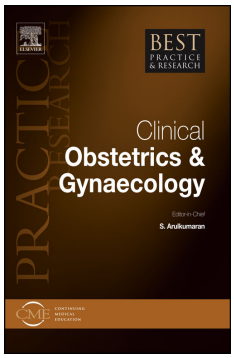
Accepted Manuscript



Chapter: Genetic Markers on Ultrasound Scan

Janani Sivanathan, Basky Thilaganathan

PII: S1521-6934(17)30052-4

DOI: 10.1016/j.bpobgyn.2017.03.005

Reference: YBEOG 1704

To appear in: *Best Practice & Research Clinical Obstetrics & Gynaecology*

Received Date: 18 November 2016

Revised Date: 8 March 2017

Accepted Date: 10 March 2017

Please cite this article as: Sivanathan J, Thilaganathan B, Chapter: Genetic Markers on Ultrasound Scan, *Best Practice & Research Clinical Obstetrics & Gynaecology* (2017), doi: 10.1016/j.bpobgyn.2017.03.005.

BOOK: GENETICS FOR OBSTETRICIANS AND GYNAECOLOGISTS

CHAPTER: GENETIC MARKERS ON ULTRASOUND SCAN

Janani Sivanathan and Basky Thilaganathan

Corresponding author:

Professor Basky Thilaganathan

Fetal Medicine Unit

St George's University of London

Cranmer Terrace,

London SW17 0RE

Tel: +44 20 8725 0071

Fax: +44 20 8725 0079

E-mail: basky@pobox.com

ABSTRACT

Prenatal diagnosis is a rapidly evolving speciality. Screening for aneuploidy began with non-sonographic features of background risk of maternal age, past and family history. It was possible to diagnose major structural defects in the fetus with the 2nd trimester scans. Serum biochemistry markers in the early 2nd trimester were added to increase the detection rate of aneuploidy. However, as some of these abnormalities were amenable to detection earlier in the 1st trimester, newer modalities were introduced. Nuchal translucency (NT) measurement was one of the main advances with regards to first trimester screening. Additional markers such as presence of nasal bone, tricuspid regurgitation, ductus venosus and megacystis; together with 1st trimester serum biochemistry, further enhanced detection rate of chromosomal abnormalities.

Advances in research and technology has resulted in the availability of non-invasive prenatal testing from 10 weeks of gestation. This has facilitated detection of the 3 major chromosomal aneuploidies at a very early gestation. However, there are a wide range of genetic syndromes, that are not confined to the main trisomies. There are specific markers on ultrasound that can be linked to specific syndromes. Hence, a structured and stepwise approach is needed to identify and reach a possible diagnosis. As anomalies are classified into malformations, deformations and disruptions, it is important to note that not all markers detected are due to genetic syndromes, and not all genetic syndromes can be detected on ultrasound scan. In this chapter, we outline common structural markers and their association with main genetic syndromes.

Keywords: ultrasound, markers, genetics, prenatal, structural anomalies.

INTRODUCTION

Ultrasound assessment of fetal abnormalities can be performed as early as the first trimester. A NT measurement of more or equal to 3.5mm should warrant an anatomical survey and appropriate genetic testing, depending on the risk profile [1]. The second trimester anomaly scan is routinely performed to elucidate congenital malformations which may suggest an aneuploidy or genetic disorder. There are some abnormalities which become apparent in late gestation such as cardiac anomalies, skeletal dysplasias and neuromigrational disorders of the brain as these lesions are progressive in nature. It is pertinent to take a structured approach of the various organ systems in order not to miss out relevant findings. We have approached this topic in an individual organ based manner, dealing with important aspects of each system followed by a brief outlook on ultrasound appearances of various genetic syndromes.

ULTRASOUND MARKERS

Ultrasound markers are described according to various body systems, progressing craniocaudally. This is a deliberate approach to enable an organ and problem-based strategy to reach a diagnosis.

Central nervous system (CNS) markers

CNS markers represent the second commonest serious congenital anomaly after the heart [2]. Ultrasound is an effective modality to detect the anomaly but would typically need further imaging such as magnetic resonance imaging (MRI) to confirm the diagnosis to aid in management.

