10.5005/jp-journals-10009-1482

ORIGINAL SCIENTIFIC ARTICLE

Surgically Correctable Congenital Fetal Anomalies: Ultrasound Diagnosis and Management

[1]Sanja Zaputović, [2]Nina Medić

ABSTRACT

A great number of lifelong disabilities are due to congenital malformations. Evolution of prenatal ultrasound diagnosis and improvement of surgical technique have enabled us to detect most of these malformations *in utero* early and accurately with a possibility of early surgical management in selected cases even *in utero*. Advances in pre-/perinatal management have enabled us to interfere and change the origin of the disease in order to optimize the best postsurgical outcome. Only a multidisciplinary team of specialists could provide such appropriate treatment.

Keywords: Fetal anomalies, Prenatal diagnosis, Surgical correction, Ultrasound.

How to cite this article: Zaputović S, Medić N. Surgically Correctable Congenital Fetal Anomalies: Ultrasound Diagnosis and Management. Donald School J Ultrasound Obstet Gynecol 2016;10(3):338-349.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Congenital malformations are single or multiple defects of the morphogenesis of organs or body identifiable at birth or during intrauterine life. Their global birth prevalence is about 2 to 3%. The etiology is unknown in more than 50%, while the other half is caused by genetics and the environment, or their combination.[1] According to the World Health Organization (WHO), congenital malformations result in approximately 3.2 million birth defect-related disabilities every year, and 270,000 newborns die during the first 28 days of life every year from congenital anomalies.[2] Therefore, they continue to represent a significant and growing problem of perinatal/neonatal morbidity and mortality.

Prevention of congenital anomalies is unfortunately mostly impossible. With the era of advanced ultrasound diagnostics, most of the major anomalies are detectable prenatally.[3-5]

[1]Professor, [2]Resident

[1,2]Department of Obstetrics and Gynecology, Clinical Hospital Sveti Duh, Zagreb, Croatia

Corresponding Author: Sanja Zaputović, Professor Department of Obstetrics and Gynecology, Clinical Hospital Sveti Duh, Zagreb, Croatia, e-mail: sanjazaputovic@yahoo.com

Prenatal diagnosis has significantly improved our understanding of surgically correctable congenital malformations. It has enabled us to influence the delivery of the baby, offer prenatal surgical management, and discuss the option of termination of pregnancy for lethal conditions.[6]

Although the most prenatally diagnosed congenital malformations are best treated surgically after birth, the outcome of a small proportion of severe structural malformations with predicted fetal demise or devastating sequelae postnatally can be improved by correction before birth. Prenatal intervention is restricted to those anatomic malformations that interfere with normal organ development and which, if alleviated, may permit normal development. Advances in antenatal ultrasound detection and technical innovations in the surgical approach to the fetus have resulted in an increase in the successful clinical application of fetal intervention over the past three decades.[7]

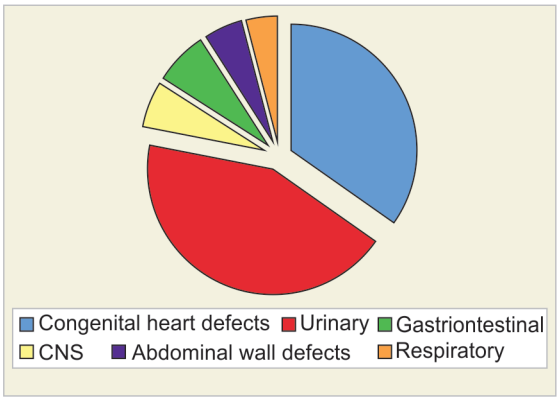
The aim of the article is to present data on surgically correctable congenital malformations in the past 10 years in the tertiary medical institution of perinatal care in Zagreb at Clinical Hospital "Sveti Duh" and their management and outcome.

MATERIALS AND METHODS

In the 10-year period from 2005 to 2014, there were 32,556 live-born neonates, of whom 408 (1.25%) were prenatally diagnosed with surgically correctable congenital malformation (Table 1). Case records of these children and of

Table 1: Number of live-born neonates from 2005 to 2014 and number of neonates with surgical correctable congenital malformations in Clinical Hospital "Sveti Duh," Zagreb

Years	*No. live-born neonates*	*No. with surgically correctable congenital malformation*
2005	3,075	30
2006	3,103	30
2007	3,237	31
2008	3,370	36
2009	3,548	34
2010	3,543	37
2011	3,226	43
2012	3,197	65
2013	3,182	39
2014	3,075	63
	32,556	408



Graph 1: Distribution of surgically correctable congenital anomalies in the 10-year period (2005–2014) in Clinical Hospital "Sveti Duh," Zagreb

other children with the same condition diagnosed postnatally have been studied in order to assess the accuracy of the prenatal diagnosis and its potential influence on the neonatal management and outcome.

RESULTS

Total number of live-borns was 32,556, of whom 408 (prevalence rate 1.25%) had surgically correctable gross congenital malformations. Distribution of surgically correctable congenital anomalies in the 10 yeas period in Clinical Hospital "Sveti Duh," Zagreb is presented in Graph 1.

We will analyze them separately in more detail.

Urinary Tract

Urinary tract malformations were detected prenatally in 175 neonates (43% out of 408 live born neonates).

Development of genitourinary system is a complex process.[8,9] In our cases, congenital anomalies of the genitourinary tract were the most common ultrasound identified anomalies in the prenatal period. Obstructive uropathies account for the majority of cases.[9]

Accurate and early prenatal diagnosis of anomalies enabled us to influence the outcome of the affected fetus. Early recognition and treatment of critical obstruction and urinary tract infection provide further prevention of renal damage and loss of its function.[10]

Most of the correctable lesions are best treated after normal term delivery, while some have bad prognosis from the very beginning. Only few could be treated before birth.[11]

From a practical point of view, it is crucial to make a distinction between unilateral and bilateral malformations of the urinary tract. For most of the unilateral urinary pathology where the other kidney is healthy, prenatal intervention is usually not necessarily. Regular weekly follow-ups until delivery are sufficient. At birth, the newborn will undergo all necessary check-ups including clinical examination, laboratory work-up, and imaging and if needed surgical correction will be done at the most appropriate time when the accurate diagnosis would be achieved.[12,13]

With the introduction of fetal therapy, termination of pregnancy becomes an option when dealing with conditions that are not compatible with extrauterine life (bilateral renal agenesis, bilateral multicystic kidneys, bilateral infantile polycystic kidneys). Therefore, obstetricians and parents may choose to terminate the pregnancy when the prognosis is lethal.[14,15]

Most urinary pathologies do not interfere with the mode of delivery, although elective cesarean delivery should be considered in cases of massive enlargement of fetal abdomen in order to prevent possible dystocia that might occur with vaginal delivery and to prevent damage to the vital organs.

