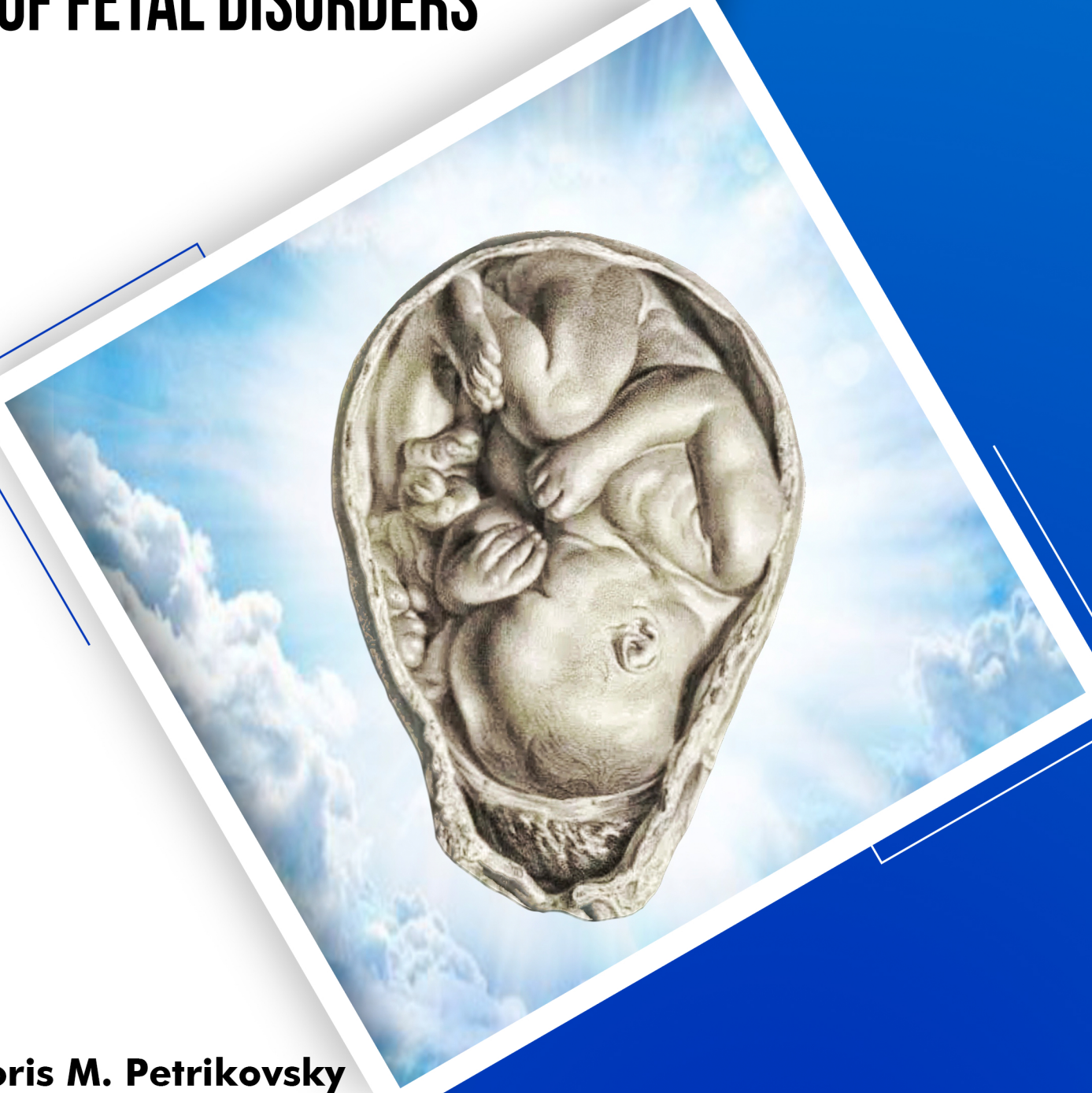
DIAGNOSIS AND MANAGEMENT OF FETAL DISORDERS



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Diagnosis and Management of Fetal Disorders

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FOREWORD

The prenatal diagnosis and management of fetal disorders are some of the most common challenges in obstetrics since some of these disorders can have devastating consequences for both the mother and fetus or neonate. Close antenatal surveillance is of paramount importance because these fetal disorders are the cause of an increased risk of stillbirth, neonatal death, spontaneous or indicated preterm birth, neonatal morbidity and abnormal short and long-term neurodevelopment. Some of these disorders may also carry a significant risk for recurrence in the pregnancies to follow, which makes genetics an integral part of the evaluation.

Given the tremendous technological advances in fetal imaging, by ultrasound and MRI, over the last four decades and the huge impact of fetal disorders on both maternal and fetal/neonatal health, this book on "Diagnosis and Management of Fetal Disorders" will hopefully be an extremely significant and timely contribution. This textbook is unique because it provides brief, clear, succinct information on the most commonly diagnosed fetal disorders. Front line health care providers can use this current information in the initial care of patients and before referral to subspecialists for the most complicated cases. The book's strength lies in its simplicity and its world-renowned experts as contributors.

Given the short and long-term health consequences of fetal disorders, it remains vital for the international community to be familiar with cutting-edge fetal medicine information including not only fetal structural malformations but also disorders such as intrauterine fetal death and fetal infections. This textbook covers the most important topics in Fetal Medicine. Each chapter is well organized using a reader-friendly format including definition, prevalence, etiology, prenatal imaging (ultrasound and/or MRI) diagnosis, genetics, and prenatal and postnatal counseling of each disorder.

The textbook "Diagnostic and Management of Fetal Disorders" results from a combined effort of distinguished contributors, Dr. Boris Petrikovsky and Dr. Harris Cohen who are well-recognized authorities in the field of fetal medicine.

In my view, this textbook on "Diagnostic and Management of Fetal Disorders" covers every aspect of the most common fetal disorders and provides clear and succinct up-to-date information like no other text. This textbook will serve as *the* source of valuable information for front line healthcare providers. Therefore, I strongly recommend its reading by all those frontline health care providers who are involved in prenatal diagnosis and management of fetal disorders.

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PREFACE

Fetal Medicine is one of the fastest developing fields of medicine. This century has witnessed exponential developments in fetal medicine and surgery prompted by advancements in fetal imaging, including but not limited to 3D and 4D ultrasound and fetal MRI. New developments in prenatal genetics (*e.g*., screening based on non-invasive analysis of fetal cells in maternal circulation) have pushed investigators to make earlier and more accurate fetal diagnoses including those in the 1st trimester.

All of these developments make textbooks, even recently published ones, less accurate, with most management recommendations now obsolete. This encouraged us to put together a new manuscript. Our goal was to create a practical guide to the common fetal anomalies. Our targeted audience include medical students, medical sonographers, attendings and residents in obstetrics, pediatrics, and radiology. The structure for each chapter includes definitions and prevalence of a particular abnormality, major principles of its diagnosis, genetics, prenatal strategy, neonatal management, clinical outcomes, and prognosis. We hope this book will serve as a helpful and practical reference book.

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KEYWORDS

Chapter 1

Central nervous system anomalies, Spina bifidum, Ventriculomegaly.

Chapter 2

Absent Nasal Bone, Facial Clefts, Microphthalmia, Nuchal Translucency.

Chapter 3

Congenital lung disease, Fetal surgery, Hydrothorax.

Chapter 4

Ebstein Anomaly, Echogenic Foci, Fetal Echocardiography.

Chapter 5

Bowel Herniation, Double-Bubble, Gastroschisis, Omphalocele.

Chapter 6

Congenital Hydronephrosis, Posterior Urethral Valves, Renal Agenesis.

Chapter 7

Achondroplasia, Dwarfism, Skeletal Dysplasia.

Chapter 8

Fetal Anemia, Maternal Mirror Syndrome, Polyhydramnios.

Chapter 9

Fetal Teratoma, Placental Chorioangioma, Rhabdomyoma.

Chapter 10

Chorionicity, Twins, Triplets.

Chapter 11

Covid-19, Toxoplasmosis, Zika.

Chapter 12

Funic Presentation, Nuchal Cord, Placental Hematoma.

Chapter 13

Fetal Assessment, Fetal Demise, Perinatal Mortality.

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Alison Dillon, Eliyahu Petrikovsky, Kristina Coleman, Natalie Montgomery

DEDICATION

To the memory of my parents, my wife Muriel, my children and grandchildren. BP

To my wife, children, and grandchildren, and to my patients and their families. HLC

CHAPTER 1

Abnormalities of the Central Nervous System

INTRODUCTION

Anomalies of the central nervous system include birth defects of the brain and spinal cord. These abnormalities may be caused by a variety of factors including genetics, medications, toxins, and infectious agents, among others. Central nervous system abnormalities may be divided into three groups: incompatible with life (*e.g.*, anencephaly), requiring in-utero surgery in some cases (*e.g.*, spina bifidum), or post-delivery follow-up and/or treatment (*e.g.*, ventriculomegaly).

Agenesis Of The Corpus Callosum

Definition: The corpus callosum is the largest of the medial interhemispheric commissures connecting the right and left halves of the brain. In agenesis of the corpus callosum (ACC) the connecting neurofibers of the commissure fail to develop.

Prevalence: 3.5 per 1000 live births [1].

Major Principles of Diagnosis: At times, the sonographic diagnosis of ACC may be difficult: 10 to 15% of ACC cases may be missed including in patients who underwent more than one ultrasound examination during their pregnancy. Ultrasound signs of agenesis of the corpus callosum include wide separation of the frontal horns of the lateral ventricles and a high riding third ventricle because the corpus callosum is no longer present to prevent its upward positioning. Lateral ventricles may be teardrop shaped (colpocephaly) with only the posterior portion full or dilated. Image findings of concern for ACC include difficulty in imaging a cavum septum pellucidum and mild ventriculomegaly including the aforementioned colpocephaly with its enlargement of the occipital horns of the lateral ventricles.

At times one may see an associated midline cyst and /or lipoma [2]. The cavum septum pellucidum (CSP) which is absent in cases of ACC would normally appear as two parallel lines separated by cerebrospinal fluid (CSF). A cavum may be seen between the frontal horn as early as 14 weeks gestational age in the axial (BPD) plane. In complete agenesis of the corpus callosum, a cavum is not seen. It

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is absent in a complete ACC although it may be seen in cases of partial ACC. If a septum pellucidum cannot be found and there is dilation of the occipital horns, differential diagnostic considerations should include lobar (but not alobar holoprosencephaly with its single ventricle) and agenesis of the corpus callosum. Nonvisualization or an abnormal appearing CSP and/or ventriculomegaly are the most common indications for MRI of the fetal brain. MRI can detect most callosal dysmorphology by 22 weeks gestation. This may include complete or partial ACC and some associated abnormalities such as septo-optic dysplasia, neuromigrational abnormalities and brainstem kinking (pontomesencephalic dysmorphology). Complete brain anatomy evaluation may help note any concern for a syndromic abnormality. Such information helps in parental counselling regarding the fetal/perinatal prognosis. MRI timing should balance the need for earlier diagnosis with the greater ease of anatomical imaging of the brain in later 2nd and 3rd trimesters [3].

Early Diagnosis: Corpus callosum development is not complete until at least 18-20 weeks gestation, A first trimester diagnosis is therefore not feasible.

MRI Diagnosis: MRI can image a normal versus an abnormal corpus callosum after 22 weeks and in many cases between 20-22 weeks [4] (Fig. **1**). Examinations performed after 30 weeks can evaluate the brain's gyral pattern to rule out any associated lissencephaly.

Prenatal Management: Prenatal management should include a search for any associated abnormality, Karyotyping, microarray analysis, counseling by a pediatric neurologist or neurosurgeon, and serial ultrasounds can help note if there is progressive ventriculomegaly.