Ventriculomegaly

Normal size of the ventricles provides reassurance of normal brain development. Mild ventriculomegaly can sometimes be an early sign of abnormal or delayed brain maturation. It is the commonest noted congenital CNS anomaly with incidence of 0.3 to 1.5 per 1,000 live births. Ventriculomegaly can be isolated or associated with other abnormalities (Figure 1). The mechanism is due to obstruction at the cerebrospinal fluid (CSF) pathway, CNS malformations,

brain destruction or overproduction of CSF. Unilateral ventriculomegaly is typically physiological, but rarely occurs in brain destruction caused by congenital infection, vascular or mechanical insult; while bilateral ventriculomegaly occurs in CNS malformations [2]. Chromosomal abnormalities are found in 11% of cases, mostly trisomy 21. The commonest associated syndromes are Aicardi, Fraser, Meckel Gruber, Joubert, X-linked hydrocephalus, Miller Dieker, Neu Laxova and Walker Walburg [2].

*Figure 1 – Bilateral severe ventriculomegaly.

Agenesis of corpus callosum (ACC)

The incidence of ACC is approximately 1.4 per 10,000 live births, which may be described as either complete or partial. It is important to distinguish primary ACC (Figure 2) from secondary destruction of initially normal appearance of the corpus callosum due to trauma, infection, haemorrhage or metabolic disease. Overall rate of chromosomal abnormality is 17.8%. The genetic syndromes associated are trisomy 8, 13, 18, holoprosencephaly sequence, Aicardi and Andermann. Recurrence risk is 1% if sporadic or chromosomal, 25% if autosomal recessive and 50% in boys if X-linked recessive [2].

*Figure 2 – Agenesis of corpus callosum (arrow) with bilateral ventriculomegaly.

Holoprosencephaly

This is a heterogenous entity due to impaired midline cleavage of the forebrain. It is graded according to alobar, semilobar and lobar presentations. Associated facial malformations are cyclopia, cebocephaly and ethmocephaly. The incidence is 0.6 to 1.9 per 1,000 births. More than half are associated with trisomy 13. Familial holoprosencephaly can be inherited as autosomal dominant or recessive [2].

Lissencephaly

This is a rare cortical developmental disorder with reduced or absent brain gyri, caused by abnormal neuronal migration. It has a female predilection, associated with deletion on chromosome 17p13, including LIS1 which is inherited as an X-linked dominant form. If it occurs

de novo, the recurrence risk is low. However if inherited from one parent with balanced translocation, recurrence is 25%. The syndromes associated include Miller Dieker, Walker Walburg and Neu Laxova [2].

Mega cisterna magna

This is a cystic malformation of the posterior fossa with intact vermis, enlarged cisterna magna and normal size of the fourth ventricle. Incidence is approximately 1% and occurs mainly in trisomy 18 when non-isolated. In the absence of other ultrasound findings, mega cisterna magna is unlikely to be clinically significant [2].

Dandy Walker continuum

This describes the cystic enlargement of the 4th ventricle with upward displacement of the tentorium, with partial or complete agenesis of the vermis (Figure 3). Incidence is 1 in 25,000 to 35,000 births. The risk of chromosomal anomalies is high, with up to 35% of cases due to trisomy 18 and 13. Common associated syndromes are Aicardi, Meckel Gruber, Joubert, Walker Warburg and Neu laxova [2].

*Figure 3 – Dandy Walker malformation with calipers showing enlarged 4th ventricle and arrow pointing to agenesis of the vermis.

Cephalocele

This is a protrusion of intracranial structures through a cranial bone defect. The herniated structures may consist of meninges only or meninges and cerebral tissue. The cephalocele can occur at the frontal, parietal, occipital and frontoethmoidal regions. Occipital is the commonest site of occurrence in Europe, while frontal is commonest in South East Asia [2]. There is a high incidence of chromosomal anomalies (14-18%) especially in trisomy 13 and 18. Other syndromes are Meckel Gruber, frontonasal dysplasia and Walker Warburg. 70% to 80% of cases will have associated CNS abnormalities detectable on scan such as ACC, ventriculomegaly, holoprosencephaly, spina bifida and microcephaly [2].

