the ductus [31,32]. Similarly, readiness to perform transcatheter intervention (eg, balloon atrial septostomy for patients with d-TGA or HLHS, balloon valvuloplasty for patients with critical pulmonic or aortic stenosis)or pacing of complete heart block soon after birth enables rapid stabilization of the postnatal circulation and thus may improve outcome-fetal medicine specialist, pediatric cardiologist, geneticist, and/or neonatologist is recommended [32-36]. Suggested algorithm to follow in cases of intrauterine cardiac anomalies detected, is as follows:

Step 1. Give Accurate Information about the Diagnosis and Prognosis of the Cardiac Abnormality

The first stage is providing accurate information about the diagnosis and prognosis in a manner and at a timing that the expectant parents are able to understand. The general screening detection rates for congenital heart disease (CHD) vary between 14%–45% [37]. A standard 4 chamber view can detect 40%–50% of major CHD [38], while a 4 chamber view and outflow tract detects 70%–80% of major CHD [39]. Fetal cardiac malformations are compounded by the fact that other malformations may be present, as is the possibility of chromosomal abnormalities. The most accurate information possible should be given to the expectant parents, along with a clear explanation of what is still uncertain, unclear or

subject to change as the pregnancy progresses. The physician should keep in mind the possibility of evolving lesions [40] (e.g., a developing left and right hypoplastic heart syndrome) and inform the parents accordingly. For such condition, there is inadequate or incomplete data as far as their outcome and natural history, and this also must be conveyed to the parents.

Even in serious cardiac conditions, one is not always able to clearly define the possible outcomes. Few cardiac conditions are not amenable to at least palliative surgery, if not complete repair. In most cases the neurological development is normal or close to normal [41]. This information allows the parents to decide how to proceed with knowledge of the worst case scenario [4].

The physician needs to ensure the expectant parents understand the information about the nature of abnormality, the implications for the life of the future child, the possibility of intervention, and the risk for each intervention prenatally or postnatally. Parents also need to know the figures for local practice, for short, medium and long term outcomes, especially with respect to quality of life issues

Step 2. Identify Options

The next stage is to identify and present the options available. In brief, there are three main options: to continue with the pregnancy, to terminate the pregnancy (if legally permitted), or to consider prenatal intervention (if it is possible for the condition and available). If the decision is to continue with the pregnancy, there will perhaps be further decisions to make as to where the infant is to be delivered, the need for in utero transfer, and the mode of delivery [42]. There will also need to be an anticipatory management plan for the infant after birth. Parents will generally accept what is recommended to them on these matters, but still require them to be explicitly stated. If the decision is to terminate, there may be a need to shift hospitals, or change the obstetrician if termination is not personally acceptable to him or her. The parents should be made aware of these implications, not in an attempt to change their mind, but to inform and prepare them for the process.

During the counseling, assuming a "neutral" tone on the part of the clinician—not overly pessimistic or optimistic—is vital but may be extremely difficult to achieve [43]. The ultimate aim is to allow the expectant parents to form their own assessment of the impact the condition would have on their future child.

Step 3. Discuss Options

The next stage is discussing the options with parents which is the most ethically contentious stage. There are different views even about which matters are ethically appropriate to raise and discuss, let alone about the degree to which it is appropriate to recommend or favor a particular option, rather than being as neutral as possible. It is important to realize that the impact of counseling is affected by the physician's approach, speech, tone, and so forth [44]. In many counseling sessions, selective information is provided, whether deliberately and inadvertently, though some feel obligated to provide all the information available. There is also the question as to who is the best person to do the counseling. Cardiologists, genetic counselors or obstetricians have counseled independently or together [40].

Making a decision may not be easy for the parents. They have to come to terms with the abnormality and grieve the loss of a normal infant, as well as grapple with the questions of what they think about abortion, disability, their personal capacity to care for such an infant/child and their ideas about parenthood and family life.

The reasons for considering termination may be very variable, complicated and as Shaffer et al [45]. A common understanding of physicians is that most terminations for fetal cardiac anomaly are done to minimize distress and grief to the parents of having a child with reduced physical activity who may die young. This allows mother time for other important aspects of her life, care of the other children and to prevent hardship to others [44]. There may be also be other social reasons, or a medical condition of the pregnant woman.

Specialist prenatal genetic counselors may be particularly helpful for the expectant parents in talking through these sorts of issues, though such counselors may not have the detailed cardiac knowledge to answer the relevant questions. What parents need most from the pediatric cardiologist is the best available understanding of what their child's life would be like, what sort of interventions would be needed and the risks of these to the child in the local setting.