Renal tract anomalies are mostly caused by single gene disorder and are isolated, but sometimes they can also be associated with other congenital anomalies. Therefore, a thorough examination of the other systems is mandatory to exclude possible genetic disorders.[10]

Obstructive Uropathies

Obstructive uropathies are the most frequently diagnosed pathologies of the urinary system. Many of them are transient or physiological and will resolve spontaneously after birth, while a few of them have serious underlying urinary pathologies. If left untreated, these will increase child mortality and morbidity. Antenatal ultrasonography provides us to detect those anomalies and evaluate its progression and to plan its treatment early and electively. The main aim of treatment is prevention of urinary tract infections and its long-term complications like renal scarring, hypertension, and impaired renal function. With the introduction of antenatal ultrasonography of the urinary system, about 60% of children had surgery for renal or urinary tract problems in their first 5 years. Once pathology of the urinary system is suspected and diagnosis established, regular weekly ultrasound examinations are warranted. Evaluation of renal damage is based on dilatation of the collecting system, renal parenchymal appearance and thickness, changes in renal pelvis size and fetal urine flow, and appearance of ureter and bladder. These parameters affect prenatal management, as well as the gestational age and maturity of fetal lungs.[13-16]

Urinary tract obstruction results in renal dysplasia and renal failure, and pulmonary development might be influenced by the decreased amount of amniotic fluid.

Prenatal management is considered when the obstructing lesions are prograding and lead to renal failure when premature delivery cannot be reasonably

undertaken. Early interventions are necessary because unless otherwise they may interfere with fetal development and cause serious disability depending on the degree and duration of obstruction. These interventions are reserved for fetuses with posterior urethral valves and oligohydramnios, or fetuses with solitary kidney and severe hydronephrosis and oligohydramnios. They are only recommended in the second and the third trimester and are associated with significant morbidity and mortality. Nevertheless, at the time we do not know whether such interventions would be justified in terms of the additional time to be gained *in utero*. Parents should be warned that irreversible changes may already have occurred and the operation which could appear to be technically successful may be of no benefit. These cases should be managed under the guidance of a multidisciplinary team of experts including the obstetrician, neonatologist, and pediatric urologist.[10-17]

Prune belly syndrome has an estimated incidence of 1 in 30,000 to 50,000 newborn babies. At an early stage in the first trimester, there is the typical presentation of keyhole sign of dilated proximal urethra and oligohydramnios.

Today, there are several alternatives for decompressing an obstructed fetal urinary tract. The fetal bladder or renal pelvis can be aspirated percutaneously under ultrasound guidance. Another possibility is early delivery and decompression of the urinary tract *ex utero*. This will maximize the opportunity for further renal development and minimize adverse effects of oligohydramnios. The ideal management is early decompression of the urinary tract and continued gestation. The first successful urinary tract bypass *in utero* was performed by Golbus and others in 1982. They developed techniques for ultrasonographic-guided percutaneous placement of fetal shunt catheters and for the surgical exteriorization of fetal urinary tract.[18] Unfortunately, we still do not know which fetus will markedly benefit from the procedure.

Dilatation of the urinary system is the main characteristic of obstructive uropathies, with hydronephrosis as a following diagnosis. Upper urinary tract dilatation is caused by obstruction at the level of the pelviureteric junction and vesicoureteric junction. Obstruction may be anatomical or more frequently functional. The typical ultrasound presentation of ureteropelvic junction stenosis is severe hydronephrosis without hydroureter and with normal aspect of the bladder. A severely dilated pelvis can rupture and evolve to perinephric urinoma and urinary ascites. Hydronephrosis and hydroureter without dilated bladder are suggestive of vesicoureteric junction stenosis. Fetal lower urinary tract obstruction is mainly caused by posterior urethral valves and urethral atresia. Thick bladder walls, dilated posterior urethra (keyhole sign), and bilateral hydroureter are suggestive of posterior urethral valves. Bilateral obstructive renal dysplasia will result in oligohydramnios or anhydramnios, causing secondary pulmonary hypoplasia and limb deformities. Untreated, it has high mortality rate (45%) and about 25 to 30% of neonatal survivors will develop chronic renal disease. Vesicoamniotic shunting and fetal cystoscopy are at present possible methods of prenatal treatment. Cystoscopy allows a more accurate diagnosis of underlying etiology with the possibility to treat posterior urethral valves by hydro- or laser ablation. However, when compared with vesicoamniotic shunting, no significant improvement in perinatal survival was found.[9,10]

Multicystic Kidneys

This is a disorder characterized by the presence of multiple well-defined cysts within the kidney that do not communicate with each other or to the renal pelvis. The cysts are variable in number and size. A similar cystic appearance maybe sometimes produced by hydronephrosis. The main difference between these two conditions are noncommunicating cysts in multicystic kidney. They are more than 70% unilateral and therefore, prognosis is better. In some cases, postnatally, multicystic kidney can undergo spontaneous involution but if it is associated with hematuria, infection, or hypertension, nephrectomy is indicated. However, postnatal evaluation and follow-up are warranted. If the lesion is bilateral, then the prognosis is fatal. Multicystic kidney is one of the most common diagnosed neonatal abdominal mass. They account for 20% of all masses. They are usually not treated for life in early neonatal period, and after birth accurate diagnosis with noninvasive techniques is easily established and therefore distinction is made from other abdominal masses. Unilateral nephrectomy is the most performed surgical procedure.[19]

Congenital Renal Tumors

Congenital renal tumors are rare. Their appearance is from 2.5 to 7% of all perinatal tumors. Around 90% are diagnosed during the first year of life, 50 to 70% are found in infants before they reach 3 years of age. They include congenital mesoblastic nephroma (CMN), Wilm's tumor, rhabdoid tumor, clear cell sarcoma, hamartomas (e.g., angiomyolipoma), and ossifying tumor of infancy. Congenital mesoblastic nephroma also known as Boland tumor is the most common. It is usually a benign tumor and develops from renal mesenchyma. Less than 5% of all pediatric renal tumors turn out as CMN.[20] With the advances in prenatal ultrasound diagnostics, the number of prenatally diagnosed tumors has increased. The most common presentation is as a unilateral solid mass with homogenous echogenicity near the renal hilus. The mass

is well-demarcated from the renal tissue, although there is no discernible capsule. Typical finding is "ring" sign, an anechoic ring surrounding the tumor. Doppler signals registered in the ring indicate intense peripheral vascularity, which is confirmed with histopathological evaluation afterward. Polyhydramnios is seen in approximately 70% of cases and in 25% of them are delivered prematurely due to the development of uterine contraction. Prognosis is excellent after unilateral nephrectomy.[21,22]

Central Nervous System

Hydrocephalus

Hydrocephalus does not identify a specific disease, but includes a variety of clinicopathological conditions caused by excessive cerebrospinal fluid (CSF) based on the disturbed circulation. The prevalence rate in Europe is 5.84 per 10,000 births after 20 weeks of gestation. New classification of hydrocephalus and standards for clinicopathological evaluation of hydrocephalus have been developed in Japan.[23-25]

Dilatation of the fetal cerebral ventricles is often described with terms "hydrocephalus" or "ventriculomegaly." However, they are not synonyms and the distinction among them should be made. Ventriculomegaly refers to abnormal ultrasound finding independently from the etiology.[26]

Aqueductal stenosis, myelomeningocele (MMC), post intraventricular hemorrhage due to prematurity, congenital hydrocephalus, cyst, tumor, posthead injury, postinfectious are the most important clinical conditions associated with hydrocephalus.[27]

If not treated, hydrocephalus with high intracranial pressure is one of the leading causes of severe brain damage in fetuses and newborns. High intracranial pressure can cause marked separation of cranial sutures and the setting sun sign. The main goal of hydrocephalus treatment is achieving arrested hydrocephalus by shunt surgeries. It is essential to perform the derivation of CSF as early as possible in order to minimize intracranial pressure and to avoid brain damage. In the future, to achieve arrested hydrocephalus, minimum quantity of CSF to be drained should be elucidated.[23,28,29]