Spina bifida

Most open spinal tube defects are amenable to detection by scan. The skin and muscles overlying the defect are absent, but the neural canal may be exposed or covered by a thin meningeal membrane. The defect consists of meninges (meningocele) or neural tissue and meninges (meningomyelocele). 75% of these defects occur at the lumbar region (Figure 4a and 4b). Chromosomal abnormalities occur in approximately 8% to 16% of cases; frequently associated are trisomy 13, 18, triploidy, Meckel Gruber, Walker Warburg, Marfan and Ehlers-Danlos syndrome. Associated abnormalities are ventriculomegaly and hypoplasia of the posterior fossa structures, especially Arnold Chiari II malformation. Club foot may also occur [2].

*Figure 4a – arrow points towards the defect at the lumbar region with protrusion of the meninges.

*Figure 4b – Coronal view of lumbosacral spina bifida.

Skull shape markers

Skull shape deformities are amenable to detection in the early second trimester ultrasound study. The commonest is the lemon-shaped skull associated with spina bifida (Figure 5) [3]. This is postulated to be due to the reduced intraspinal pressure resulting in reduced intracranial pressure and eventual downward shift of the brain. The frontal bones respond by flattening or scalloping forward. Dolicocephaly is the second commonest skull deformity and seen in malpresentations such as breech and in oligo or anhydramnios. This is likely due to the compression effect of the uterine fundus and diminished amniotic fluid environment on to the fetal cranium. Aneuploidies such as trisomy 21 is associated with brachycephaly, while trisomy 18 with strawberry shaped head (Figure 6). Other deformities occur as a result of premature closure of the fetal cranial sutures or craniosynostosis. Closure of the sagittal sutures causes scaphocephaly *or* dolicocephaly, coronal sutures brachycephaly and metopic sutures trigonocephaly [4]. Apert, Crouzon and Pfeiffer syndromes present with brachycephaly. Thanatophoric dysplasia has clover-leaf shaped skull (Figure 7).

*Figure 5 – Lemon shaped skull with calipers denoting ventriculomegaly

*Figure 6 – Strawberry shaped skull

*Figure 7 – Clover-leaf shaped skull

Facial markers

Cleft lip and palate

Cleft lip with or without cleft palate is relatively common with an incidence of 1 in 700 to 1,000 live births. 80% of cleft lip cases have associated cleft palate. If the cleft is an isolated finding, then there is a very low risk of karyotypic abnormality. However, if it is a midline cleft, there is very frequently an associated karyotypic abnormality [5]. The risk of chromosomal abnormality increases to approximately 28 to 32% in the presence of other structural abnormalities [5]. Frequently associated aneuploidies are trisomy 13 and trisomy 18.

Micrognathia

The mandible represents a common site for effects associated with genetic conditions. Agnathia is the most severe form of maldevelopment with complete agenesis or hypoplasia of the mandible. Micrognathia and retrognathia refers to arrested development of the mandible, with the former resulting in a small chin and the latter a posteriorly positioned chin in relation to the maxilla (Figure 8). As micrognathia is almost always an ominous sign, it is important to look for associated abnormalities [6]. Chromosomal abnormalities such as trisomy 18, Cri du Chat, Cat Eye, Pallister Kilian and triploidy are among those associated, as are various neuromuscular disorders. If there is concurrent cleft palate, Pierre Robin sequence maybe considered as a diagnosis [6].

*Figure 8 – Micrognathia (arrow) with thickened nuchal translucency.

Lung lesions and thoracic wall deformity

Congenital diaphragmatic hernia

This is a defect in the diaphragm resulting in herniation of the abdominal contents into the chest cavity (Figure 9). 80% occurs on the left side with 50-60% being isolated finding. The majority of congenital diaphragmatic hernias (80%) have no genetic association. Associated

chromosomal anomalies are trisomy 18, 13, Fryns, Cornelia de Lange, Pallister Killian and Marfan syndrome [7].

*Figure 9 – Congenital diaphragmatic hernia with calipers denoting residual left lung.