Step 4. Intrauterine Intervention: Ethical Issues

If intrauterine interventions are available the further important issue is the pregnant woman's autonomy versus the potential beneficence to the fetus and future child, where the pregnancy is going to continue and the fetus can reasonably be regarded as a patient. In this situation, the pregnant woman is in the ethical role of parent making decisions for the health of her future child—but she is also making decisions about herself and her own health. There is a conflict between American College of Obstetricians

and Gynecologists and the American Academy of Pediatrics regarding the issue of fetal interventions [46]. The latter accords less weight to maternal decision making and is more tolerant of overriding maternal refusal of intervention which may be suggested for fetal benefit.

- *Fetal Abdominal Wall*

Fetal abdominal wall defects are easy to diagnose and manage with ultrasound. When we see them, we exclude associated malformations by carrying out detailed anomaly scans, karyotyping the fetuses, and terminating the chromosomally abnormal ones at the parents' request. We follow-up the remaining ones throughout pregnancy, and deliver the babies. The pediatric surgeons correct the condition, and 'they all live happily ever after'.

Omphalocele

Normal development of the anterior abdominal wall depends on the fusion of four ectomesodermic folds; cephalic, caudal and two lateral folds. Failure of lateral body folds to migrate centrally results in omphalocele. Pregnancies in which isolated omphalocele is detected at early ultrasound, follow-up scan is advised especially at 20-24 weeks gestation for the detection of late-manifesting fetal anomalies. Follow-up ultrasound also helps in detection of complete disappearance of a small defect, which may occur later in the pregnancy [47]. Additional follow-up ultrasound examinations are also required until delivery.

A higher proportion of omphaloceles is associated with concurrent malformations, syndromes and chromosomal anomalies [48]. Cardiac anomalies gastrointestinal, genitourinary, neural tube, and musculoskeletal defects are frequently found in association with exomphalos [49-51]. Omphalocele is involved in many polymalformative syndromes such as Beckwith-Widemann , pentalogy of Cantrell, Meckel-Gruber syndrome and lethal cleft palate-omphalocele syndrome [52-55]. The most common syndrome associated with omphalocele is Beckwith-Widemann syndrome, which is characterized by omphalocele, organomegaly, gigantism, hemihypertrophy, and polyhydramnios [56]. Associated chromosomal anomalies include trisomies 18, 13, and 21, Turner, Klinefelter, and triploidy syndromes [67,58]. Karyotypic abnormalities are more common in association with omphaloceles that contains only bowel compared with those that contains only liver or bowel and liver both [59,60]. Nonsyndromal omphalocele may be familial [61]. Prevalence of chromosomal defects increase with maternal age and decrease with gestational age [62]. Associated polyhydramnios or oligohydramnios also suggests increased risk of chromosomal anomalies.

Isolated omphalocele diagnosed during the early stages of gestation typically has a good prognosis [63]. Perinatal mortality rate is low in such case [64].

Pentalogy of Cantrell

Pentalogy of Cantrell This syndrome was first described by Cantrell and his colleagues in 1958 [65]. Anomalies observed in this disorder are (1) a midline, supraumbilical abdominal wall defect (2) a defect of the lower sternum (3) a deficiency of the anterior diaphragm (4) a defect in the diaphragmatic pericardium (5) congenital intracardiac defects [65,66]. The most common intracardiac defects are atrial septal defect, ventricular septal defect, and teratology of Fallot [67].

The syndrome may be associated with other anomalies such as agenesis of the gallbladder, and polysplenia, cystic hygroma, renal dysplasia, exencephaly and amniotic band syndrome [68-70]. Differential diagnosis includes isolated ectopia cordis, ectopia cordis associated with amniotic band syndrome, omphalocele and body stalk anomaly. In isolated defects, primary repair in the neonatal period is the best type of management for this rare condition [71]. However, the outcome depends on the severity of congenital cardiac anomaly [72].

Gastroschisis

In gastroschisis, the bowel loops herniate through an abdominal wall defect located lateral and usually to the right of the umbilical cord insertion. Prenatal US diagnosis is based on demonstration of the normal position of the umbilicus and herniated bowel loops, which are freely floating in the amniotic fluid. Associated chromosomal abnormalities are rare. Affected patients have malrotated bowel. Vascular compromise may occur from a volvulus. Serial ultrasound follow-up is important because later in pregnancy bowel obstruction, peritonitis, bowel perforation, and fetal growth restriction may occur [73]. Sonographic findings of bowel abnormalities are associated with difficult abdominal wall repair and increased incidence of complications. Overall prognosis is usually favorable. Postoperative survival is about 95% and is largely the result of lack of other severe anomalies associated with this defect [74]. However, the postoperative hospital stay is often lengthy and complications related to the gastrointestinal tract are very common [75]. Mortality is usually the consequence of short gut syndrome

- *Fetal Urinary Tract*

Urologic abnormalities are detected in 1 of 500 routine obstetric sonographic studies. Serial sonographic observations in human fetuses have taught us much about the natural history of many potentially correctable lesions. Most urinary tract abnormalities are best corrected after birth, and prenatal diagnosis allows planning of the place, time, and method of delivery. For a few abnormalities, repair before birth may be necessary. Experimental evidence and clinical experience have taught us that fetal intervention is physiologically sound and technically feasible. As we have overcome the major obstacles in fetal surgical therapy—maternal and fetal anesthesia, tocolysis and surgical technique—prenatal treatment of urologic abnormalities has become a reality [76-78].