Prognosis: At least 60% of children with isolated ACC may have mild behavioral problems. Agenesis of the corpus callosum (whether partial or complete) seems to have no bearing on the prognosis. Patients with agenesis of the corpus callosum may have difficulties with language (expressive) and/or social skills. Familial recurrence of ACC depends on its etiology and ranges between 2 to 4% [5 - 9].

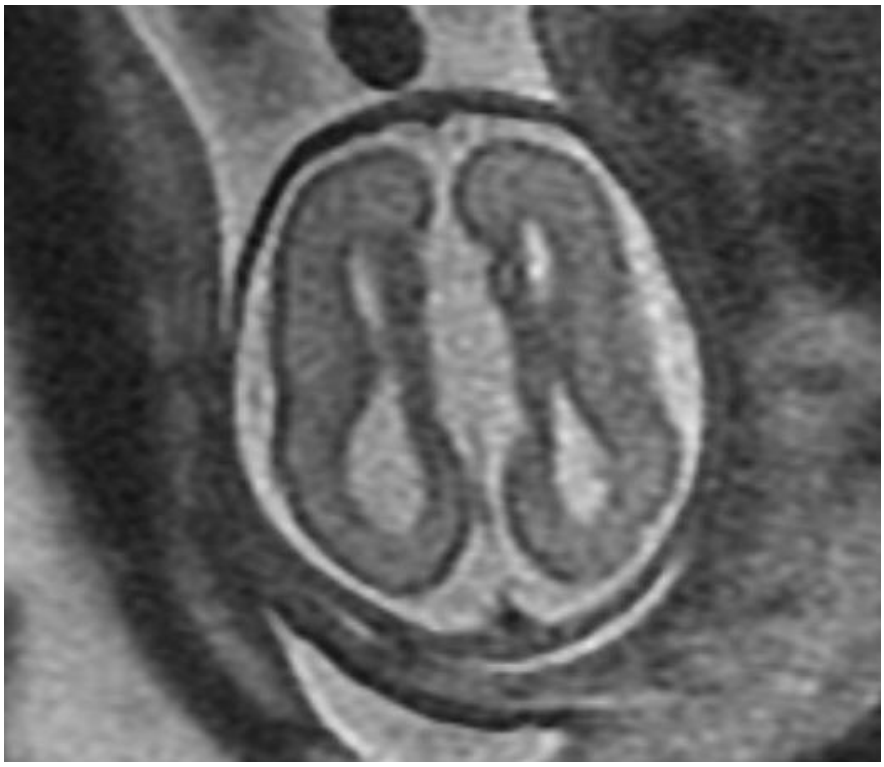

Fig. (1). Agenesis of Corpus Callosum. MRI.

Anencephaly and Acrania

Definition: Anencephaly is an anomaly in which the cerebral hemisphere and skull are absent. Acrania, or exencephaly, is characterized by the absence of the skull, bones, or cranium. Despite this, substantial brain tissue may be present.

Prevalence: Anencephaly is the commonest neural tube defect (NTD) occurring in 1/1000 pregnancies [10]. Anencephaly occurs when there is failed closure of the rostral neuropore. This occurs during the first 28 days following conception [11].

Acrania develops early in the fourth week of gestation. The cranial bones do not develop, and the brain is exposed to amniotic fluid [10].

Major Principles of Diagnosis: Anencephaly is diagnosed when the upper portion of the cranial vault is not visualized. Despite some sources suggesting a normal facial appearance, the orbits without the calvarium look like those of a frog (frog eyes) or Mickey Mouse ears linked to the fetal face (Fig. **2**).

CHAPTER 2

Face and Neck Abnormalities

INTRODUCTION

Fetal face and neck abnormalities can have major psychological impacts on future parents. A 3-D image of a fetal face is the most desirable view of the fetus for the expecting parents. The timely and accurate detection of facial anomalies is very important from a clinical point of view since many of them are associated with chromosomal aberrations and genetic syndromes. The introduction of 3-D ultrasound and fetal MRI led to a marked improvement in the diagnosis of face and neck abnormalities.

Cleft Lip and/or Palate

Definition: Cleft lip with or without a cleft palate is the most common congenital malformation of the face. The upper lip is usually affected; unilateral, bilateral, or midline defects can occur. A separation or notching of the lip on one side of the face with a normal contralateral side is defined as a unilateral cleft lip. In bilateral paramedian clefts, there is a separation of the lip on each side of the face. A complete cleft extends to the nostril and may cause flaring or flattening of that nostril. Clefts are incomplete when the defect does not extend to the nostril. Isolated cleft palate with an intact lip often evades prenatal diagnosis.

Prevalence: The prevalence of cleft lip and/or palate is 1 in 800 live births [1]. Males are more commonly affected than females. About two-thirds of cases involve both the lip and the palate. In cases of unilateral cleft lip and/or palate, the left side of the face is more often affected than the right side.

Major Principles of Diagnosis: Facial clefting is caused by the failure, embryologically, of the frontal processes to fuse with the maxillary swellings. Isolated orofacial clefting is multifactorial, with a 40%-60% concordance in monozygotic twins. The morphologic features of the face are best seen in the coronal or axial plane (Fig. **21**). Surface rendering with three-dimensional sonography or analysis with fetal MRI is helpful in the identification of soft tissue defects. These defects need to be discussed with the parents by a multidisciplinary craniofacial team [2]. A color Doppler may help demonstrate any abnormal flow of amniotic fluid from the mouth, or nares.

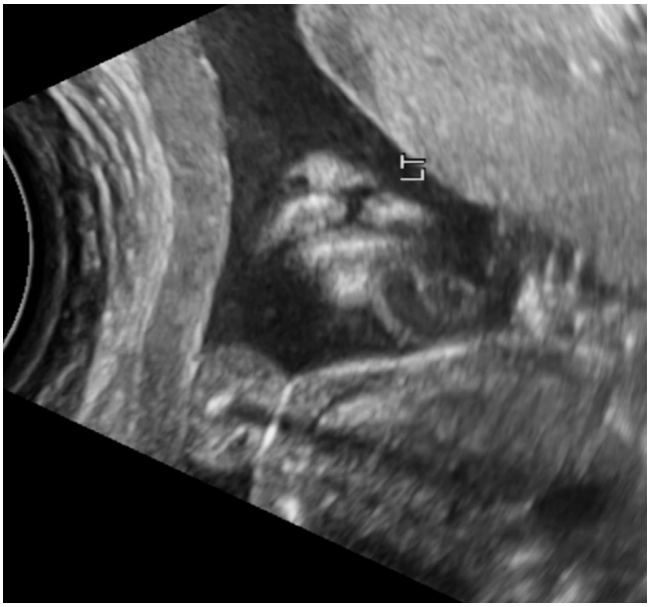

Fig. (21). Facial Clefting. Ultrasound (Coronal plane).

First Trimester Diagnosis: The diagnosis of a facial cleft in the first trimester may be suspected on the standard midsagittal view that is used to measure the nuchal translucency. A maxillary gap of more than 1.5 mm is considered abnormal [3 - 5]. Follow up ultrasound examination is often required to confirm the diagnosis.

Genetic Counseling: Cleft lip and/or palate have been reported as a part of over 400 genetic syndromes, most notably, 22q 11.2 microdeletion (DiGeorge syndrome). However, the vast majority of cases of isolated cleft lip and/or palate are isolated events [6]. Genetic recommendations should include karyotyping (*via* CVS or amniocentesis) or fluorescent in situ hybridization. If the cleft lip and/or palate is not an isolated finding, gene panel testing (genome sequencing) is recommended to detect Van der Woude Stickler or facial digital syndromes among others [7]. Cell-free DNA screening remains an option for the patient who declines invasive testing when an aneuploidy is suspected [2]. Recurrence rates depend on etiology. In cases of isolated sporadic cleft lip and/or palate, recurrence is low.

Prenatal Management and Prognosis: Diagnosis of cleft lip and/or palate is an indication for a detailed sonographic assessment with special attention to the brain (cerebellar vermis and corpus callosum) and cardiac anatomy. A referral to a pediatric maxillofacial surgeon should be provided. Currently, cosmetic results

after surgical repairs of orofacial clefts are excellent. Labor management is not affected by the presence of orofacial clefts [8].

Enlarged Nuchal Translucency

Definition: Nuchal translucency is the term used for the subcutaneous fluid collection behind the fetal neck. The size of the nuchal translucency (NT) increases with gestational age until 12-13 weeks of pregnancy and disappears around 14 weeks of gestation [9]. Only an enlarged nuchal translucency (Fig. **22**) measurement above the 95 percentile for gestational age, is considered an abnormal [9].

Prevalence: 1 in 50 pregnancies [10].

Major Principles of Diagnosis: The Fetal Medicine Foundation recommends that measurements of nuchal translucency thickness be performed according to the following guidelines:

Ultrasound scans are carried out transabdominally using curvilinear transducers. If visualization is difficult the transvaginal scanning technique is used. The image is magnified to fill at least 75% of the ultrasound screen. The maximum thickness of the subcutaneous translucency is measured between the skin and soft tissue overlying the cervical spine.

Genetics and Prenatal Management: Enlarged nuchal translucencies are associated with a 60% detection rate for Down syndrome and a 5% false-positive rate. The enlarged nuchal translucency is associated with other chromosomal abnormalities (trisomy 18 and 13, Turner syndrome, and triploidy) and congenital heart defects. In the ACOG guidelines, an enlarged nuchal translucency is defined as a measurement of 3.0 mm or one that is above the 99th percentile for the determined crown rump length [11]. Fetal echocardiography is recommended for such fetuses [12].

CHAPTER 3

Abnormalities of the Chest

INTRODUCTION

Lung lesions represent a group of fetal anomalies usually not associated with chromosomal abnormalities or genetic syndromes with the exception of pleural effusions and diaphragmatic hernias. They include bronchopulmonary sequestration, congenital pulmonary airway malformation, hydrothorax/pleural effusion, and congenital diaphragmatic hernia, among others. Some lung lesions have features of bronchopulmonary sequestration and congenital pulmonary airway malformation and are called hybrid lesions. Some of the lung lesions (*e.g.*, pleural effusion, diaphragmatic hernia) may benefit from in-utero surgery.

Bronchopulmonary Sequestration

Definition: A bronchopulmonary sequestration is a mass of nonfunctioning bronchopulmonary tissue that is not connected to the tracheobronchial tree or pulmonary arteries. The pulmonary sequestration receives its blood supply from a systemic artery, often the thoracic aorta but also possibly from the abdominal aorta or its branches. Pulmonary sequestration can be divided into two subtypes. Sequestrations may be found within the lung and are called intralobar sequestrations representing 75-85% of the total, with the remaining 15-25% found adjacent to the remainder of the lung but within its own pleura called extralobar sequestrations [1].

Prevalence: 1 per 1000 births. The intralobar variant has equal male to female ratios. The extralobar variant has a male/female ratio of four to one [2].

Major Principles of Diagnosis: A pulmonary sequestration often is seen on prenatal ultrasound as a well-defined triangular echogenic mass in the lower portion of the lung (usually the left lung) or the suprarenal area of the fetal abdomen [3] (Fig. **31**). Gray scale ultrasound may suggest a feeding vessel by noting a tubular echoless structure entering it. Color Doppler may prove this to be the arterial feeder (other than the pulmonary artery) helping confirm the diagnosis and separate the mass from a simulator such as a (type 3) congentical pulmonary airway malformation (CPAM) whose arterial supply is from the pulmonary artery.