Congenital pulmonary airway malformation (CPAM) and bronchopulmonary sequestration (BPS)

CPAM and BPS are collectively termed echogenic lung lesions and are the commonest hyperechogenic lung lesions in the fetus (Figure 10) with an incidence of 1 in 3,000 live births. Though it is known that the main differentiating factor between the two entities is that BPS derives an anomalous systemic vascular supply, there seems to be hybrid lesions to suggest that there might be an overlap and similar embryological origin for CPAM and BPS. It is usually not related to chromosomal aberration especially if isolated. However in the presence of a large lung lesion, cardiac defects (mainly conotruncal), congenital diaphragmatic hernia or tracheoesophageal fistula, genetic analysis is recommended [7].

*Figure 10 – CPAM hyperechogenic lung lesion with mediastinal shift.

Rib abnormalities

Increased number of ribs is rarely seen as a normal variant. It is usually associated with trisomy 21 and VACTERL (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal or radial anomalies and limb defects) syndrome. Although reduced number of ribs can be a normal variant, it can be seen in 1/3rd of Down syndrome cases, as well as in cleidocranial dysplasia and camptomelic dysplasia. Short ribs do not extend beyond the anterior axillary line, resulting in a narrow chest (Figure 11a, b and c). Many syndromes and skeletal dysplasias are associated and it is important to identify lethal skeletal dysplasia. The differential diagnoses are thanatophoric dysplasia, Jeune asphyxiating thoracic dysplasia, achondrogenesis, Ellis Van Creveld syndrome and short-rib polydactyly syndrome [7].

Figure 11a – Transverse view of short ribs.

Figure 11b – Sagittal view of short ribs (arrow).

Figure 11c – Large arrow denoting narrow chest and smaller arrow pointing to short ribs.

Cardiac defects

The incidence of congenital heart disease (CHD) is 2 to 6.5 per 1000 births. For fetal heart ultrasound screening, the views of abdominal situs, 4 chamber view, outflow tracts views, 3 vessel view and 3 vessel trachea view are basic requirements. Some genetic syndromes are strongly associated with cardiac defects.

40 to 50% of trisomy 21 fetuses have CHD, mainly atrioventricular septal defects (AVSD), ventricular septal defects (VSD) or atrial septal defects (ASD). 90 to 100% of trisomy 18 cases have either AVSD, VSD, patent ductus arteriosus (PDA), Tetralogy of Fallot (TOF), double outlet left ventricle (DORV) and transposition of great arteries (TGA). As for trisomy 13, 80% would be affected by ASD, VSD, PDA, hypoplastic left heart syndrome (HLHS), laterality defects or atrial isomerism. Interrupted aortic arch type B or truncus arteriosus occur in 75% of 22q11 deletion syndrome. Monosomy X fetuses would have coarctation of aorta (CoA), valvar aortic stenosis (AS), HLHS or bicuspid aortic valve in 25 to 35% of cases [8].

Cardiac tumours such as rhabdomyoma occur in almost all cases of tuberous sclerosis, while fibroma can be detected in Beckwith-Weidemann syndrome or Gorlin syndrome.

Cardiomyopathies occur in single gene disorders such as Noonan syndrome, familial cardiomyopathy and metabolic abnormalities [8].

Abdominal wall defects

The most common abdominal wall defects are omphalocele, gastrochisis, bladder exstrophy and ectopia cordis. Omphalocele or exomphalos is due to the failure of physiologically herniated bowel to return to the abdominal cavity by 12 weeks of gestation. The latter 3 defects are due to abnormal closure of the body wall folds at the midline. Exomphalos may contain bowel loops or liver (Figure 12). Spontaneous resolution of the hernia detected in the 1st trimester is seen in about 95% of euploid fetus, but has not been observed in cases of herniated liver [9]. Spontaneous rupture of the sac in utero mimicking gastrochisis can be differentiated by the umbilical cord inserting on a normal segment of the abdominal wall in gastrochisis. Almost 60% of exomphalos cases have underlying chromosomal abnormality; the most frequent being trisomy 18. Other associations include trisomy 13, Beckwith-Weidemann

syndrome, X-linked disorder (gene locus between Xq25-p26.1) and Pentalogy of Cantrell [9]. Gastrochisis (Figure 13) being associated with chromosomal abnormality is rare.

*Figure 12 – Exomphalos with liver as content.