In the trial of Stranjalis et al,[30] 12-year hospital outcome in patients with idiopathic hydrocephalus was presented. All babies postnatally had clinical neurological and ophthalmological assessment together with ultrasound examination, while multislice computed tomography and magnetic resonance imaging were performed when needed. Based on these findings, neurosurgical treatment has been indicated whenever appropriate. A favorable outcome was reported for 66.8% of patients, no change in 31.5%, and overall inpatient mortality was 1.7%. Concerning the long-term outcome, in one study 132 patients underwent 179 shunt surgeries. Forty-four (33%), 79 (60%), and 99 (75%) patients demonstrated objective improvement at 3, 6, and 24 months respectively, after shunt surgery. Giant improvement was achieved in 93% of patients. Radiological evidence of corpus callosum distension, gaint impairment as the primary symptom predicted improvement. Urinary incontinence and dementia were twofold less likely to improve.[31]

Posthemorrhagic hydrocephalus and hydrocephalus connected with craniospinal dysraphism had significantly earlier revisions than congenital and other etiologies.[32]

Neural Tube Defects

According to EUROCAT, the prevalence rate of all neural tube defects in Europe from 2008 to 2012 was 9.69 per 10,000 births. Prevalence rate of specific malformations per 10,000 births after 20 weeks of gestation were encephalocele, 1.13; spina bifida, 4.88.[24]

Encephalocele

Encephalocele is a neural tube defect characterized by protrusion of the brain and meninges through opening in the cranium (Fig. 1). Occipital region represent its most common localization (67%) and it is in almost 50% of cases associated with hydrocephalus. After careful preoperative planning, surgery should be done at the earliest opportunity, especially if dealing with anterior encephalocele.[33,34]

Spina Bifida and Meningomyelocele

Spina bifida malformations are often prenatally detected in the second and third trimester although early detection in the first trimester is possible.[35] The most common localization of these malformations is the lumbar and sacral areas of spinal cord. Spina bifida malformations

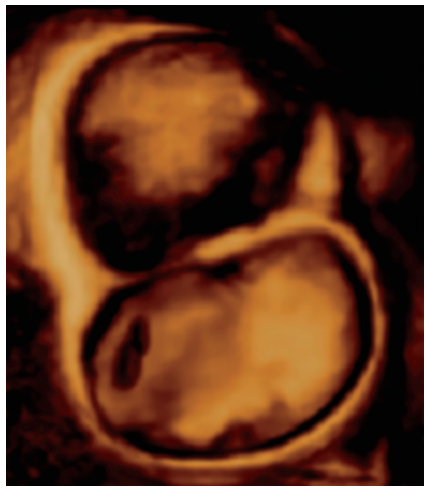


Fig. 1: Encephalocele – 3D ultrasound presentation

are divided into three categories: Spina bifida occulta, spina bifida cystica with meningocele, and spina bifida cystica with MMC.[36] Open spina bifida or MMC is the most common congenital anomaly of the central nervous system compatible with long-term survival and is associated with significant lifelong disabilities in affected individuals. The incidence of spina bifida can be decreased by up to 70% when daily folic acid supplements are taken prior to conception.[37,38]

Spina bifida malformations have indication for immediate surgical correction after birth although today selected individuals can be treated *in utero*.[35,36]

Postnatal surgery is aimed at covering the exposed spinal cord, preventing infection, and treating hydrocephalus with a ventricular shunt. In the past few decades, little progress has been made in the postnatal surgical management of the child with spina bifida. The aim of postnatal MMC surgery is not to reverse or prevent the neurologic injury seen, but to palliate. According to the two-hit hypothesis, the neurologic defects result from primary incomplete neurulation and secondary chronic *in utero* damage of spinal cord and nerves caused by long-term exposure to amniotic fluid. With the introduction of accurate prenatal ultrasound diagnosis and acknowledgment of two-hit theory *in utero* repair was conceived. First, it was performed in experimental and animal models.[37] In 2011, a prospective, randomized study (the MOMS trial) has shown that fetal surgery for MMC before 26 weeks gestation may preserve neurologic function, reverse the hindbrain herniation of the Chiari II malformation, and obviate the need for postnatal placement of a ventriculoperitoneal shunt. However, this study also demonstrates that fetal surgery is associated with significant risks related to the uterine scar and premature birth. Consequently, additional research is necessary to further elucidate the pathophysiology of MMC, to define the ideal timing and technique of fetal closure, and to evaluate the long-term implications of prenatal intervention.

In utero repair of open spina bifida is now performed in selected patients and provides an additional therapeutic alternative.[39]

Vein Galen Aneurysm Malformation

Vein Galen aneurysm malformation is a rare intracranial vascular anomaly. The malformation is due to an arteriovenous fistula of the median prosencephalic vein, a precursor of the vein of Galen, which fails to regress. It represents complex malformation consisting of one or more arteriovenous shunts from arterial feeders from the carotid and vertebrobasilar systems in the midbrain, to the vein of Galen. High flow of blood into the vein causes it to dilate so it is not a true aneurysm. The high rate of blood flow may result in cardiac failure due to increasingly pronounced venous return via jugular veins and vena cava superior. About 80% of the cardiac output may shunt through the fistula.[40,41]

Ultrasound represents the main diagnostic tool for prenatal detection of vein Galen aneurysm malformation with the identification of blood flow in the cyst using spectral or color Doppler. Power Doppler has the capacity to obtain signal in vessels with low-flow velocity, and the three-dimensional (3D) power Doppler can reconstruct the architecture of the vessel.[42] In color Doppler imaging, the focal lesions fill with blue-orange (aliasing) color signals due to turbulence of venous flow. The sonographic appearance of the dilated vein of Galen in the midsagittal plane is large, well-defined, irregular, supratentorial, and sometimes pulsatile structure along the corpus callosum above the cerebellum to the calvaria. In the coronal plane, the dilated vein appears as a round, cystic, centrally located structure. Signs of high-output heart failure as cardiomegaly, fetal hydrops, and polyhydramnios may be presented. Dilated vena cava superior and jugular veins can be additional ultrasound findings. The enlarged vein of Galen may cause obstruction of the Sylvian aqueduct, eventually resulting in hydrocephaly.[40] The high incidence of cardiomegaly in neonates with arteriovenous malformations suggests that high-output cardiac failure is already present in a significant number of cases during the 3rd trimester. Prognosis of malformation depends on the severity of heart failure and the extent of cerebral ischemia caused by increased venous pressure and so-called cerebral steal. Treatment of choice involves performing transarterial embolization in the postnatal period.[43,44]

Fetal Intracranial Hemorrhage

Intracranial hemorrhage (ICH) has high incidence in premature infants. It has been estimated in 40% of infants of less than 32 weeks gestation. It may occur spontaneously or it can be associated with different fetal and maternal condition. Fetal conditions predisposing to ICH include congenital factor X and factor V deficiencies, hemorrhage into various congenital tumors, twin-twin transfusion, and demise of a cotwin of fetomaternal hemorrhage. Predisposing maternal conditions include alloimmune and idiopathic thrombocytopenia, von Willebrand's disease, specific medication (warfarin) or illicit drug (cocaine) abuse, seizures, severe abdominal trauma inflicting subsequent fetal injury, amniocentesis, cholestasis of pregnancy, and febrile disease.[45-48]

Hemorrhage may occur within the cerebral ventricles, subdural space, or infratentorial fossa.