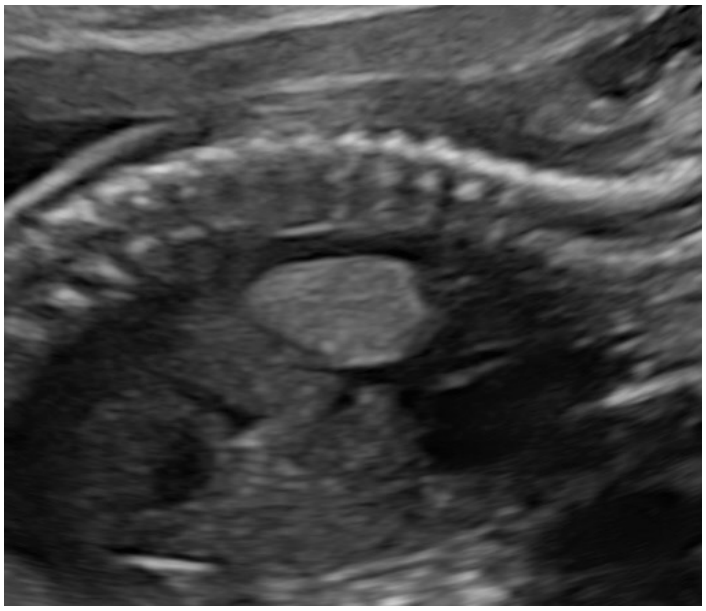

Fig. (31). Bronchopulmonary Sequestration. Ultrasound (Sagittal plane).

Early Diagnosis: Diagnosis as early as 16 weeks of pregnancy has been reported [3]. The antenatal diagnosis is suggested when a usually homogeneously echogenic solid lung mass with an aortic arterial supply adjacent to the diaphragm is detected.

Genetics and Prenatal Management

1. Extralobar sequestration. About 8-15% will have another congenital lung abnormality (*e.g*., congenital lobar emphysema or bronchogenic cyst) [3]. Anomalies associated with bronchopulmonary sequestration include pectus excavatum, pericardial cysts, truncus arteriosus, total anomalous pulmonary venous drainage, dextrocardia, vertebral anomalies or accessory spleen. Up to 50% have some other associated anomaly. Congenital diaphragmatic hernia is the most common.

2. Intralobar sequestrations are more common (85%) and are usually located at the lung bases. 10% have associated anomalies including diaphragmatic hernia, tracheoesophageal fistula, congenital heart defects, and foregut duplications [2]. Intrathoracic lesions can cause a mediastinal shift, cardiac compression, hydrops, and pulmonary hypoplasia.

***In-Utero Intervention*:** Bronchopulmonary sequestrations, particularly smaller ones, may regress in-utero. While some may enlarge in the second trimester, most

remain the same or are somewhat smaller (perhaps proportionately) in the 3rd trimester of pregnancy. Interventions are needed at times with the development of large pleural effusions causing mediastinal shift. Hydropic fetuses with large sequestrations have been treated by ultrasound-guided Nd:YAG laser ablation of the feeding vessels and consequent shrinkage of the lesion, and resolution of hydrops fetalis [4].

Neonatal Management: Children presenting with chronic ailments relating to pulmonary sequestration require surgical resection, (segmentectomy or lobectomy). However, the treatment of pulmonary sequestration in asymptomatic patients is controversial. Occlusion of the feeding vessel to the sequestration may lead to its eventual involution. Current methods used for such arterial embolization include microcoils, alcohol, histoacryl, and gelatin sponge particles [5].

Congenital Diaphragmatic Hernia

Definition: Congenital diaphragmatic hernia occurs when a portion of the diaphragm fails to develop. Without a diaphragm to separate the abdomen from the thorax, the fetal abdominal contents such as the stomach, spleen, small bowel, large bowel, and often liver may herniate into the chest. The space occupied by the herniated viscera within the thorax may cause a mediastinal shift, which results in diminished space for lung development, leading to pulmonary hypoplasia [6].

Prevalence: 1 in 3000 live births [7].

Major Principles of Diagnosis: There are 3 main types of congenital diaphragmatic hernia: the posteriolateral (Bochdalek hernia), the anterior (Morgagni hernia) and the hiatal hernia. At times, a defect of the central tendon with associated herniation into the pericardium may occur. This anomaly results in communication between the pericardial and peritoneal cavities [6]. Deviation of the heart to the right in association with tubular echoless area(s) (stomach and/or small bowel) in the normally homogenous echogenicity of the left chest is usually diagnostic of a left-sided congenital diaphragmatic hernia. In right-sided hernias, the heart is usually pushed to the left by the herniated liver. Polyhydramnios is often present. Direct imaging of the defect is the hallmark of the diagnosis with the presence of the stomach bubble or other abdominal contents in the fetal chest [8] (Figs. **32** and **33**).

CHAPTER 4

Congenital Heart Disease

INTRODUCTION

Congenital heart diseases are the most common fetal abnormalities with a prevalence of 3 to 12 per 1000 pregnancies [1]. Despite this fact, congenital heart disease detection rates remain the lowest among congenital anomalies. Improvements in imaging methods and modalities and specific attention paid to cardiac anomaly analysis have allowed for improved detection of cardiac defects [2, 3]. Screening for cardiac anatomy has become an essential part of any comprehensive ultrasound examinations. Technical advances in high-frequency ultrasound and the use of 3D and 4D techniques have also contributed to an increase in the detection of cardiac diseases in the early stages of pregnancy [4]. Evaluation of situs, cardiac connections, the atrioventricular junction, right-and left sided symmetry and septo-aortic continuity are necessary constituents of a proper fetal cardiac ultrasound examination [5, 6].

Timing of Detection of Congenital Cardiac Malfor mations

Cardiac Defects that can be Detected at 11-13 Weeks of Pregnancy

• Transposition of the great arteries; double outlet right ventricle; hypoplastic left heart.

• Coarctation of the aorta

• Tetralogy of Fallot

• AV Canal or atrioventricular septal defects

• Truncus arteriosus

Cardiac Defects Unlikely to be Detected at 11-13 Weeks of Pregnancy

• Ventricular septal defects

• Ebstein anomaly

• Aortic and pulmonary arterial stenosis

• Cardiac tumors

• Myocardial hypertrophy

• Abnormal pulmonary venous return.

The following views and cardiac structures may be identified between 10 and 15 weeks of pregnancy: four-chamber view, 3-vessel view, crossing of the great arteries, aortic and ductal arches, superior and inferior venae cavae, and at minimum two pulmonary veins [7, 8].

The preferred scanning routes between 10 and 13 weeks of pregnancy, is transvaginal (TV) and transabdominal (TA). Between 12 and 14 weeks gestation, TV & TA ultrasound have similar detection rates. At 15 weeks of pregnancy, and beyond, the transabdominal route is preferred. A cross-sectional plane of the fetal thorax with the fetal spine in the lower part of the screen is optimal for cardiac evaluation. The 4-chamber view, 5-chamber view, the great vessels (aorta and pulmonary artery), and 3-vessel view can be obtained. The two outflow tracts can be visualized by rotating the ultrasound probe clockwise or counterclockwise from the 4-chamber view. Color Doppler is helpful in assessing the integrity of the intraventricular septum. The combination of color Doppler ultrasound and STIC volume analysis allows the identification of most of the fetal cardiac planes in 90% of fetuses, whether the STIC volumes are obtained transabdominally or transvaginally [7].

Ebstein Anomaly

Definition: Ebstein anomaly involves the malformation and malposition of tricuspid valve leaflets. The septal and/or posterior leaflets are displaced inferiorly and tacked down in the right ventricle. The abnormality is sometimes described as due to atrialization of the right ventricle. The degree of displacement and malformation of the leaflets determines to a large degree the severity of the lesion.

Prevalence: 1 in 20,000 live births [9].

Major Principles of Diagnosis: Anomalies of the tricuspid valve can be identified on the standard four-chamber view, and the degree of regurgitation can be estimated by color flow Doppler [10]. The four-chamber view of the heart demonstrates marked dilation of the right atrium with septal and posterior leaflets of the tricuspid valve displaced into the cavity of the right ventricle. The left ventricle appears smaller being compressed by the dilated right (Fig. **36**).

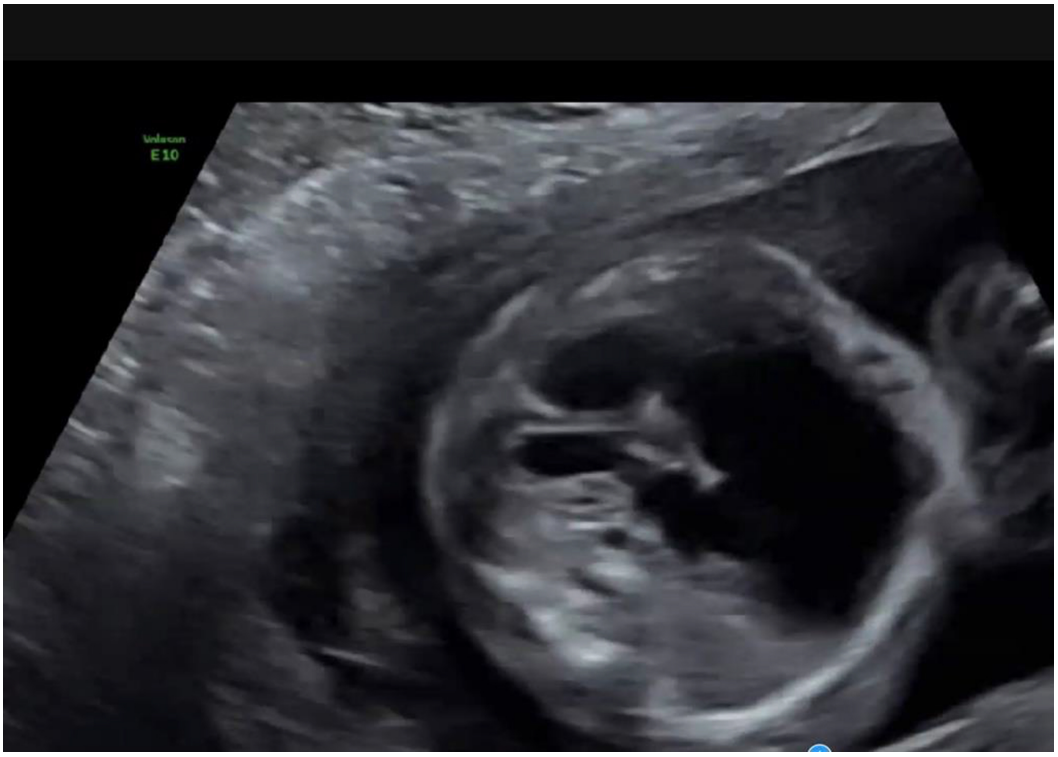

Fig. (36). Ebstein Anomaly. Ultrasound (Axial plane). Image courtesy of P. Argoti MD, University of Tennessee, Department of Obstetrics & Gynecology.

Genetics: Ebstein anomaly is usually not associated with chromosome abnormalities or malformations syndromes [11]. Although the degree of risk for Ebstein anomaly, after lithium exposure is still under debate, accepted estimates vary from 1 to 5% [12]. Prenatal evaluation includes a detailed sonogram, prenatal exposure history, and detailed family history for congenital heart defects and/or arrhythmias. The recurrence risk for siblings with isolated Ebstein anomaly is 1% [13].