Adrenal

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) combines a set of autosomal recessive disorders]. CAH can also be diagnosed using amniocentesis [79]. Management of CAH can be done using glucocorticoid replacement therapy [80]. A prenatal treatment option for female fetuses diagnosed with CAH, can be done using dexamethasone [79,81].The last line of treatment for CAH, only utilized in the most serve cases, involves bilateral adrenalectomy [82,83].

Adrenal Cystic Neuroblastoma

Neuroblastoma is the most common intra-abdominal tumor in children [84]. It is derived from the neural crest ectoderm, when cells fail to respond to normal signaling. Incidence of adrenal cystic neuroblastoma is 1 in 10,000 cases [85]. These cases can be diagnosed using US or fetal MRI, both of which can clearly identify the disorder [86,87]. To treat and manage neuroblastoma, surgery is the ideal option [88,89].

Renal

Bilateral Renal Agenesis

Bilateral renal agenesis (BRA) is a congenital absence of both kidneys. This is also known as Potter's syndrome, Potter's sequence or Oligohydramnios sequence, coined by pathologist Using US, it is possible to identify BRA after 16 weeks of gestation because the amount of amniotic fluid is no longer dependent on transmembrane flow, but rather due to fetal urine production [90]. If a fetus has BRA, you will be able to see a condition of oligohydramnios because the volume of amniotic fluid is less than normal in the amniotic cavity [91]. Genetic aspects of BRA are not fully understood. BRA is estimated to occur in 0.1 per 1000 births [92]. Survival rate of fetuses with BRA is extremely low, as BRA is a lethal congenital anomaly [93]. Recent research has shown success for the in utero intervention for bilateral renal agenesis using serial amnioinfusion [94].

Unilateral Renal Agenesis

Unilateral renal agenesis (URA) is a congenital absence of one kidney. This condition is not fatal, unlike BRA, and patients can have a normal life expectancy. However, urological anomalies often accompany URA and patients should be monitored to decrease the risk of renal failure. Urological anomalies found in patients with URA included ureterovesical junction obstruction, bladder dysfunction, vesicoureteral reflux (VUR), ureteropelvic junction obstruction, ureterovesical and ureteropelvic junction obstruction, duplicated collecting system plus grade IV VUR, ectopic kidney plus grade V VUR, ectopic kidney, and development of chronic renal insufficiency [95]. URA is more common than BRA and the general incidence is 1 in 2000 [96]. Patients with URA have an increased risk of hypertension [97].

Polycystic Kidney Disease

Polycystic kidney disease is a disorder that can be found in both adult and pediatric patients. It involves the development of bilateral renal cysts with dysplasia. For prenatal evaluations, the first line method to identify these disorders should be US. When US findings are suboptimal, fetal MRI serves as a useful tool in prenatal diagnosis [98-100].

Duplex Kidneys

Duplex kidney is a renal system containing a single renal parenchyma and drained by two pyelocaliceal systems [101]. Duplex kidneys occur in 0.8% of the general population [102]. When examining a patient with duplex kidney, the duplex kidney is often more elongated than their non-duplex kidney and may contribute more to total renal function [103]. Renal duplex anomalies can be diagnosed by prenatal US. Antenatal diagnosis and proper postnatal care may prevent urinary tract infections and renal function impairment [104]. Children with duplex kidneys can be prone to urinary tract infections due to vesico-ureteric reflux or obstruction [102].

Hydronephrosis

Hydronephrosis is a common clinical condition encountered by physicians when visualizing the fetus

using US [103,104]. Detection of hydronephrosis is possible as early as the 12th to 14th week of gestation [105]. Hydronephrosis is seen in 1-5% of pregnancies, and persists in 30-75% of infants postnatally [104,106]. It can result from interruption of urine flow, and obstruction can be from anywhere along the urinary tract. Obstruction is the key cause of hydronephrosis and is reported in 5-60% of cases [107]. No surgical treatment is necessary, as the condition generally resolves itself. Postnatal check-ups should be repeated every 3 to 6 months [108]. However, higher grades of hydronephrosis would require surgery to treat [109].

Advancement in technology with enhanced skills has improved the sensitivity of prenatal diagnosis of fetal anomalies with ultrasonography, coupled with maternal serum biochemistry. This information should assist in decision making with respect to timely intervention in terms of termination of pregnancy for anomalies which threaten viability or has high likelihood of irreversible physical or mental handicap. However, we strongly recommend to exercise caution along with meticulous skills and individual discretion while indentifying potentially benign, self limiting minor anomalies compared to major, multi-organ irreversible life threatening anomalies with high propensity for crippled neonate with compromised functions.

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