The classification of ICH includes five major types: Intraventricular hemorrhage (IVH), cerebellar, subdural, primary subarachnoidal hemorrhages, and miscellaneous

intraparenchymal hemorrhages. Intraventricular hemorrhages are characteristic hemorrhage of the immature brain; they represent the most common pattern of neonatal ICH. They are subdivided into four grades according to their severity. The first three grades are limited to the ventricles, while the fourth grade includes parenchymal involvement occurring in the most severe cases.[48]

Intacranial hemorrhage does not have uniform sonographic presentation. The most common ultrasound findings include hyperechoic lesions in the lateral ventricle and ventriculomegaly, irregular echogenic brain mass, intraventricular echogenic foci or periventricular echodensities, and posthemorrhagic hydrocephalus (PHH). Unfortunately, outcome is usually poor, especially in fetuses dealing with high grade of IVH. Ventriculoperitoneal shunting postpartum in cases of PHH constitutes an option to enable neurological development as best as possible.[46,48]

Intracranial hemorrhage is associated with significant neonatal neurological impairment. Fetal neurological impairment can be prenatally assessed with the new Kurjak antenatal neurodevelopmental test where intrauterine fetal behavior is visualized with four-dimensional ultrasound and evaluated. Antepartum fetal ICH has potential medicolegal implications, so obstetricians and sonographers should be familiar with predisposing factors and typical diagnostic imaging findings of these events.[49]

Fetal Face

Cleft Lip and Palate

Prevalence of orofacial clefts is 15.96 per 10,000 births (cleft lip with or without cleft palate 9.41 and cleft palate 5.45 per 10,000). These malformations are usually isolated and in less than 10% are associated with abnormal karyotype. Cleft lip may be unilateral or bilateral anomaly.[50]

Prenatal diagnosis of these malformation is helpful in psychological preparation of parents because of cosmetic implications of the neonate and adequate postnatal management of affected child. Despite advances in ultrasound technology, the sensitivity for detection of facial clefts at the routine midtrimester detail scan remains relatively poor. Routine use of 3D ultrasound screening protocol could improve its diagnosis. Recent 3D tomographic ultrasound can demonstrate the anterior maxillary structure, showing evidence of alveolar cleft. When anomaly is suspected, further ultrasound exploration is required to evaluate the extent of the cleft and presence or absence of any other abnormalities. Involvement of the fetal palate is an important finding that will determine the requirement for surgery, audiology, and orthodontic services well into teenage years. Functional and cosmetic repair are usually completed before the age of 10.[51-53]

Congenital Pulmonary Anomalies

Congenital pulmonary anomalies are uncommon but potentially life-threatening and warrant an urgent diagnostic work-up. Congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), bronchogenic cyst, and congenital lobar emphysema (CLE) are four major congenital cystic lesions. Congenital cystic adenomatoid malformation and BPS have often similar ultrasound presentation as homogenous hyperechogenic lesions.[54-56]

Color Doppler helps to make differentiation between these two lesions because of their different origin of vascularization. Congenital cystic adenomatoid malformation is vascularized by the branches of the pulmonary artery, while PC is vascularized directly from artery that arises directly from aorta. Most of the malformations have good outcome, with the possibility of spontaneous regression. Prognosis depends on the size of malformation, macrocystic or microcystic presentation of CCAM, presence of pleural effusion, and consequently development of hydrops.[57,58]

Definitive treatment is surgical removal of the lesion within the 1st year of life in order to prevent infection and rare possibility of neoplastic transformation of the lesion. Congenital cystic adenomatoid malformation (types I and II) and CLE should be treated promptly in newborns for respiratory distress and pneumothorax. Early surgical resection within 1 month of age is safe in symptomatic patients.[54,55]

In selected cases, effective antenatal intervention is possible. It involves placement of thoracoamniotic shunts and consequent resolution of effusions or occlusion of the feeding vessel or the tumor by ultrasound-guided laser coagulation or injection of sclerosing agent. This treatment merits further investigation.[57]

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) represents a congenital anomaly where abdominal organs are herniated into the thoracic cavity due to a congenital defect of the diaphragm. Defective migration of muscle and nerve cell precursor to the diaphragm during its formation is considered the cause of CDH. The diaphragm develops anteriorly as a septum between the heart and liver, and then grows posteriorly. Final closure is at the left Bochdalek foramen between 8 and 10 weeks of gestational age. Bowel migrates from yolk sac to abdominal cavity at 10 weeks. If bowel arrives before the foramen closes, hernia can occur.[59]

Visceral herniation into the thoracic cavity during the critical period of lung development when bronchi and pulmonary undergo branching at 5 to 16 weeks leads to

decreased bronchial branching, pulmonary hypoplasia, truncation of the pulmonary arterial tree, and dysfunctional surfactant postpartum.[60]

Prevalence rate of CDH in Europe is 2.71 per 10,000 births.[24] With the implementation of ultrasound prenatal diagnostics, it is recognized in more than 50% of cases. It can be isolated malformation or associated with other structural anomalies, the latter with poor prognosis. Cariotypization is warranted in cases of CDH in order to exclude genetic disorders linked with this malformation.[61]

Prenatal assessment aims to rule out associated anomalies and to make an individual prognosis. Prediction of outcome is based on measurements of lung size and vasculature as well as on liver herniation.[60-62] The head-to-lung ratio <1 and liver herniation are associated with poor postnatal prognosis and more often require extracorporeal membrane oxygenation (ECMO) support.

The leading cause of CDH morbidity and mortality is respiratory failure resulting from pulmonary hypoplasia and pulmonary hypertension. In those selected fetuses with predicted poor postnatal prognosis, prenatal intervention should be considered.[61]

Prenatal intervention aims at stimulating lung development, clinically achieved by percutaneous fetal tracheal occlusion (FETO) under local anesthesia. Lack of lung expansion 2 to 7 days after tracheal occlusion is considered a poor prognostic sign. The tracheal Occlusion To Accelerate Lung growth trial (www.totaltrial.eu) is an international randomized trial investigating the role of fetal therapy for severe and moderate pulmonary hypoplasia. Despite an apparent increase in survival following FETO, the search for laser-invasive and more potent prenatal interventions must continue.[63]

Recent improvements of newborn transportation, breathing assistance, and intensive care have significantly reduced high mortality rate (50–80%) of the newborns with CDH suffering severe respiratory insufficiency at birth. Introduction of ECMO enables buying time for further lung growth and maturation. Survival rate is improved if hernia repair is delayed to allow resolution of early pulmonary insufficiency and acute pulmonary hypertension. Postnatal treatment of neonate with suspected CDH is based on immediate endotracheal intubation together with orogastric tube insertion. Mask ventilation is abandoned because it can cause severe damage to hypoplastic lungs and acute shift of the mediastinum by inflating stomach, causing further reduction of survival rates.[61]

Advances in prenatal diagnosis and the institution of standardized delivery and postnatal care protocols have led to improved survival. Chronic respiratory tract disease, neurodevelopmental problems, neurosensorial hearing loss, and gastroesophageal reflux are common problems in survivors. Therefore, the increased survival and subsequent morbidity of CDH survivors have resulted in the need to provide resources for the long-term follow-up and support of the CDH population.[64]