Perinatal, Neonatal Management and Prognosis: The risk factors for increased perinatal mortality are a diagnosis at a gestational age of less than 32 weeks, a large TV annulus diameter, and pericardial effusion. More severe disease is likely to be detected by obstetric ultrasound earlier in pregnancy as a result of cardiomegaly or pericardial effusion [14]. Lack of antegrade pulmonary valve flow, retrograde duct flow, and increased right ventricular pressure were found to be associated with adverse outcomes [14]. Weekly monitoring should be undertaken especially in the third trimester of pregnancy. As opposed to other forms of congenital heart disease in which fetuses have relatively stable in-utero

CHAPTER 5

Abnormalities of the Gastrointestinal Tract

INTRODUCTION

Key gastrointestinal anomalies to diagnose include those in which bowel (and other abdominal contents) are seen beyond the confines of the abdomen, such as congenital diaphragmatic hernias (discussed in the chest abnormalities section) with abdominal contents seen in the thorax or gastroschisis and omphalocele in which bowel is seen anterior to the abdominal wall. Other abnormalities to search for include bowel atresias, stenoses and duplications, and echogenic bowel. Physiologic bowel herniation (physiologic exomphalos) that occurs as part of the normal development of bowel rotation makes an early diagnosis of omphalocele a challenging one. Gastrointestinal abnormalities have multiple causes, including chromosomal anomalies, genetic syndromes, congenital infections, and arterial emboli, among others. A frequent manifestation of proximal fetal gastrointestinal abnormalities is polyhydramnios due to limitations in amniotic fluid ingestion. Gastrointestinal abnormalities also include bowel dysrotations (*e.g.*, nonrotation or volvulus) or organ maldevelopment.

Bowel Calcifications/Meconium Peritonitis

Definition: Meconium peritonitis is a sterile chemical peritonitis resulting from spillage of bowel contents into the fetal peritoneal cavity due to bowel perforation. Three forms of meconium peritonitis can be identified on prenatal ultrasound: cystic (meconium pseudocyst), diffuse and fibroadhesive [1, 2].

Prevalence: 3 in 10.000 births [1].

Major Principles of Diagnosis: Prenatal sonographic findings, which support the diagnosis of meconium peritonitis include intra-abdominal calcifications (Fig. **43**), isolated ascites, bowel dilation, and polyhydramnios [3]. Perforations are thought to occur after bowel peristalsis begins at 20 weeks' gestation [4]. Visualization of calcifications at the liver periphery is often evidence of past meconium spillage which is different from considerations with regard to intrahepatic calcifications that may be due to infection (*e.g.*, cytomegalovirus) as well as tumor.

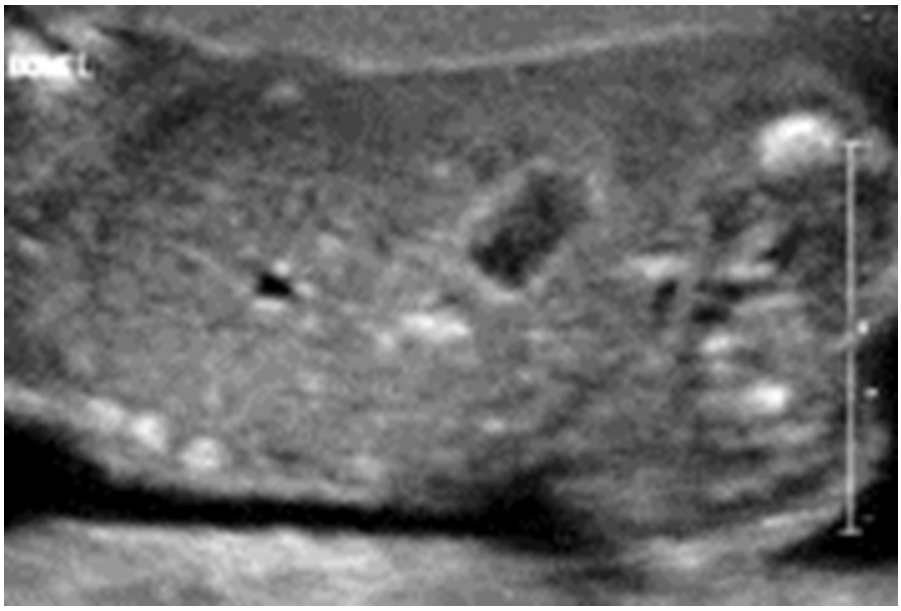

Fig. (43). Bowel Calcifications. Ultrasound (Coronal/Oblique plane).

Genetics and Prenatal Course: Most common bowel pathologies associated with meconium peritonitis are: volvulus, bowel atresia, meconium ileus, intussusception, internal hernia, congenital band and perforation of a Meckel diverticulum [3]. An association of meconium peritonitis with fetal cytomegalovirus infection has been reported [3, 5]. Meconium peritonitis is not associated with an increased incidence of chromosomal anomalies.

Prenatal Management: If the diagnosis is made prior to fetal viability, the possibility of cystic fibrosis should be ruled out. Serial ultrasound examinations are indicated to assess the degree of ascites. Cesarean section had not been shown to improve neonatal outcomes. Fetuses with meconium peritonitis should be delivered in tertiary care centers where pediatric surgery services are available.

Postnatal Management: The postnatal surgical approach is dependent on patients' clinical presentation and the cause of the bowel perforation [5]. Most newborns diagnosed with meconium peritonitis will merely have some calcification peripheral to the liver as evidence of a prior perforation and subsequent healing/closure. They do not need a surgical procedure [4, 5].

Duodenal Atresia and Stenosis

Definition: Duodenal atresia is the most common type of small bowel atresia. Duodenal atresia is three times more common than duodenal stenosis [6].

Prevalence: One in 10.000 live birth [7].

Major Principles of Diagnosis: Duodenal atresia and/or stenosis usually appear on prenatal ultrasound as the "double bubble" sign. The first bubble represents the stomach; the second – a dilated proximal duodenum. One should be aware of a simulator, a transitory double bubble due to intestinal peristalsis [8]. Ultrasound reevaluation in 2-5 minutes can confirm the diagnosis of obstruction by noting the continued presence of a double bubble (Fig. **44**). Real-time evaluation of the fetal bowel can denote the quality of the peristalsis. The diagnosis of duodenal atresia is aided by noting fluid within a blind-ending structure just distal to the stomach, the obstructed proximal duodenum. Stenosis will not show a continuously seen blind ending area, particularly when assessed over the entire examination. Noting more than 2 bubbles or circular radiolucencies within the abdomen suggests a more distal bowel obstruction *e.g.*, jejunal atresia.

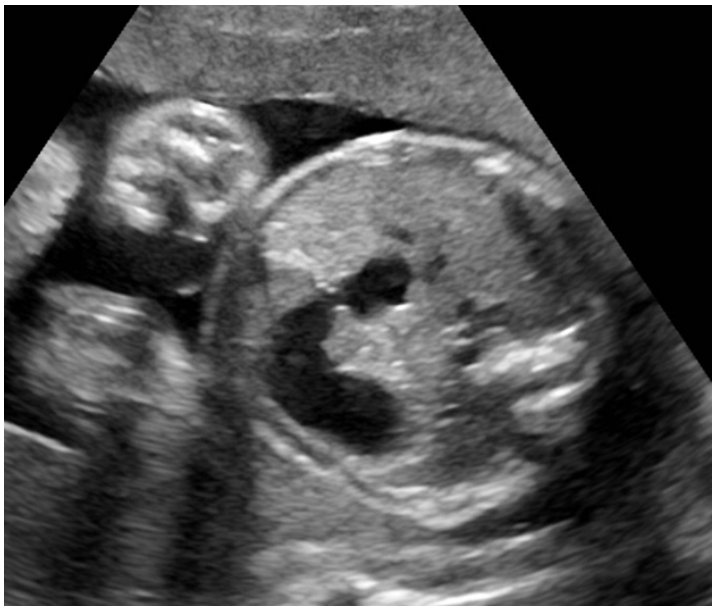

Fig. (44). Double Bubble Sign in Duodenal Atresia. Ultrasound (Axial plane).

Early Presentation: First trimester diagnoses have been reported [8, 9].

Genetic Counseling, Prenatal Management, and Prognosis: Duodenal atresia or stenosis may be associated with other structural and/or chromosomal anomalies in 50% of cases with the most common association being trisomy 21 [10]. Therefore, amniocentesis and fetal echocardiography are recommended. After

CHAPTER 6

Urogenital Abnormalities

INTRODUCTION

Anomalies of the kidney and urinary tract account for a third of all fetal abnormalities. Table **2** shows a classification of urinary tract disorders proposed by Woolf and Winyard in Pediatric and Developmental Pathology, 2002.

Table 3. Disorders of the Urinary Tract.

Malformation	Characteristic(s)
Upper Renal Tract	
Agenesis	The kidney is absent (one or both)
Dysplasia	The kidney contains undifferentiated tissue and may be very small (aplasia) or contain cysts (cystic dysplasia)
Hypoplasia	The kidney contains significantly fewer nephrons
Duplication Anomaly	The kidney is separated into an upper moiety often obstructed and a lower moiety often having vesicoureteral reflux.
Horseshoe kidney	Both the kidneys are fused to each other
Lower Renal Tract	
Agenesis	Ureter, bladder, and/or kidney are missing
Hydronephrosis	The renal pelvis is enlarged
Duplication	A partial or complete double ureter may occur with a duplicated kidney; insertion into the bladder of the upper pole moiety is often ectopic. The moiety may be obstructed by a usually intravesical ureterocele
Vesico-ureteric reflux	Urine flows retrogradely from the bladder into the ureter and collecting system of the kidney
Posterior urethral valves	Outflow to the urinary bladder is obstructed

Autosomal Recessive Polycystic Kidney Disease

Definition: Autosomal recessive polycystic kidney disease formerly known as infantile polycystic kidney disease is characterized by enlarged highly echogenic kidneys. There may be associated cysts in the liver, seminal vesicles and pancreas. Possible associated abnormalities may include extrarenal abnormalities including

intracranial aneurysms, dilatation of aortic root, aortic dissection, mitral valve prolapse, and abdominal wall hernias [1].

Prevalence: 1 in 16,000-55,000 live births [1].

Major Principles of Diagnosis: Autosomal recessive polycystic kidney disease can be classified based on the time of onset. There are fetal, neonatal, infantile, and juvenile types. The optimal gestational age to evaluate and diagnose this entity is at or after 18 to 21 weeks of pregnancy [2, 3]. From 16 weeks of pregnancy and onward, both affected kidneys appear echogenic and enlarged. When cysts are seen they are very small. The affected kidney typically is echogenic without evident cysts since the cysts are made up of multiple 1-3mm dilated tubules that are too small to be differentiated by the ultrasound beam into individual cysts (Fig. **48**).

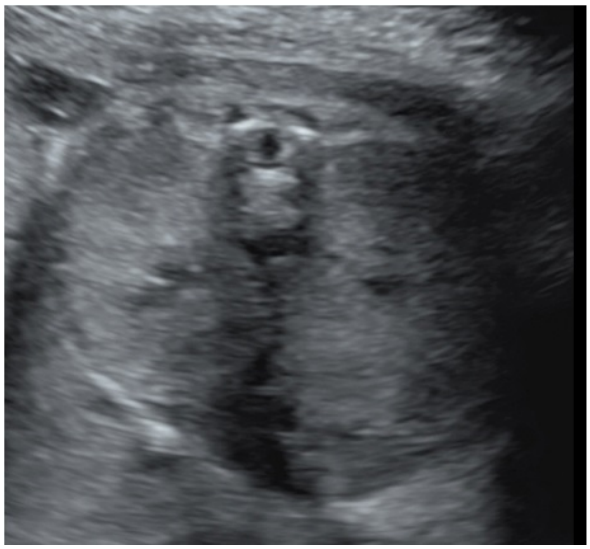

Fig. (48). Autosomal Recessive Polycystic Kidney Disease. Ultrasound (Axial plane).

Genetics and Prenatal Management: Oligohydramnios may develop gradually. When seen, it is associated with a poor prognosis. There is no fetal therapy available. Termination of pregnancy is offered for severe oligohydramnios or anhydramnios because pulmonary hypoplasia is likely. Genetic counseling is essential. The recurrence risk of autosomal dominant polycystic kidney disease is 25%. Severely affected fetuses are born with Potter's face, and some will develop respiratory insufficiency, but many survive the neonatal period. Of all neonatal survivors, approximately 40% have severe hepatic and renal disease [4 - 8].