*Figure 13 – Arrow pointing to gastrochisis detected in 1st trimester scan.

Renal abnormalities

Renal agenesis

The congenital absence of kidneys can be unilateral or bilateral. Bilateral renal agenesis occurs in 0.1 to 0.3 per 1,000 births and is a lethal condition. The lumbar fossa appears empty, the adrenals elongated (lying down adrenal sign), lack of recognisable renal arteries on colour Doppler and oligo or anhydramnios can clinch the diagnosis. Risk of genetic syndromes can be as high as 30%, including Fraser, Smith-Lemli-Opitz and Gorlin syndromes [10].

Multicystic dysplastic kidneys

The kidneys appear large, bright with multiple thin walled cysts occupying the renal parenchyma (Figure 14). Bilateral involvement results in lung hypoplasia due to oligohydramnios and is lethal. Presence of other anomalies suggest genetic or syndromic link. Mosaic trisomy 7, 8, triploidy, VACTERL, Meckel-Gruber and Fraser syndrome are some of the associations [10].

*Figure 14 – Left multicystic dysplastic kidney with normal right kidney.

Polycystic kidney disease

Polycystic kidney disease can be classed as infantile and adult types. Infantile (IPKD) is autosomal recessive and carries 25% risk of recurrence. It is a single gene disorder caused by mutations in the PKHD1 gene on the short arm of chromosome 6. The age of onset varies and is divided into perinatal, neonatal, infantile and juvenile. Ultrasound features are enlarged echogenic kidneys with small cysts of 1 to 2mm and normal renal pelvis with or without oligohydramnios. These findings may not be present till late in the second trimester. Adult polycystic kidneys (APKD) is autosomal dominant and the most common type. The recurrence

rate is 50% and the genes involved are on 6p and 4q. The scan findings can be normal or similar to infantile type, except the bladder and amniotic fluid appears normal. Therefore, it is pertinent that the family history, renal ultrasound of the parents, karyotype and genetic referral be considered [10].

Bilateral renal pelvis dilatation (RPD)

Renal pelvic dilatation is caused by transient obstruction at the level of the pelvi-ureteric junction (PUJ) or vesico-ureteric junction (VUJ), which mostly improve over time (Figure 15). Mild RPD (7-10mm) if associated with other anomalies or maternal risk factors, is a risk for trisomy 21. In isolated RPD, or where prior aneuploidy screening has been undertaken, the risk for aneuploidy is low [10].

*Figure 15 – Bilateral renal pelvicalyceal dilatation.

Megacystis

It is defined by longitudinal diameter of the bladder measuring more than 7mm in the 1st trimester (Figure 16). At this gestation, there is a 25% risk of aneuploidy, mainly trisomy 13 and 18 and other associated malformations in the fetus [10].

*Figure 16 – Megacystis (arrow) in 1st trimester.

Limb abnormalities

The prevalence of limb abnormalities is 6 in 10,000 live births. It is more common in the upper limb, unilateral and right side. Limb abnormalities are generally sporadic, but may be due to single gene disorders or chromosomal abnormalities [11].

Clubfoot (congenital talipes equino varus CTEV)

CTEV is due to the subluxation of the talo-calcaneo-navicular joint which usually occurs secondary to a neurological deficit resulting in underdevelopment and weakness of the muscles on the lateral side of the calf or from intrauterine crowding (Figure 17). 1/3rd of the cases are an

isolated deformity. Nevertheless, it is important to look for CNS abnormalities, and if present to rule out chromosomal abnormality [11].

*Figure 17 – Bilateral CTEV.

Clinodactyly

This is commonly seen in the fifth finger. It is due to the fixed deviation of the digit due to hypoplasia of the mid phalanx. 18% of the normal population have clinodactyly. However, it can be seen in 60% of Down syndrome cases [11].

Clenched hands

In this abnormality, the second and the fifth fingers overlap the third and fourth fingers and the thumb is adducted. If this is constant throughout the scan, it can be associated with trisomy 18 or fetal akinesia sequence and has poor prognosis [11].

Clubhand

Can be either due to radial or ulnar deficiency, though ulnar is more common. It is often associated with other abnormalities and is mostly inherited. Examples are thrombocytopenia absent radius (TAR) syndrome (Figure 18), skeletal dysplasia and arthrogryposis [11].