Congenital Heart Defects

Congenital heart defects (CHDs) have an overall incidence of about 1% in live-born infants, and account for 20% of all stillbirths and 30% of neonatal deaths due to congenital anomalies. Major CHDs have an estimated prevalence of 2 to 4 per 1,000 live births and are either lethal or require surgical repair or intervention within the first year of life.[65,66]

The etiology of CHD includes maternal diseases like diabetes mellitus and phenylketonuria, exposure to substances (anticonvulsants, lithium), infections (parvovirus, rubella), chromosomal anomalies (trisomies 21 and 18), and specific mutant gene defects. The aneuploidy of the fetus with CHD is 30%. The recurrence risk of cardiac anomalies in the absence of known genetic syndromes is 2 to 4% and with two previously affected siblings is 10%.[67]

Congenital heart defects can be diagnosed during fetal life using echocardiography. Prenatal screening programs typically recommend detailed assessment of fetuses judged to be at high-risk of congenital heart disease. However, most cases of congenital heart disease arise in the low-risk population. Prenatal diagnosis allows full investigation of affected fetuses for coexisting abnormalities and gives time for parents to be informed about the prognosis of the fetus and treatments that might be required. In a minority of cases, where the natural history suggests an unfavorable outcome, prenatal diagnosis provides an opportunity for fetal cardiac intervention. For some cardiac lesions, notably hypoplastic left heart syndrome, transposition of the great arteries, and coarctation of the aorta, prenatal diagnosis has been shown to reduce postnatal morbidity and mortality.[68]

Gastrointestinal Tract

The fetal gastrointestinal tract is one of the most common sites of surgically correctable malformation detected by ultrasound. Antenatal detection of potentially correctable major gastrointestinal malformation may be life saving since appropriate prenatal preparation allows planning of delivery and subsequent postnatal corrective surgery in the best equipped available center and in the most suitable conditions.[69]

Importance of early antenatal detection of gastrointestinal malformation is evident, because in antenatally unrecognized cases, surgical management of neonatal intestine obstruction may be compromised by delayed diagnosis and consequently complicated by vomiting,

electrolyte imbalance, aspiration, sepsis, peritonitis due to intestinal perforation, or bowel gangrene in cases of intestinal volvulus. Therefore, if corrective surgery is not performed, gastrointestinal obstruction will ultimately lead to death of the neonate.[70]

Abdominal Wall Defects (Omphalocele and Gastroschisis)

Omphalocele and gastroschisis represent the most common congenital abdominal wall defects. In both malformations, the abdominal content is placed outside the abdomen through abdominal wall defect with membrane in omphalocele and without membrane in gastroschisis.

Prenatal ultrasound has a high sensitivity for these abnormalities already at the time of the first-trimester nuchal scan. Differentiation of these anomalies can be successful using 3D color Doppler ultrasound.

Major unrelated defects are associated with gastroschisis in about 10% of cases, whereas omphalocele is associated with chromosomal or genetic abnormalities in a much higher proportion of cases. Challenges in management of gastroschisis are related to the prevention of late intrauterine death, and the prediction and treatment of complex forms. With omphalocele, the main difficulty is the exclusion of associated conditions, not all diagnosed prenatally. Postnatal prognosis for omphalocele is related to the number and severity of associated anomalies and the karyotype, while in gastroschisis is primarily determined by the degree of bowel injury.

The definitive treatment of these anomalies is surgery with closure of the abdominal wall defects. Options include primary closure or a variety of staged approaches. Most of the infants that undergo surgical repair have a good long-term outcome.[71-80]

Management of gastroschisis has shifted from early primary closure to performed silo placement and delayed closure. This resulted in prolonged intensive care unit stay and time to full feeds but reduced postoperative hernias and wound infections. Therefore, most newborns need only one operation for definitive surgical treatment.[75,76]

Esophageal Atresia with or without Fistula

Ultrasound findings suggestive of esophageal atresia with or without fistula are polyhydramnios followed with very small stomach.[81,82]

Duodenal Atresia and Jejunoileal Atresia

Duodenal atresia is usually asymptomatic immediately after birth, but later persistent vomiting follows the mentioned diagnosis.[83-85] A typical X-ray image is presented by "double-bubble" sign of total duodenal obstruction.[86]

Typical ultrasound presentation of jejunoileal atresia is the presence of polyhydramnios and visualization of several dilated loops of fluid-filled intestine in the fetal abdomen.[86,87] When dealing with jejunal atresia, parents should be informed of the possibility of an associated apple peel with short bowel syndrome, which could be often followed by intestinal failure-associated liver disease.[88,89]

Sometimes, intestinal obstruction may be due to the meconium ileus with cystic fibrosis as the underlying pathology.[90,91] Diagnosis of anorectal malformations is usually done in late pregnancy or in the early neonatal period. Timing of diagnosis does not interfere with typical treatment of these malformations.[92]

Postnatal Counseling and Management

Congenital malformations are one of the leading cause of infant mortality and an important contributor to childhood and adult morbidity. They have significant impact on individuals, families, health care systems, and societies. Major congenital malformations are abnormalities that are severe enough to reduce life expectancy or compromise normal function. They cause neonatal death in more than 20% of cases. They are considered to be lethal if they cause stillbirth or infant death in 50% of cases. If newborn infant with major malformation cannot survive without medical intervention, then they are considered severe.[8,93,94]

Fetuses and neonates with congenital malformations can be divided into six groups[94]:

1. Those who have potential for total recovery.
2. Those with anomalies that would allow for a nearly normal life.
3. Those with malformations requiring permanent supervision and/or medical care.
4. These with somatic rest defect and subnormal development.
5. Those with serious somatic and mental damage.
6. Those with anomalies that are incompatible with life.

According to the American Academy of Pediatrics, there are three possibilities concerning the treatment with intensive care in decision-making process based on infant's prognosis[95]:

1. Intensive care is indicated if survival is likely and the risk of severe morbidity is low.
2. Intensive care is not indicated if the survival is not likely and would be accompanied by severe unacceptable morbidity and suffering.
3. In some cases the situation could be in between those two situations and prognosis is not certain, but likely to be very poor. In that situation, parental desires should determine the treatment approach.

In the first situation, affected child with deformation is considered normal because deformation is curable and child can lead a normal life thereafter. This accounts for infants with single defects like cleft lip, some CHDs, pyloric stenosis, hexadactyly. Parents should be familiar with the information that their child is normal and that defect is curable and can be adequately and easily solved. It is very important for the physician to establish reliable, trustful relationship with parents so they could face realistically with their child's condition. In cases when physicians fail to make acceptance of infant's condition, then relations between parents and their child may develop into an undesirable condition: Rejection or overprotection.[95]

In the second situation, when dealing with a severely affected child, physician must give parents the option of no medical intervention. This accounts for cases of anencephaly, severe neural tube defects, hydranencephaly, holoprosencephaly, trisomy 13 and 18 syndrome, the 4p-syndrome, the Meckel-Gruber syndrome, or Potter syndrome. These disorders severely limit the infant's capacity to survive and function in spite of full medical support including intensive care.[95] Parents should be informed that even if the life will be preserved for some time, the infant will not be able to continue survival. In case of intervention, the functional capability of the infant will be very limited. When dealing with this kind of situation, physicians must inform parents that the kindest approach to the infant is to do no intervention, and ask parents for the permission for such approach. Parents should be aware that the baby will be provided with compassionate care and that suffering will be minimal. It is very hard and emotional for parents when they are faced with end-of-life decisions and some of them will need psychological or social worker help to overcome their problem.[96] Parental complaints are more likely to occur due to misunderstanding, confusion, and tension among staff and parents as a result of a failure to have in place or to implement agreed protocols.[97]