Multicystic Dysplastic Kidney

Definition: Multicystic dysplastic kidney is a condition where one or both kidneys contain cysts of varying sizes as well as varying amounts of intervening and dysplastic fibrous/connective tissue.

Prevalence: Unilateral multicystic dysplastic kidney (MDK) has a prevalence of 1 in 3,000-5,000 live births compared to 1 in 10,000 for bilateral MDK. It is one of the most common causes of abdominal mass in the neonatal period. It occurs more frequently in male fetuses. It more typically affects the left kidney. Bilateral involvement may be more typical in females [9].

Major Principles of Diagnosis: Antenatal ultrasonography shows one or both kidneys containing multiple cysts of varying sizes seen throughout the kidney substance (Fig. **49**). The cysts are distributed randomly. Unlike severe hydronephrosis, the largest "cyst" is not the central cyst which in the case of hydronephrosis is the renal pelvis surrounded by dilated calyces. The dilated calyces of hydronephrosis are similar in size to one another. The size of an MDK may be normal, larger than normal, or smaller than normal. MDK may, at times, not retain their reniform shape. Smaller dysplastic kidneys are difficult to detect especially in the presence of oligohydramnios. Oligohydramnios or anhydramnios is only a problem in cases of bilateral MDKs which are not compatible with life, or in cases, where the MDK has an associated contralateral obstructing renal abnormality. The vast majority of MDKs are unilateral. When there is a unilateral MDK, a normal contralateral kidney, will undergo compensatory hypertrophy even in fetal life.

Early Diagnosis: Typically, multicystic dysplastic kidneys can be seen by 15 weeks of pregnancy. However, multicystic dysplastic kidneys have been detected as early as 12 weeks of pregnancy. It is usually imaged as a normal sized to enlarged kidney consisting of multiple cysts (*e.g.*, 2-4) of varying sizes [10 - 12].

Genetics and Prenatal Management: Multicystic dysplastic kidney can be associated with aneuploidy (*e.g.*, trisomy 13) or various genetic syndromes (Meckel- Gruber, Roberts, brachial-oto-renal, *etc*.), which can have either an autosomal dominant or autosomal recessive inheritance pattern [9]. No specific fetal intervention is required in cases of isolated unilateral multicystic dysplastic kidneys [11].

Prognosis: The prognosis for the fetus depends on whether there is unilateral or bilateral dysplasia. Bilateral MDK is associated with a grim prognosis, with fetuses dying from pulmonary hypoplasia after birth. A patient with a unilateral MDK has an excellent prognosis. In many instances, the multicystic dysplastic

CHAPTER 7

Abnormalities of Fetal Skeleton

INTRODUCTION

There are more than 450 skeletal dysplasias, a heterogeneous group of disorders characterized by differences in the size, shape, and mineralization of the bones that result in short stature. Diagnoses are made based on physical appearance, radiological assessment, family history, and, increasingly, genetic testing. It is estimated that 30-45 per 100,000 newborns have skeletal dysplasia [1].

The European Society of Pediatric Radiologists classified skeletal dysplasias on the basis of etiology into the following categories:

1. Idiopathic osteolysis (bone resorption)

2. Dysostoses-bone(s) malformations

3. Osteochondral dysplasias-abnormalities of cartilage

4. Metabolic skeletal disorders

5. Genetic skeletal abnormalities

6. Skeletal deformations caused by a hostile uterine environment *e.g.*, oligohydramnios, presence of amniotic bands, intrauterine fibromas.

Prenatal diagnosis of skeletal dysplasias can be very challenging since these anomalies are rare and sporadic and diagnostic expertise is lacking in many institutions. From a clinical point of view, skeletal dysplasias that are detected early in pregnancy are most severe and often incompatible with life.

Increased nuchal translucency at 10-14 weeks of gestation can be an early sign of severe skeletal dysplasia. If nuchal translucency when accompanied by the findings of shortened or bowed limbs, abnormal chest or ribs, and/or an under undermineralized bones, is highly suggestive of skeletal dysplasia [2]. Most of the severe skeletal dysplasias can be detected at routine obstetrical ultrasound examinations performed at 18-20 weeks of gestation. Next generation sequencing has allowed rapid genetic testing for a number of genes simultaneously. This has revolutionized diagnostic testing for skeletal dysplasia [3]. Prenatal next genera-

tion skeletal panel gene sequencing or whole exome/genome testing should be used to increase the diagnostic yield in cases of suspected skeletal dysplasia. Most skeletal dysplasias are the consequence of a de novo mutation and thereafter have the potential for transmission to the next generation. Each type of skeletal dysplasia is associated with different musculoskeletal abnormalities (*e.g.*, degenerative diseases of the joints and the spine, kyphoscoliosis, spinal stenosis,). Determination of lethality is of obvious importance in the management of the pregnancy with suspected skeletal dysplasia [2, 3]. Key predictors of lethality at the 18-20 weeks of gestation ultrasound exam are:

• Chest to abdomen ratio <0.6

• Femur length (FL) to abdominal circumference (AC) ratio <0.16

• Micromelia

• Hydrops

• Severely decreased mineralization of the axial skeleton

The prenatal diagnosis of skeletal dysplasia with 2D ultrasound, despite the best efforts, of clinicians has sensitivity rates of only 40-60% [4]. FL is a commonly used and an easy to perform biometric measurement in the second-trimester ultrasonography. A short FL is defined as a length that is in the $<5^{th}$ percentile, 2 SD or greater below expected measurements for gestational age. Most fetuses with an FL that is 2 to 4 standard deviations below the mean are growth restricted but skeletal dysplasias are unlikely. However, if the FL is 4 standard deviations or more below the mean for gestational age the fetus will usually have some form of skeletal dysplasia. This fact does not necessarily mean that skeletal dysplasia can be excluded if the FL is within the normal range. A fetus with a skeletal dysplasia can have an FL within the normal range in-utero or until the third trimester. Even achondroplasia (the most common skeletal dysplasia) characterized by rhizomelia, may show a short femur only in the third trimester [5]. Additional imaging techniques such as 3D fetal ultrasonography, fetal MRI, and fetal CT may be useful in detecting skeletal dysplasia. However, the diagnosis of a specific skeletal dysplasia remains difficult except for achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta, which have unique imaging characteristics. Many of the skeletal dysplasias have very diverse findings and their phenotypes overlap each other [2]. From a practical standpoint, skeletal dysplasias can be divided into nonlethal and lethal types. In the case of nonlethal skeletal dysplasias (heterozygous achondroplasia, osteogenesis imperfecta type I, *etc*.), affected infants typically survive. In cases of lethal skeletal dysplasias, (*e.g*., thanatophoric

dysplasia, osteogenesis imperfecta type 2, short rib-polydactyly syndrome), newborns often die of respiratory failure or internal hemorrhages.

Achondroplasia

Definition: Achondroplasia is the most common nonlethal skeletal dysplasia. Achondroplasia is an osteochondrodysplasia with abnormalities of the tubular bones and/or axial skeleton.

***Prevalence*:** 0.24 to 5/10,000 births worldwide. The male to female distribution is equal [6].

Major Principles of Diagnosis: The bone shortening of achondroplasia may not become apparent until well after 24 weeks of gestation. The classical ultrasound images show short limbs (below the 5th percentile), a relatively small chest, a large head, and a depressed nasal bridge. The long bones have a rhizomelic (proximal bone shortening) appearance (Figs. **57 a** and **b**). Further evaluation should include measuring the length of the other long bones, evaluating their shape and mineralization, and measuring abdominal circumference (AC) and head circumference (HC) to calculate their ratio in relation to the femur.

Early Diagnosis: Widening of the proximal diaphysis-metaphysis angle of the femur has been suggested as a marker for fetal achondroplasia that can be noted before a short femur is apparent [7].

Genetic Counseling and Prognosis: The achondroplasia gene, (a fibroblast growth factor receptor 3 mutation) is found on the short arm of chromosome 4 [8]. In more than 98% of cases, this is a point mutation or single- base substitution [8]. Approximately 90% of cases result from a sporadic mutation and are, therefore, unlikely to recur. In cases in which both parents have achondroplasia, there is a one in four chance that the fetus will be homozygous for achondroplasia and therefore have the lethal form of achondroplasia, a 50% chance of being heterozygous and surviving with achondroplasia, and a 25% chance that the fetus will be normal [9].

CHAPTER 8

Hydrops Fetalis and Fetal Alloimmune Thrombocytopenia

INTRODUCTION

Hydrops fetalis is diagnosed when a collection of fluid is detected in two or more fetal compartments. Hydrops fetalis by itself is a symptom, which may be caused by multiple diseases, *i.e*., fetal anemia, aneuploidy, heart failure, metabolic diseases (lysosomal storage disease), fetal infections, *etc*. Hydrops fetalis with polyhydramnios may present a significant risk for the pregnant woman, causing severe preeclampsia (maternal mirror syndrome).

Definition: Hydrops fetalis is defined as the accumulation of fluid in two or more fetal compartments (chest, abdomen, *etc*.). It is a finding that may be seen in many fetal abnormalities [1].

Prevalence: One in 1700 pregnancies [2].

Major Principles of Diagnosis: The presence of fluid in more than one fetal cavity is characteristic of hydrops. Skin edema, cardiomegaly, and polyhydramnios may or may not be present (Fig. **67**).

Prenatal Management and Genetics: Hydrops fetalis may be seen in all trimesters of pregnancy.

First Trimester Diagnosis

In the first trimester, hydrops fetalis can appear on ultrasound as an extension of massive nuchal translucency (Fig. **68**). The fluid collection can extend down the fetal soft tissues along the spine. There is prominent skin edema. The leading causes of 1st trimester hydrops fetalis are chromosomal abnormalities (Turner syndrome, trisomy 21). Karyotyping is strongly recommended. The prognosis is usually poor. However, cases of spontaneous resolution have been reported [3].

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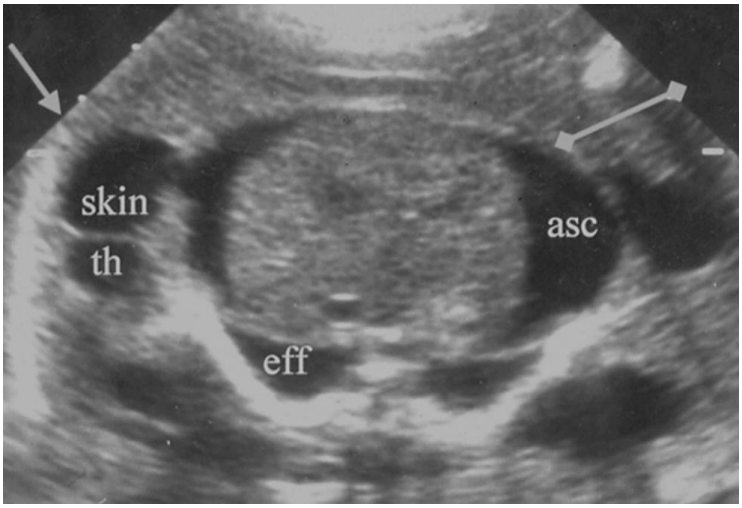

Fig. (67). Fetal Hydrops. Ultrasound (Axial plane) Skin th = skin thickening, eff = pleural effusion, asc = ascites.