*Figure 18 – Clubhand.

Polydactyly

The presence of extra digits in the upper or lower extremities is polydactyly. The incidence of polydactyly is 1 in 700 pregnancies. If it occurs on the radial side, it is preaxial and if on the ulnar side, it is postaxial. Postaxial polydactyly occurs more frequently and can be isolated or autosomal dominant in inheritance. Preaxial polydactyly (Figure 19) can be isolated and related to mutation in the genes affecting the Sonic hedgehog (SHH) pathway [11].

*Figure 19 – Preaxial polydactyly of the foot.

Syndactyly

Syndactyly is the fusion of 2 or more digits. It is the most common congenital malformation of the limbs with an incidence of 1 in 2,000 to 3,000 live births. Syndactyly is simple when it involves soft tissue only and complex when bone or nails of adjacent digits are involved. When syndactyly is associated with other abnormalities, more than 30 syndromes have been reported, the commonest being Poland, Apert, Fraser and Holt-Oram syndrome [11].

GENETIC SYNDROMES

This section covers the commonest and/or most important genetic syndromes amenable to diagnosis prenatally by ultrasound and invasive testing.

Down syndrome

Down syndrome is a chromosomal condition of trisomy 21 that is associated with intellectual disability, a characteristic facial appearance and weak muscle tone. All affected individuals experience cognitive delays, but the intellectual disability is usually mild to moderate [12]. The incidence is 1 in 800 at birth and this tends to increase with advanced maternal age. The genetics for this condition is free trisomy of chromosome 21 (95%), trisomy from Robertsonian translocation or mosaicisms (5%) [13]. The major anomalies on ultrasound are ventriculomegaly, oesophageal atresia, duodenal atresia, exomphalos and cardiac defects such as AVSD, VSD and TOF [12, 13]. There are numerous soft-markers associated with trisomy 21, but in the era of cell-free DNA screening, these are of questionable clinical significance. The recurrence risk for Down syndrome is low (1%), but is significant if the mother is a carrier of a Robertsonian translocation (10-15%).

Edward's syndrome

Trisomy 18 or Edward's syndrome is a chromosomal condition associated with abnormalities in many parts of the body. Due to the severity of the defects, many babies with trisomy 18 die before birth or within their first month. The incidence is 1 in 6,000 at birth and this increases with advanced maternal age. It may occur due to free trisomy of chromosome 18 (99%),

mosaicism (0.9%) or translocation of the long arm of chromosome 18 (0.1%) [13]. The major anomalies detectable on scan are neural tube defects, ACC, posterior fossa abnormalities, cystic hygroma, micrognathia, heart defects, exomphalos, diaphragmatic hernia, cleft lip and palate, cystic renal dysplasia, clenched hands, aplasia radii and rocker bottom feet [12, 13]. There is a 1% empirical estimate of a recurrence risk as for all autosomal trisomies.

Patau syndrome

Trisomy 13 (Patau syndrome) is associated with severe intellectual disability and physical abnormalities in many parts of the body. Due to the severity of the condition, not many babies survive past the first few days or weeks. This syndrome is more prevalent with advancing maternal age and the incidence is 1 in 12,500 at birth. The genetics for Patau syndrome is free trisomy of chromosome 13 (90%) and translocation or mosaicism (10%) [13]. There are a host of major anomalies that can be detected via ultrasound. With respect to the central nervous system, findings include holoprosencephaly, ACC, cerebellar malformations, microcephaly, nuchal thickening and neural tube defect. Craniofacial defects are micrognathia, bilateral cleft lip and palate, micro or anopthalmia, hypotelorism, midface hypoplasia and proboscis. Septal defects and absent pulmonary venous return are the cardiovascular findings, whereas urinary tract findings include echogenic enlarged kidneys, and cystic renal dysplasia. Skeletal defects are postaxial polydactyly, radial aplasia and flexion deformity of fingers while in the abdominal wall exomphalos, single umbilical artery and echogenic bowel can be detected. Intrauterine growth restriction (IUGR) is common with Patau's and there is a 1% recurrence risk [12, 13].