Parental counseling is very complicated and individualized when dealing with the intermediate situation. Further treatment depends on the nature and severity of the handicap. It is mandatory to explain to parents all the facts associated with the course of the problem, usual range of functional and other limitations, and what can be done in order to help the child to adapt to the problem. It is important to help parents to accept their child with the problem, informing them that there are other families with the same or similar problems.[96-98]

Counseling process is generally very hard working and time consuming. Adequate team of specialists should provide parents the most accurate information about their child's condition with a spectrum of possibilities, survival rate, outcome, complications of underlying disease, and quality of life. Sometimes, more than one appointment is needed for parents to face their new situation. Some parents are almost incapable to accept that their child is handicapped, while others may develop deep parental love for their handicapped and malformed child.[95-98]

CONCLUSION

Despite advances in prenatal diagnosis, improvement of surgical management and postoperative care of newborns with severe surgically correctable congenital anomalies continues to be important cause of perinatal mortality rate in developed and in developing countries. Therefore, only a multidisciplinary team approach of a group of specialists including specialists in maternal-fetal medicine, neonatology, genetics, pediatric surgery, plastic surgery, pediatric cardiology, and neurosurgery could favorably influence the perinatal management of prenatally diagnosed anomalies. More attention should be paid to the primary, secondary, and tertiary prevention of surgically correctable congenital anomalies whenever possible.

REFERENCES

1. Corsello G, Giuffrè M. Congenital malformations. J Matern Fetal Neonatal Med 2012 Apr;25(1):25-29.
2. World Health Organisation. Congenital anomalies (Internet). Geneva: World Health Organisation; 2015 Apr (cited 2016 Apr 20). Available from: http://www.who.int/mediacentre/factsheets/fs370/en/.
3. Kurjak A, Kirkinen P, Latin V, Rajhvajn B. Diagnosis and assessment of fetal malformations and abnormalities by ultrasound. J Perinat Med 1980;8(5):219-235.
4. Kurjak A, Latin V, Mandruzzato G, D'Addario V, Rajhvajn B. Ultrasound diagnosis and perinatal management of fetal genito-urinary abnormalities. J Perinat Med 1984;12(6):291-312.
5. Kurjak A, Gogolja G, Kogler A, Latin V, Rajhvajn B. Ultrasound diagnosis and perinatal management of surgically correctable fetal malformations. Ultrasound Med Biol 1984 Jul-Aug; 10(4):443-455.
6. Lakahoo K. Fetal counselling for surgical conditions. Early Hum Dev 2012 Jan;88(1):9-13.
7. Partridge EA, Flake AW. Maternal-fetal surgery for structural malformations. Best Pract Res Clin Obstet Gyneacol 2012 Oct;26(5):669-682.
8. Kumar P, Burton BK. Malformations: evidence-based evaluation and management. New York (NY): McGraw-Hill Medical; 2008.
9. Dias T, Sairam S, Kumarasiri S. Ultrasound diagnosis of fetal renal abnormalities. Best Pract Res Clin Obstet Gynaecol 2014 Apr;28(3):403-415.
10. Hindryckx A, De Catte L. Prenatal diagnosis of congenital renal and urinary tract malformations. Facts Views Vis Obgyn 2011;3(3):165-174.
11. Nelson C. Editorial comment. J Urol 2009 Oct;182 (Suppl 4):1848.
12. Gordon I, Riccabona M. Investigating the newborn kidney: update on imaging techniques. Semin Neonatol 2003 Aug;8(4):269-278.