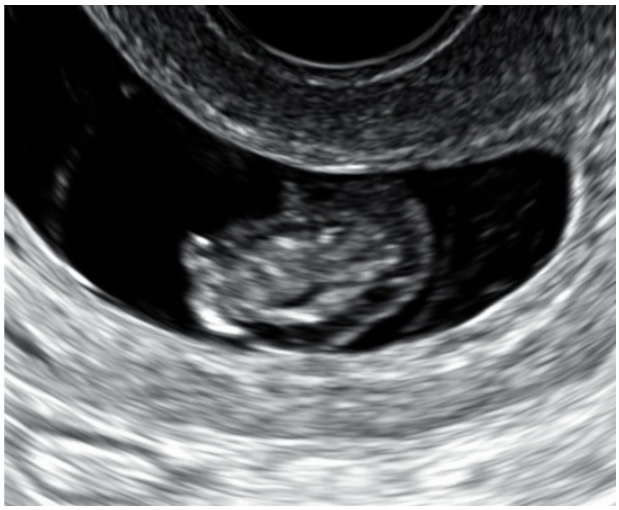

Fig. (68). Fetal Hydrops First Trimester. Ultrasound (Sagittal plane).

Hydrops Fetalis

In the second trimester, hydrops fetalis can be divided into two groups:

a. Immune hydrops fetalis
b. Non-immune hydrops fetalis
   A. Immune hydrops fetalis has almost been eradicated in industrialized countries. Cases of immune hydrops may still occur as a reaction to other antigens (*e.g.*, Kell). Analysis of maternal serum for antibodies is part of

the prenatal workup.

B. Non-immune hydrops fetalis has several key causes. These include fetal infections, hematologic causes and nonhematologic causes.

Fetal Infections

- Parvovirus B19 infections [4 - 6].
- Other fetal infectious agents, which may infrequently cause hydrops fetalis, include: cytomegalovirus, syphilis, toxoplasmosis, herpes simplex virus, and Zika virus [7, 8].

Hematologic Causes of Hydrops Fetalis

Fetal anemia due to fetal (intracranial or subdural) or feto-maternal hemorrhage can result in hydrops. The Kleihauer-Betke test will identify the presence of fetal erythrocytes in many (but not all) cases of fetal-maternal bleeding. Imaging investigation starts with the measurement of the middle cerebral artery peak systolic velocity [2, 3].

- Homozygous alpha-thalassemia usually results in fetal loss (anemia and non-immune fetal hydrops) in the third trimester.
- Congenital anemias:
- Diamond – Blackfan syndrome consists of congenital anemia, bifid or duplicated thumbs, hypoplasia of the radius, as well as facial genitourinary and cardiac abnormalities [9 - 11].

Nonhematologic Thoracic Causes of Hydrops Fetalis

a. Congenital pulmonary airway malformation and bronchopulmonary sequestration.
   - A congenital pulmonary airway malformation may spontaneously regress, possibly due to outgrowing its blood supply [12, 13].
   - Bronchopulmonary sequestrations can lead to the development of pleural effusions, non-immune fetal hydrops, and perinatal death. Treatment with thoracentesis, thoracoamniotic shunts, intraperitoneal injection of digoxin and/or laser coagulation have led to survival in some cases. Many such cases, however, may require repeat procedures due to reaccumulation of the pleural effusion [2].

b. Cardiac causes of hydrops fetalis.

Cardiac tumors can be the cause of hydrops fetalis. The most common causative cardiac tumors are rhabdomyomas, (60%) teratomas, (25%), and fibromas (12%) [14].

CHAPTER 9

Fetal Tumors

INTRODUCTION

Like adults, fetuses may develop tumors in multiple sites; but unlike adults, these tumors are rarely malignant. The most common sites of fetal tumors are the heart (*e.g.*, rhabdomyomas), head, neck, and base of the spine (*e.g.*, teratomas). The placenta may also develop tumors (*e.g.*, chorioangiomas). Some fetal tumors are associated with genetic syndromes, *e.g.*, Wilms tumor and hepatoblastoma may be part of Beckwith-Wiedemann syndrome. On very rare occasions, maternal cancers (*e.g.*, malignant melanoma, leukemia, and breast cancer) can spread to the fetus and/or placenta.

Fetal Cardiac Tumors

Definition: Neoplasms within the heart. This includes rhabdomyomas, which are the most common, followed by teratomas, fibromas, hemangiomas and myxomas [1].

Prevalence: 25 per 10,000 pregnancies [2].

Major Principles of Diagnosis: Ultrasound examination reveals an echogenic intracardiac spherical or oval mass (Fig. **69**). The important point for analysis is the site of involvement, number of tumors, and presence or absence of ventricular outflow tract obstruction. This information can be best detected from the apical four-chamber view [3].

Prenatal Management: Cardiac tumors can be divided into benign tumors (rhabdomyomas, teratomas fibromas, hemangiomas, and myxomas) and malignant tumors (rhabdomyosarcomas and fibrosarcomas). Fibromas are the second most common tumors. They are often found in the left ventricular or septal myocardium. They do not spontaneously regress like cardiac rhabdomyomas. Affected fetuses may present with arrhythmias [1]. Fetal pericardial teratomas are rare. Fetuses with pericardial teratomas may develop pericardial effusions. Fetal cardiac hemangiomas can also cause arrhythmia and hydrops fetalis.

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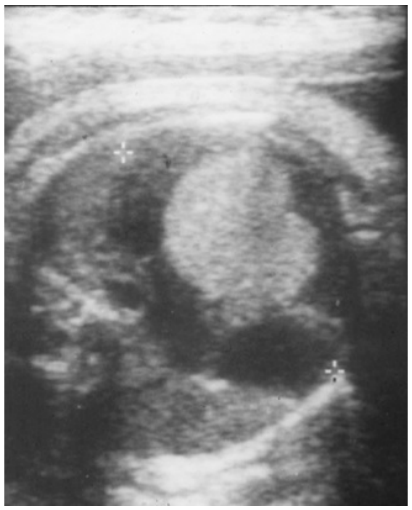

Fig. (69). Cardiac Rhabdomyoma. Ultrasound (Axial plane).

Prognosis: The outcome for affected fetuses depends not only on the nature of the tumor, but also on its location, size, number, and complications (arrhythmias, hydrops fetalis, *etc*.). In-utero surgery for fetal tumor resection remains an option for immature fetuses with hydrops fetalis [4].

Neonatal Management: Most cardiac tumors regress spontaneously [5]. Surgery is indicated when the tumor obstructs cardiac inflow or outflow causing hemodynamic compromise [5]. Neurological assessment for seizures and development delay is recommended because of the association of cardiac tumors, specifically rhabdomyoma, with tuberous sclerosis [6, 8].

Nasopharyngeal Teratoma

Definition: A teratoma that arises from the oral cavity and/or the pharynx.

Prevalence: 0.3 per 10.000 live births [9].

Major Principles of Diagnosis: Nasopharyngeal teratoma appears as a complex heterogeneous mass arising from the fetal mouth and/or nose (Fig. **70**). Its mass may cause hyperextension of the head [10].

Genetics and Prenatal Management: Associated anomalies are seen in approximately 6% of these cases, including facial clefts, bronchial cysts, hypertelorism and congenital heart defects. Nasopharyngeal teratomas are often associated with polyhydramnios, nonimmune fetal hydrops, and exophthalmos. These tumors are rarely malignant but can be fatal due to the local mass effect and

respiratory compromise [11 - 14]. In cases where the lesions are diagnosed early in pregnancy, parents should be informed of the guarded prognosis. A pediatric surgeon and neonatologist should be present at the time of delivery to provide immediate resuscitation, endotracheal intubation, and, if an airway cannot be secured, a tracheostomy.

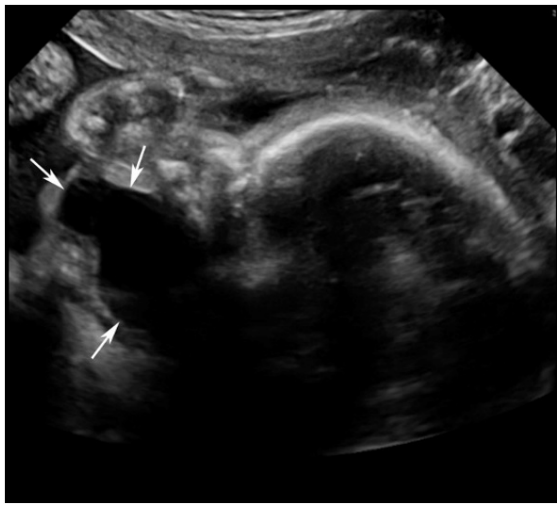

Fig. (70). Ranula, Fetal Mouth. Ultrasound (Sagittal plane).

Prognosis: Although the majority of these tumors are benign in nature, fetal and neonatal death is very common due to the local mass effect, which produces life-threatening dysfunction or cessation of function (*e.g.*, respiratory compromise from a nasopharyngeal or cervicothyroidal lesion). Recurrence risk is unknown [15].

Sacrococcygeal Teratoma

Definition: Congenital germ cell tumor derived from ectoderm, mesoderm, and endoderm. This is located at the base of the spine.

Prevalence: 1 in 40,000. There is a 3:1 female preponderance [16].

Major Principles of Diagnosis: Sacrococcygeal teratomas (SCT) are mixed (solid and cystic) or predominantly solid or predominantly cystic masses originating from the base of the fetal spine (Figs. **71**, **72** and **73**). Sacrococcygeal teratomas may be classified as benign (mature) and/or malignant or immature. Most are benign. The tumor may be highly vascular, usually related to its solid components or less vascular, usually related to its predominantly cystic components [17]. Staging (Altman staging system) is based on the amount of intrapelvic (presacral)

CHAPTER 10

Multifetal Pregnancy

INTRODUCTION

The rate of twin deliveries has risen from 18.9 in 1980 to 33.3 per 1,000 in 2009 [1]. The rate of triplet and higher-order gestations increased to 153.4 per 100,000 births by 2009 [2]. The increased incidence of multifetal gestations has been attributed to 1) an older maternal age at conception and 2) the increased use of assisted reproductive technology [3].

Multifetal gestations are associated with an increased risk of fetal and infant morbidity and mortality. There is a fivefold increased risk for stillbirth and a sevenfold increased risk for neonatal death [4]. Fetal risk is largely dependent on chorionicity. The chorionicity of a multifetal pregnancy should be established as early as possible. Before 10 weeks' gestation, several sonographic signs determine chorionicity: (1) the number of gestational sacs; (2) the number of amniotic sacs; and (3) the number of yolk sacs [5].

Number of Gestational Sacs

Each gestational sac forms its own placenta and chorion. The presence of two gestational sacs implies a dichorionic pregnancy.

Number of Amniotic Sacs Within the Chorionic Cavity

When diamniotic twins are identified before 10 weeks' gestation, separate and distinct amnions may be visible on ultrasound.

Number of Yolk Sacs

When two yolk sacs are seen, the pregnancy is diamniotic. A single yolk sac indicates monoamniotic twins.

After 10 weeks of pregnancy, these sonographic signs are no longer present. Beyond 10 weeks, a new set of sonographic findings helps determine amnionicity/chorionicity. These findings are (1) placental number; (2) chorionic peak sign; and (3) characteristics of the intertwin or multiple gestation membrane.

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Presence or Absence of the Chorionic Peak (Twin Peak or Lambda Sign)

The presence of a twin peak sign identifies dichorionicity (Fig. **75**). Monochorionicity can be determined by the absence of a twin peak sign [6].

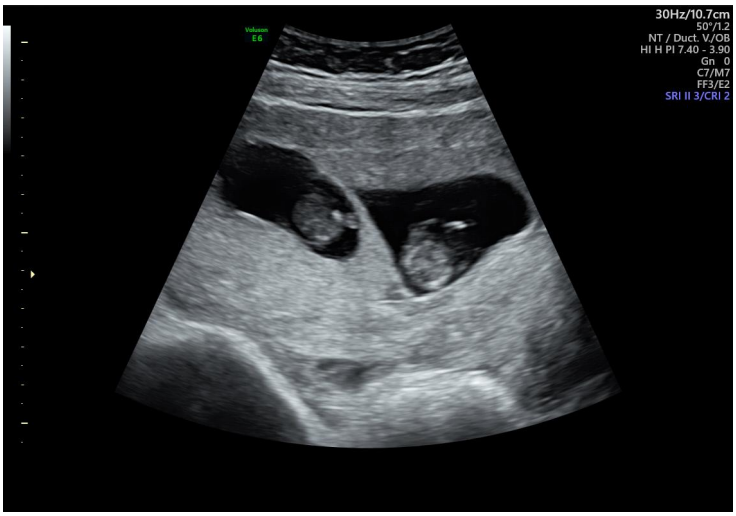

Fig. (75). Twin Peak or Lambda Sign. Ultrasound (Transverse plane).