13. Yang Y, Hou Y, Niu ZB, Wang CL. Long-term follow-up and management of prenatally detected, isolated hydronephrosis. J Pediatr Surg 2010 Aug;45(8):1701-1706.
14. Herndon CD, Kitchens DM. The management of uteropelvic junction obstruction presenting with prenatal hydronephrosis. Scientific World J 2009 May 29;9:400-403.
15. Ville Y. Fetal therapy: practical ethical considerations. Prenat Diagn 2011 Jul;31(7):621-627.
16. Nguyen HT, Benson CB, Bromley B, Campbell JB, Chow J, Coleman B, Cooper C, Crino J, Darge K, Herndon CD, et al. Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system). J Pediatr Urol 2014 Dec;10(6):982-998.
17. Tsai YL, Seow KM, Yieh CH, Chong KM, Hwang JL, Lin YH, Huang LW. Comparative study of conservative and surgical management for symptomatic moderate and severe hydronephrosis in pregnancy: a prospective randomized study. Acta Obstet Gynecol Scand 2007;86(9):1047-1050.
18. Golbus MS, Harrison MR, Filly RA, Callen PW, Katz M. In utero treatment of urinary tract obstruction. Am J Obstet Gynecol 1982 Feb 15;142(4):383-388.
19. Dally EA, Raman A, Webb NR, Farnsworth RH. Unilateral multicystic dysplastic kidney with progressive infundibular stenosis in the contralateral kidney: experience at 1 center and review of literature. J Urol 2011 Sep;186(3):1053-1058.
20. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Tumors of the urinary system and male genital organs: pathology and genetics. Geneva: World Health Organization; 2004.
21. Kelner M, Droulle P, Didier F, Hoeffel JC. The vascular "ring" sign in mesoblastic nephroma: report of two cases. Pediatr Radiol 2003 Feb;33(2):123-128.
22. Leclair MD, El-Ghoneimi A, Audry G, Ravasse P, Moscovici J, Heloury Y, French Pediatric Urology Study Group. The outcome of prenatally diagnosed renal tumors. J Urol 2005 Jan;173(1):186-189.
23. Oi S, Inagaki T, Shinoda M, Takahashi S, Ono S, Date I, Nomura S, Miwa T, Araki T, Ito S, et al. Guideline for management and treatment of fetal and congenital hydrocephalus: Center of Excellence-Fetal and Congenital Hydrocephalus: Top 10 Japan Guidelines 2011. Childs Nerv Syst 2011 Oct;27(10): 1563-1570.
24. European Concerted Action on Congenital anomalies and Twins. European surveillance of congenital anomalies. Access prevalence tables. Prevalence tables. (Internet). European Concerted Action on Congenital anomalies and Twins; 2013 (cited 2016 Apr 25). Available from: http://www.eurocat-network.eu/accessprevalencedata/prevalencetables.
25. Pooh RK. Malformations of the central nervous system. In: D'Addario V, editor. Donald school basic text book of ultrasound in obstetrics and gynecology. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2015.
26. D'Addario V, Rossi AC. Fetal cerebral ventriculomegaly sonographic diagnostic workup. Donald School J Ultrasound Obstet Gynecol 2008 Jul-Sep;2(3):100-111.
27. Simon TD, Whitlock KB, Riva-Cambrin J, Kestle JR, Rosenfeld M, Dean JM, Holubkov R, Langley M, Mayer-Hamblett N. Association of intraventricular hemorrhage secondary to prematurity with cerebrospinal fluid shunt surgery in the first year following initial shunt placement. J Neurosurg Pediatr 2012 Jan;9(1):54-63.
28. Cavalheiro S, Moron AF, Almodin CG, Suriano IC, Hisaba V, Dastoli P, Barbosa MM. Fetal hydrocephalus. Childs Nerv Syst 2011 Oct;27(10):1575-1583.
29. Girard NJ. Magnetic resonance imaging of fetal developmental anomalies. Top Magn Reson Imaging 2011 Feb;22(1):11-23.
30. Stranjalis G, Kalamatianos T, Koutsarnakis C, Loufardaki M, Stavrinou L, Sakas DE. Twelve-year hospital outcomes in patients with idiopathic hydrocephalus. Acta Neurochir 2012;113(Suppl):115-117.
31. McGirt MJ, Woodworth G, Coon AL, Thomas G, Williams MA, Rigamonti D. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. Neurosurgery 2008 Feb;62 (Suppl 2):670-677.
32. Notarianni C, Vannemreddy P, Caldito G, Bollam P, Wylen E, Willis B, Nanda A. Congenital hydrocephalus and ventriculoperitoneal shunts: influence of etiology and programmable shunts on revisions. J Neurosurg Pediatr 2009 Dec;4(6): 547-552.
33. Mahajan C, Rath GP, Dash HH, Bithal PK. Perioperative management of children with encephalocele: an institutional experience. J Neurosurg Anesthesiol 2011 Oct;23(4):352-356.
34. Alexiou GA, Sfakianos G, Prodromou N. Diagnosis and management of cephaloceles. J Craniofac Surg 2010 Sep;21(5): 1581-1582.
35. Pooh RK, Kurjak A. Novel application of three dimensional HD live imaging in prenatal diagnosis from the first trimester. J Perinat Med 2015 Mar;43(2):147-158.
36. Bulbul A, Can E, Bulbul LG, Cömert S, Nuhoglu A. Clinical characteristics of neonatal meningomyelocele cases and effect of operation time on mortality and morbidity. Pediatr Neurosurg 2010;46(3):199-204.
37. Moldenhauer JS. In utero repair of spina bifida. Am J Perinatol 2014 Aug;31(7):595-604.
38. De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, Evans JA, Van den Hof MC, Zimmer P, Crowley M, et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med 2007 Jul 12;357(2):135-142.
39. Adzick NS. Fetal surgery for spina bifida: past, present, future. Semin Pediatr Surg 2013 Feb;22(1):10-17.
40. Gupta AK, Varma DR. Vein of Galen malformations: review. Neurol India 2004 Mar;52(1):43-53.
41. Pooh RK, Kurjak A, editors. Fetal neurology. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2011.
42. Rios LT, Araujo Júnior E, Nardozza LM, Moron AF, Martins Mda G. Prenatal diagnosis of an aneurysm of the vein of Galen by three-dimensional power and color Doppler ultrasonography. Clin Med Insights Case Rep 2012;5:77-80.
43. Li AH, Armstrong D, Bruggeter KG. Endovascular treatment of vein of Galen aneurysmal malformation: management strategy and 21-year experience in Toronto. J Neurosurg Pediatr 2011 Jan;7(1):3-10.
44. Lasjaunias P. Vascular diseases in neonates, infants, and children: interventional neuroradiology management. Berlin, Heidelberg: Springer-Verlag; 1997. p. 67-202.
45. Sherer DM, Anyaegbunam A, Onyeije C. Antepartum fetal intracranial hemorrhage, predisposing factors and prenatal sonography: a review. Am J Perinatol 1998 Jul;15(7):431-441.
46. Huang YF, Chen WC, Tseng JJ, Ho ES, Chou MM. Fetal intracranial hemorrhage (fetal stroke): report of four antenatally diagnosed cases and review of the literature. Taiwan J Obstet Gynecol 2006 Jun;45(2):135-141.
47. Elchalal U, Yagel S, Gomori JM, Porat S, Beni-Adani L, Yanai N, Nadjari M. Fetal intracranial hemorrhage (fetal stroke): does grade matter? Ultrasound Obstet Gynecol 2005 Sep;26(3):233-243.