Intertwin Membrane

The membrane of a dichorionic diamniotic pregnancy is thicker than that of a monochorionic diamniotic pregnancy. The dichorionic membrane consists of 2 layers of amnion and 2 layers of the chorion. Membrane thickness of more than 2 mm identifies dichorionicity [7].

When an intertwin membrane is not seen, the differential considerations include monoamniotic twinning, a twin with oligohydramnios (stuck twin), or a diamniotic twin pregnancy in which the membrane is present but not visualized [5].

Congenital Malformations

Congenital anomalies are twice as common in a twin gestation as compared to a singleton pregnancy [8]. The most common structural abnormalities are neural tube and brain defects, facial clefts, cardiac and gastrointestinal abnormalities as well as anterior abdominal wall defects.

There are 3 types of congenital anomalies unique to twin pregnancies [8].

1. Midline defects as a consequence of the twinning process.

2. Malformations resulting from vascular events as a consequence of placental anastomoses.
3. Deformities from intrauterine crowding: *e.g*., foot deformities, hip dislocation, and skull asymmetry

Prenatal Screening of Women with Multifetal Gestations

All women with multifetal gestations are candidates for routine aneuploidy screening [4].

Screening For Preterm Birth

Preterm birth is a major cause of mortality and morbidity in twins. Sonographic assessment of the cervical length can identify twins at risk for preterm delivery. Cervical length decreases with increasing gestational age. Mothers who deliver preterm have cervical shortening rates greater than those who do not [5].

Discordant Fetal Growth

Discordant fetal growth is defined as a 20% difference in estimated fetal weight between the larger and smaller fetus of a set of twins. This growth discordance ratio is calculated by determining the difference in the estimated fetal weight between the two fetuses, divided by the weight of the larger fetus. Another parameter of growth discordance includes abdominal circumference measurements with differences of >20mm. Multifetal gestations with discordant growth and pregnancies with one growth-restricted fetus have a 7.7-fold increase in risk for major neonatal morbidity. Growth-restricted twins have higher perinatal mortality rates compared with age-matched singletons [9 - 11].

Fetal Demise

In the first trimester, a number of women undergo a spontaneous reduction of one or more fetuses, referred to as the “vanishing twin.” This reduction increases with the number of fetuses: 36% when there are twins, 53% for triplets, and 65% for quadruplets [12]. Chorionicity influences the rate of loss and predicts outcomes in the survivor. Monochorionic diamniotic twins have a greater risk of stillbirth compared with dichorionic-diamniotic twins [13, 14]. The risk of neurological abnormality in the surviving twin is greater in monochorionic (18%) versus dichorionic gestations (1%). Although the death of a co-twin in a monochorionic pregnancy in the second trimester or early third trimester is associated with significant morbidity and mortality for the remaining fetus, immediate delivery of the co-twin has not demonstrated to be beneficial [15].

CHAPTER 11

Congenital Infections

INTRODUCTION

Infections during pregnancy carry a risk for intrauterine transmission, which may result in fetal disease. Primary infections are more damaging than secondary infections. The effect on the fetus depends on the gestational age at which the infection occurs. In general, infections in the first trimester are more likely to cause major malformations compared with infections that occur later in pregnancy.

Cytomegalovirus (CMV) Infection

Definition: CMV is caused by a DNA herpes virus transmitted *via* infected urine, blood, and saliva. The mean incubation period is 40 days (range: 28-60). Viremia occurs within 2-3 weeks after primary infection.

Prevalence: 0.7%-4% for primary CMV, 13.5% for secondary infection [1]. Cytomegalovirus is the most common cause of congenital infection, occurring in 0.2-2.2% of all neonates [2].

Major Principles of Diagnosis: Sonographic signs suggestive of CMV infection include: ventriculomegaly, microcephaly, brain parenchyma calcifications, intracranial hemorrhage, periventricular cysts, cerebellar hypoplasia, liver calcifications, echogenic bowel, fetal growth restriction, pericardial effusion, ascites, and/or fetal hydrops [3, 4]. Transmission rates for primary infection are 30% in the first trimester, 34-38% in the second trimester, and 40-72% in the third trimester. The most serious fetal sequelae occur during the first trimester of pregnancy [5, 6]. CMV-specific IgG testing should be performed with IgM along with IgG avidity testing for seropositive women. A low avidity index (< 30%) is suggestive of recent primary infection (i.e., within the past 3 months), while a high avidity index (> 60%) is suggestive of prior (i.e., greater than 3 months) or secondary infection [7].

Neonatal Outcome and Prognosis: Clinical findings of a CMV-infected fetus at birth include: small for gestational age, microcephaly, jaundice, petechiae, ‘blueberry muffin’ rash, and hepatosplenomegaly [7]. The main sonographic

prognostic indicator for symptomatic fetal CMV infection is cerebral abnormality. If an ultrasound examination of the fetal brain is normal, then a normal early neuropsychological outcome is likely [8]. When both ultrasound and MRI of the fetal brain are normal, the neonatal outcome is good, and the same may be said for a normal brain ultrasound examination with only subtle findings on MRI [9]. Fetuses with severe cerebral ultrasound abnormality (e.g., microcephaly, ventriculomegaly, white-matter cavitations, intracerebral hemorrhage, delayed cortical development, *etc*.) associated with thrombocytopenia carry a poor prognosis.

Treatment: Currently, there is no therapy for CMV infection. Valacyclovir should be considered only as a part of a clinical trial.

Toxoplasmosis

Definition: Toxoplasmosis is caused by the intracellular parasite Toxoplasma gondii. Human infection is acquired by consumption of cysts in undercooked meat, contact with oocysts from the feces of infected cats, or contact with infected materials in the soil [10].

Prevalence: 2-5 per 1,000 [11].

Major Principles of Diagnosis: Sonographically evident abnormalities suggestive of congenital toxoplasmosis infection include: ventriculomegaly, intracranial calcification, microcephaly, ascites, hepatosplenomegaly, and intrauterine growth restriction. Polymerase chain reaction of amniotic fluid is the preferred diagnostic test. Amniocentesis should be performed after 18 weeks of gestation to lessen the chance of a false-negative result [12]. The combination of negative IgM and negative IgG test indicates either the absence of infection or an acute infection that developed without enough time for seroconversion. The combination of negative IgM and positive IgG indicates remote infection and no risk of fetal transmission. The combination of positive IgM and positive IgG test results either indicates that the mother has had a recent infection or has a false-positive IgM result [13, 14]. High avidity is associated with primary infection occurring greater than 4-5 months previously; low avidity indicates infection occurring more recently.

Neonatal Outcome and Prognosis: The risk of congenital toxoplasmosis ranges from 20% to 50% [7]. The risk of fetal infection increases with the gestational age at the time of maternal infection (4-15% at 13 weeks and > 60% at 36 weeks). The earlier the gestational age at the time of infection, the greater the risk that the fetus will be affected [7]. Congenital toxoplasmosis infection involves the CNS (microcephaly, hydrocephalus, ventriculomegaly, and the eyes (chorioretinitis).

The infection may result in developmental delay, epilepsy, and blindness. Hepatosplenomegaly, anemia, jaundice, and pneumonitis also may occur. Most infants do not have clinical signs of infection at birth, but up to 90% will develop sequelae later in life [15].

Treatment: Fetal infection should be treated by spiramycin for 1 week (1-g three times daily), followed by pyrimethamine (50 mg once daily) plus sulfadiazine (1 g three times daily) plus folinic acid (50 mg weekly) throughout the pregnancy. The infant should then be treated over the first year of life.

Prevention and Screening: Routine serologic screening of pregnant women for toxoplasmosis is not recommended. Prenatal screening should be limited to women who are immunosuppressed or are human immunodeficiency virus (HIV) positive. Pregnant women should be counseled on proper hand washing, pet care measures, and dietary recommendations to prevent toxoplasmosis [6].

Human Parvovirus B19

Definition: Parvovirus B19 is a single-stranded DNA virus spread by respiratory droplets from infected people, by blood or blood-product transfusion or by transplacental passage.

Prevalence: 1-2 in 100 pregnancies [16].

Major Principles of Diagnosis: Pregnant women with positive IgM, regardless of IgG status, should be monitored for fetal infection. Negative IgM with positive IgG indicates immunity, and such women are not at risk for transplacental transmission. Those in whom both IgM and IgG are negative, are susceptible, and serologic testing should be repeated in 4 weeks. Serial ultrasound examinations, looking for ascites, cardiomegaly, hydrops fetalis and elevated MCA-PSV, should be performed every 1-2 weeks for 8-12 weeks after exposure [7]. Fetal blood sampling is indicated when MCA-PSV is greater than 1.5 multiples of the mean (MoM), or when there is fetal ascites or hydrops. When fetal anemia is confirmed, intrauterine blood transfusion is indicated [17]. Non-hydropic fetuses usually need only one transfusion, whereas hydropic fetuses may need two or more transfusions. The risk of fetal demise depends on the presence of hydrops and the gestational age at the time of transfusion [18]. At later gestations, it may be preferable to deliver the baby early and transfuse the neonate. Fetal hydrops usually resolves within 6 weeks of intrauterine blood transfusion.

Prognosis: The risk of perinatal death is 30% for fetuses with hydrops vs. 6% for non-hydropic fetuses. Evidence regarding the long-term outcome of infected

CHAPTER 12

Abnormalities Of Placenta, Amniotic Fluid, And Umbilical Cord

INTRODUCTION

A number of abnormalities may affect the placenta, fetal membranes, amniotic fluid volume, and umbilical cord. This chapter deals with those abnormalities and their management in the first trimester (subchorionic hematomas and chorionic bumps) and, after that, (amniotic band syndromes, oligohydramnios, polyhydramnios, *etc*).

Amniotic Band Syndrome

Definition: Amniotic band syndrome includes a wide range of fetal disorders caused by the entrapment of various fetal structures and organs with fibrous amniotic bands.

Prevalence: 1 in 1200 live births [1].

Major Principles of Diagnosis: Multiple or isolated anomalies (asymmetric extremities, constrictions, amputations of fingers and/or toes, craniofacial deformations *etc*.) may be detected sonographically (Fig. **78**). Amniotic bands themselves may or may not be visualized [1, 2].

Early Diagnosis: The gestational age at which the amniotic sac ruptures, determines the range and severity of abnormalities. Early rupture (before day 45 of gestation) is associated with multiple severe deformities (encephaloceles, facial clefts, abdominal and thoracic defects, limb amputations, *etc*.). Late amnion rupture (after day 45 of gestation) tends to produce limb constrictions.

Genetics and Prenatal Management: Amniotic band syndrome has no genetic basis. It occurs sporadically, and the recurrence risk is low. The mode of delivery should be based on the usual obstetric indications [1].

Fetal Surgery: Fetoscopic or ultrasound-guided divisions of bands have been attempted giving fair results [3, 4]. Presently, fetal surgery of amniotic band syndrome should be considered only after extensive counseling in carefully

selected cases. The successful early release of amniotic bands using a 1.0-mm fetoscope at 15 and 5/7th weeks of pregnancy has been recently reported [5].

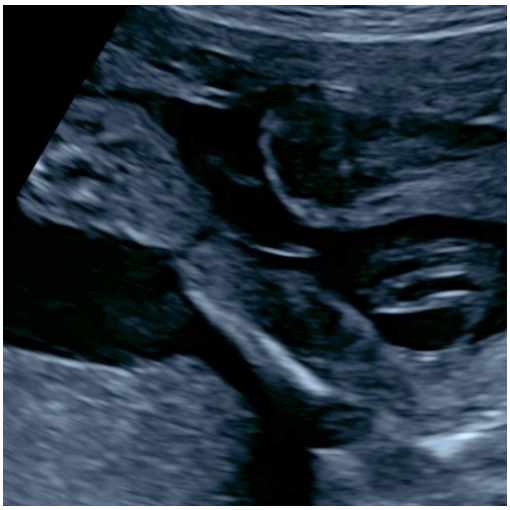

Fig. (78). Amniotic band constricting the upper extremity. Ultrasound (Sagittal plane).

Prognosis: The prognosis is variable and depends on the nature and the extent of the injuries.

Placental Hematoma

Definition: Collection of blood in various locations within or around the placenta. The term placental hematoma encompasses several entities, including retroplacental, subchorionic, and subamniotic hematomas. Retroplacental and marginal intraplacental hematomas are located in the intervillous space of the placenta. Retroplacental hematomas are located between the basal plate and myometrium, i.e., between the uterine wall and placenta [6, 7].

Prevalence: 0.46% to 9.5% [8].

Major Principles of Diagnosis: The echogenicity of clotted blood varies with time. Initially, it appears hyperechoic, then becomes hypoechoic (usually a week later), and finally, it appears sonolucent [9, 10] (Fig. **79**).

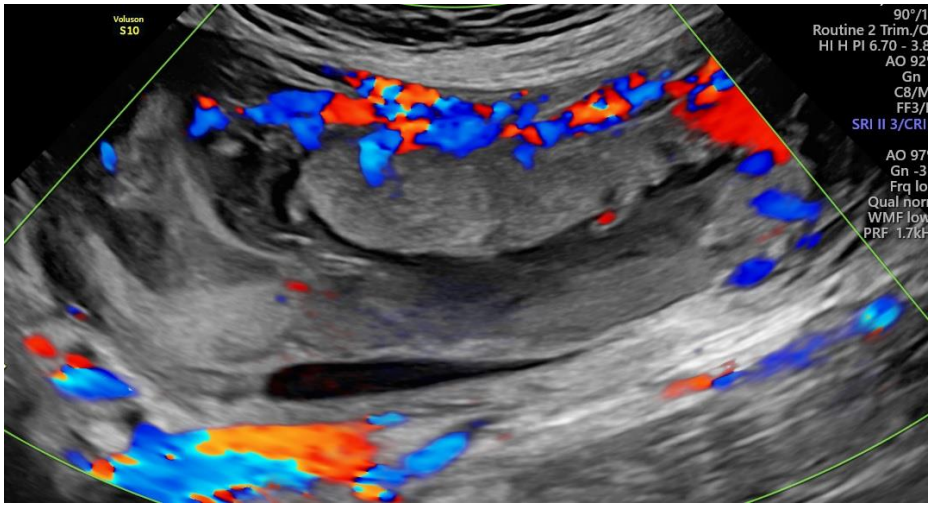

Fig. (79). Placental Hematoma. Color Doppler Ultrasound (Longitudinal plane).

Prenatal Management and Prognosis: Currently, there is no treatment strategy for placental hematomas. Prognosis largely depends on the location and size of the lesion. Retroplacental hematomas are seen much earlier (first trimester) than intraplacental hematomas (second trimester). Intraplacental hematomas are risk factors for placental insufficiency and fetal growth restrictions. Retroplacental hematomas carry a risk of premature preterm rupture of membranes and fetal demise [6]. Preterm labor is more common in women with intraplacental hematomas [6]. Retroplacental hematomas result from placental detachment, whereas placental abruption result from ruptures of spiral arteries [10].

A retroplacental hematoma, whose size is two-thirds or greater of the gestational sac circumference, is a predictor of miscarriage. Retroplacental hematomas decrease in size after patients experience vaginal bleeding. The risk for unfavorable outcomes is significantly less in patients with a diminishing hematoma size.

Chorionic Bump

Definition: Chorionic bump is a consistent focal chorionic protrusion or bulge within the gestational sac.

Prevalence: 1.5 in 1,000 pregnancies [11].

Major Principles of Diagnosis: Chorionic protrusions into the gestational sac with central hypoechoic and peripheral hyperechoic areas with no vascularity on

CHAPTER 13

Still Birth

INTRODUCTION

The American College of Obstetricians and Gynecologists committee's opinions on when to begin antenatal fetal surveillance can be divided into three categories: (1) at or by 32 0/7 weeks, (2) at or by 36 0/7 weeks, or (3) at or beyond 0/7 weeks of gestation [1]. The rate of stillbirth increases rapidly with advancing gestation: from 0.21 at 37 weeks, 0.27 at 38 weeks, 0.35 at 39 weeks, 0.42 at 40 weeks, 0.61 at 41 weeks, and 1.08 at 42 weeks [2]. Table **4** is a modified summary of MFM recommendations on the onset of fetal testing [2].

Intrauterine Fetal Death

Definition: Absence of heartbeat is confirmatory of fetal demise beyond 20 weeks. Fetal death may be classified as antepartum (occurring before the onset of labor) or intrapartum (those occurring after the onset of labor)

Prevalence: 7.7 per 1000 live birth [3].

Major Principles of Diagnosis: Diagnosis can be made reliably using real-time ultrasound which has 100% sensitivity and specificity for the diagnosis of fetal death. The fetal heart can now be detected within 6 weeks using high-resolution ultrasound. Failure to detect fetal heart activities is diagnostic for fetal death. Other ultrasound evidence of fetal death includes the absence of fetal movements, overlapping of cranial bones, and skin and scalp edema (Fig. **86**). Rarely intrafetal gas can be noted [4].

Evaluation of Fetal Death: The diagnostic evaluation of fetal death includes ultrasound examination, genetic maternal tests, placental cultures, placental pathology and autopsy.

Ultrasound Examination: An assessment of long bone length can accurately assess the gestational age at the time of death (except for those with lethal skeletal dysplasias). In multiple gestations, the sonographer should look for evidence of a twin-to-twin transfusion syndrome (such as polyhydramnios/oligohydramnios and discordant fetal weights), and note the number of placentas. Ultrasound can be used to search for congenital anomalies, even in the presence of fetal death. Lethal

Table 4. Recommendations for Antepartum Testing in High-risk Pregnancies.

Condition	At diagnosis	Inpatient management
Multiple gestations		
Twins, uncomplicated dichorionic	36 0/7 weeks	Weekly
Twins, uncomplicated monochorionic-diamniotic	32 0/7 weeks	Weekly
Twins, complicated monochorionic-diamniotic (i.e., TTTS)	Individualized	Individualized
Twins, monoamniotic	Individualized	Individualized
Decreased fetal movement	At diagnosis [3]	Once [5]
Maternal		
Hypertension, chronic		
Controlled with medications	32 0/7 weeks	Weekly
Gestational hypertension/preeclampsia	At diagnosis	Twice weekly
Diabetes		
Gestational, controlled on medications	32 0/7 weeks	Twice weekly
Gestational, poorly controlled	32 0/7 weeks	Twice weekly
Pregestational	32 0/7 weeks [6]	Twice weekly
Systemic lupus erythematosus	By 32 0/7 weeks	Weekly
Antiphospholipid syndrome	By 32 0/7 weeks	Twice weekly
Sickle cell disease		
Complicated	32 0/7 weeks	Once or twice weekly
Renal disease (Cr greater than 1.4 mg/dL)	32 0/7 weeks	Once or twice weekly
In vitro fertilization	36 0/7 weeks	Weekly
Pregnancy BMI		
Prepregnancy BMI 35.0-39.9 kg/m2	37 0/7 weeks	Weekly
Prepregnancy BMI 40 kg/m2 or above	34 0/7 weeks	Weekly
Previous stillbirth		
At or after 32 0/7 weeks	32 0/7 weeks	Twice weekly
Previous fetal growth restriction requiring preterm delivery	32 0/7 weeks	Weekly
Previous preeclampsia requiring preterm delivery	32 0/7 weeks	Weekly
Cholestasis	At diagnosis [2]	Twice weekly
Placental	-	-
Chronic placental abruption	At diagnosis [2]	Twice weekly
Velamentous cord insertion	36 0/7 weeks	Weekly
Single umbilical artery (isolated)	36 0/7 weeks	Weekly
Isolated oligohydramnios (isolated)	At diagnosis	Twice weekly

(Table 4) cont.....

Condition	At diagnosis	Inpatient management
Polyhydramnios, moderate to severe	32 0/7- 34 0/7 weeks	Twice weekly

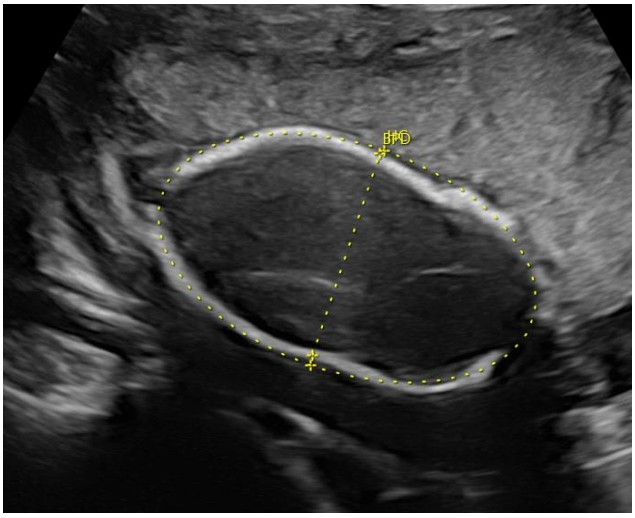

Fig. (86). Skull Deformation in Fetal Demise. Ultrasound (Axial plane).

skeletal dysplasias, anencephaly, and central nervous system abnormalities are examples of defects that can be readily detected in a stillborn fetus. The intrauterine environment can be assessed, including denoting placental location, evidence of a retroplacental clot, and any features of perinatal infections (such as hydrops and placentomegaly). Finally, the amniotic fluid volume can be assessed with specific attention given to the presence of oligohydramnios or polyhydramnios, which might offer clues to the cause of fetal death. A significant percentage of fetal loss is associated with chromosome abnormalities at any gestational age. In the first trimester, approximately 50% of fetal loss is associated with chromosomal abnormalities; at 16 to 19 weeks, approximately 24% and beyond 20 weeks gestation, between 6 and 13% are associated with chromosome abnormalities [5, 6].

Maternal Tests: In cases of fetal death, maternal tests include hemoglobin A1C to rule out diabetes, serologic test for syphilis (VDRL or rapid plasma reagent test), toxoplasmosis, and parvovirus B19, Kleihauer-Betke test to detect fetomaternal hemorrhage, antinuclear antibodies (ANA), lupus anticoagulant, anticardiolipin antibodies, and a urine toxicology screen [5 - 9].

Placental Cultures and Pathology: Upon delivery, the placenta should be cultured for listeria, and placental pathology should be performed.

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Diagnosis and Management of Fetal Disorders reviews key points in obstetrics/maternal fetal medicine imagery analysis of the pregnant uterus and its contents. Specifically, chapters cover ultrasound of different fetal organs, physiological systems and diseases. The authors also provide radiological correlation to help the obstetrician, pediatrician, radiologist, and other specialists know the basics and some more advanced concepts that will allow diagnosis of fetal abnormality, and what those findings mean to the patient and their families vis-a-vis the fetus in their pregnancy. It is, therefore, a handbook that helps medical residents and professionals to assess cases in real-time or to review a given clinical problem.

Book Cover Designed By ***Dr. Steven Swancoat***