48. Ghi T, Simonazzi G, Perolo A, Savelli L, Sandri F, Bernardi B, Santini D, Bovicelli L, Pilu G. Outcome of antenatally diagnosed intracranial hemorrhage: case series and review of the literature. Ultrasound Obstet Gynecol 2003 Aug;22(2):121-130.
49. Kurjak A, Miskovic B, Amiel-Tisson C, Ahmed B, Azumendi G, Vasilij O, Andonotopo T, Turudic T, Salihagic-Kadic A. New scoring system for fetal neurobehavior assessed by three and four-dimensional sonography. J Perinat Med 2008;36(1):73-81.
50. Kirbschus A, Gesch D, Heinrich A, Gedrange T. Presurgical nasoalveolar molding in patients with unilateral clefts of lip, alveolus and palate. Case study and review of the literature. J Craniomaxillofac Surg 2006 Sep;34 (Suppl 2):45-48.
51. Hassan WA, Lees CC. Facial cleft detected: is the palate normal? Best Pract Res Clin Obstet Gynaecol 2014 Apr;28(3):379-389.
52. Wiggman K, Larson M, Larson O, Semb G, Brattström V. The influence of the initial width of the cleft in patients with unilateral cleft lip and palate related to final treatment outcome in the maxilla at 17 years of age. Eur J Orthod 2013 Jun;35(3):335-340.
53. Knežević P, Grgurević L, Uglešić V, Grgurević J. Modified Millard's technique in operations for unilateral cleft lip. J Plast Surg Hand Surg 2012 Oct;46(5):326-329.
54. Lima M, Gargano T, Ruggeri G, Manuele R, Gentili A, Pilu G, Tani G, Salfi N. Clinical spectrum and management of congenital pulmonary cystic lesions. Pediatr Med Chir 2008 Mar-Apr;30(2):79-88.
55. Chen HW, Hsu WM, Lu FL, Chen PC, Jeng SF, Peng SS, Chen CY, Chou HC, Tsao PN, Hsieh WS. Management of congenital cystic adenomatoid malformation and bronchopulmonary sequestration in newborns. Pediatr Neonatol 2010 Jun;51(3):172-177.
56. Şen C, Aksoy F, Ramazanoglur R. Congenital cystic adenomatoid malformation type III associated with congenital anomalies. Perinat J 2000;8(3):123-125.
57. Cavoretto P, Molina F, Poggi S, Davenport M, Nicolaides KH. Prenatal diagnosis and outcome of echogenic fetal lung lesions. Ultrasound Obstet Gynecol 2008 Nov;32(6):769-783.
58. Benachi A. Echogenic fetal lung lesions. Ultrasound Obstet Gynecol 2008 Nov;32(6):729-731.
59. Sadler TW. Langman's medical embryology. 9th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2004.
60. Deprest JA, De Coppi P. Antenatal management of isolated congenital diaphragmatic hernia today and tomorrow: ongoing collaborative research and development. J Pediatr Surg 2012 Feb;47(2):282-290.
61. Tovar JA. Congenital diaphragmatic hernia. Orphanet J Rare Dis 2012;7:1. Available from: http://www.ojrd.com/content/7/1/1.
62. Deprest JA, Nicolaides K, Gratacos E. Fetal surgery for congenital diaphragmatic hernia is back from never gone. Fetal Diagn Ther 2011;29(1):6-17.
63. Deprest J, Brady P, Nicolaides K, Benachi A, Berg C, Vermeesch J, Gardener G, Gratacos E. Prenatal management of the fetus with isolated congenital diaphragmatic hernia in the era of the TOTAL trial. Semin Fetal Neonatal Med 2014 Dec;19(6):338-348.
64. Badillo A, Gingalewski C. Congenital diaphragmatic hernia: treatment and outcomes. Semin Perinatol 2014 Mar;38(2):92-96.
65. Ikonomou T, Theodora M. Prenatal screening for congenital heart defects. Donald School J Ultrasound Obstet Gynecol 2008;2:16-19.
66. Allan LD, Sharland GK, Chita SK, Lockhart S, Maxwell DJ. Chromosomal anomalies in fetal heart congenital disease. Ultrasound Obstet Gynecol 1991 Jan 1;1(1):8-11.
67. Allan LD, Cook AC, Huggon IC. Fetal echocardiography. A practical guide. Cambridge: Cambridge University Press; 2009.
68. Hunter LE, Simpson JM. Prenatal screening for structural congenital heart disease. Nat Rev Cardiol 2014 Jun;11(6):323-334.
69. De Grazia E, Di Pace MR, Caruso AM, Catalano P, Cimador P. Different types of intestinal atresia in identical twins. J Pediatr Surg 2008 Dec;43(12):2301-2304.
70. Watanabe T, Nakano M, Yamazawa K, Maeyama K, Endo M. Neonatal intestinal volvulus and preduodenal portal vein associated with situs ambiguus: report of a case. Surg Today 2011 May;41(5):726-729.
71. Mann S, Blinman TA, Douglas Wilson R. Prenatal and postnatal management of omphalocoele. Prenat Diagn 2008 Jul;28(7);626-632.
72. Christison-Lagay ER, Kelleher CM, Langer JC. Neonatal abdominal wall defects. Semin Fetal Neonatal Med 2011 Jun;16(3):164-172.
73. Payne NR, Pfleghaar K, Assel B, Johnson A, Rich RH. Predicting the outcome of newborns with gastroschisis. J Pediatr Surg 2009 May;44(5):918-923.
74. David AL, Tan A, Curry J. Gastroschisis: sonographic diagnosis, associations, management and outcome. Prenat Diagn 2008 Jul;28(7):633-644.
75. Weil BR, Leys CM, Rescorla FJ. The jury is still out: changes in gastroschisis management over the last decade are associated with both benefits and shortcomings. J Pediatr Surg 2012 Jan;47(1):119-124.
76. Juhasz-Böss I, Goelz R, Solomayer EF, Fuchs JR, Meyberg-Solomayer G. Fetal and neonatal outcome in patients with anterior abdominal wall defects (gastroschisis and omphalocele). J Perinat Med 2011 Nov 16;40(1):85-90.
77. Mortellaro VE, St Peter SD, Fike FB, Islam S. Review of the evidence on the closure of abdominal wall defects. Pediatr Surg Int 2011 Apr;27(4):391-397.
78. Martin AE, Khan A, Kim DS, Muratore CS, luks FI. The use of intraabdominal tissue expanders as a primary strategy for closure of giant omphaloceles. J Pediatr Surg 2009 Jan;44(1):178-182.
79. Henrich K, Huemmer HP, Reingruber B, Weber PG. Gastroschisis and omphalocele: treatments and long-term outcomes. Pediatr Surg Int 2008 Feb;24(2):167-173.
80. Prefumo F, Izzi C. Fetal abdominal wall defects. Best Pract Res Clin Obstet Gynaecol 2014 Apr;28(3):391-402.
81. Houben CH, Curry JI. Current status of prenatal diagnosis, operative management and outcome of esophageal atresia/tracheo-esophageal fistula. Prenat Diagn 2008 Jul;28(7):667-675.
82. Mourali M, Essoussi-Chikhaoui J, Fatnassi A, El Fekih C, Ghorbel S, Ben Zineb N, Oueslati B. Prenatal diagnosis of esophageal atresia. Tunis Med 2011 Feb;89(2):213-214.
83. Kilbride H, Castor C, Andrews W. Congenital duodenal obstruction: timing of diagnosis during the newborn period. J Perinatol 2010 Mar;30(3):197-200.
84. Choudhry MS, Rahman N, Boyd P, Lakhoo K. Duodenal atresia: associated anomalies, prenatal diagnosis and outcome. Pediatr Surg Int 2009 Aug;25(8):727-730.
85. Rao P. Neonatal gastrointestinal imaging. Eur J Radiol 2006 Nov;60(2):171-186.

86. Yang HC, Chen SJ, Liu KL. Double bubble sign. Emerg Med J 2011 Dec;28(12):1084.
87. Ohyama M, Itani Y, Ishikawa H, Tanaka Y. Is umbilical cord ulcer associated with congenital upper intestinal atresia so rare? Japanese case series and review of the literature. Fetal Diagn Ther 2010;28(4):236-237.
88. Miraglia R, Catalano P, Maruzzelli L, Riva S, Spada M, Alberti D, Luca A, Gridelli B. Balloon dilatation of postoperative small bowel anastomotic stricture in an infant with apple peel intestinal atresia after serial transverse enteroplasty and jejunoileal anastomosis. J Pediatr Surg 2010 Dec;45(12):e25-e28.
89. Lilja HE, Finkel Y, Paulsson M, Lucas S. Prevention and reversal of intestinal failure-associated liver disease in premature infants with short bowel syndrome using intravenous fish oil in combination with omega-6/9 lipid emulsions. J Pediatr Surg 2011 Jul;46(7):1361-1367.
90. van der Doef HP, Kokke FT, van der Ent CK, Houwen RH. Intestinal obstruction syndromes in cystic fibrosis: meconium ileus, distal intestinal obstruction syndrome, and constipation. Curr Gastroenterol Rep 2011 Jun;13(3):265-270.
91. Paradiso VF, Briganti V, Oriolo L, Coletta R, Calisti A. Meconium obstruction in absence of cystic fibrosis in low birth weight infants: an emerging challenge from increasing survival. Ital J Pediatr 2011 Nov 14;37:55.
92. Mirza B, Ijaz L, Saleem M, Sharif M, Sheikh A. Anorectal malformations in neonates. Afr J Paediatr Surg 2011 May-Aug;8(2): 151-154.
93. Zaputovic S, Stanojevic M, Honemeyer U, Turudic T, Kurjak A. Surgically correctable fetal anomalies – ultrasound diagnosis and management. Donald School J Ultrasound Obstet Gynecol 2012;6(3):237-256.
94. Pinter AB. End-of-life decision before and after birth: changing ethical considerations. J Pediatr Surg 2008 Mar;43(3): 430-436.
95. Committee on Fetus and Newborn. Noninitiation or withdrawal of intensive care for high-risk newborns. Pediatrics 2007 Feb;119(2):401-403.
96. Provoost V, Cools F, Deconinck P, Ramet J, Deschepper R, Bilsen J, Mortier F, Vandenplas Y, Deliens L. Consultation of parents in actual end-of-life decision-making in neonates and infants. Eur J Pediatr 2006 Dec;165(12):859-866.
97. Chiswick M. Infants of borderline viability: ethical and clinical considerations. Semin Fetal Neonatal Med 2008 Feb;13(1): 8-15.
98. Stanojevic M. Medical management of newborn with severe malformations – ethical aspects. In: Schenker GJ, editor. Ethical dilemmas in perinatal medicine. Delhi: Jaypee Brothers Medical Publishers; 2010. p. 197-204.