Turner syndrome (Monosomy X)

Turner syndrome is characterized in early pregnancy by large cystic hygroma and lymphangiectasia leading to fetal hydrops. Most prenatally-detectable cases of Turner syndrome pregnancies miscarry in the first trimester and fetuses that survive gestation are more likely to exhibit mosaic Turners. The incidence is 1 in 2,500 to 5,000 births and this condition is not known to be associated with advancing maternal age. The genetics involved in Turner's are monosomy of chromosome X (XO), a structural rearrangement of the X

chromosome, mosaicism and disturbed function of the SHOX gene, responsible for bone development and growth [13]. Ultrasound findings include cystic hygroma, non-immune hydrops fetalis, CoA, HLHS, horseshoe kidney and short femur [12]. The recurrence risk is sporadic and not modified in comparison with the normal population.

Triploidy

Triploidy occurs due to an extra set of chromosomes of either maternal or paternal origin. The incidence is 1 in 2,500 to 5,000 births and it has no relationship with advancing maternal age. Two-thirds of cases are paternal in origin (69XXY) and one third are maternal (68XXX). The majority of pregnancies end in early miscarriage. The ultrasound findings include large, cystic, hydropic appearing placenta, associated with partial mole and preeclampsia for those that are paternal in origin. In those of maternal origin (XXX), severe early onset asymmetrical IUGR (affecting the skeleton more than the head), ACC, Dandy Walker malformations, holoprosencephaly, meningomyelocele, syndactyly, micrognathia, micropthalmia, cardiac defect, renal dysplasia, 'hitch-hiker' toe deformity and small thin placenta of normal consistency are detected [12, 13]. The recurrence rate is low.

Noonan Syndrome

Noonan syndrome is phenotypically similar to Turner syndrome, but with a normal karyotype and can affect both males and females. The incidence is 4 to 10 per 10,000 live births. It follows autosomal dominant inheritance and almost half of the cases are due to sporadic new mutations. Ultrasound findings include thickened nuchal translucency in the 1st trimester, cystic hygroma, right heart defects such as pulmonary stenosis, septal defects, hypertelorism, hemivertebra, pleural effusions, renal abnormalities, short stature, hydrops and polyhydramnios. Hydrops can lead to intrauterine death, but thoraco-amniotic shunts for pleural effusion result in a 57% survival rate [13]. Affected children have short stature and webbed neck. 25% have a mild degree of mental retardation. Life expectancy depends on the severity of the cardiac defects. The recurrence risk is 50% if there is an affected parent. A neonate with Noonan syndrome should trigger genetic screening of the family [14].

Fryn Syndrome

Fryn syndrome is characterized by dysmorphic facial features, diaphragmatic defects and limb hypoplasia. It occurs in 1 in 3,000-5,000 live births with a male to female ratio of 3:2. It is an autosomal recessive condition; however the exact gene involved is unknown. Ultrasound findings include diaphragmatic hernia, micrognathia, broad and flat nasal bridge, hypertelorism, cloudy corneas, cleft lip and palate, micropthalmia, cystic hygroma, ventriculomegaly, ACC, Dandy Walker malformation and polyhydramnios. Hypoplasia of distal limbs, phalanges and nails, as well as postaxial oligodactyly are seen. Cardiac findings include persistent truncus arteriosus, interrupted aortic arch and left isomerism [12, 13]. Majority of affected infants are stillborn or die in the neonatal period. Those who survive have severe mental and developmental retardation. There is a recurrence risk of 25%.

DiGeorge Syndrome (Shprintzen syndrome, Velocardiofacial syndrome)

DiGeorge syndrome is characterised by congenital cardiac outflow tract abnormalities, abnormal facies, hypocalcaemia and thymus aplasia. These findings in combination were described to be manifestations of 22q11 microdeletion. The incidence is 1 in 4,000 to 10,000 live births. This is genetically a microdeletion on chromosome 22q11 and follows autosomal dominant inheritance. It may be a new mutation (most cases), inherited from an affected parent or, rarely, an unbalanced translocation inherited from a parent with balanced translocation [15]. The ultrasound findings of the heart include aortic arch abnormalities, conotruncal abnormalities such as TOF, pulmonary atresia with VSD, DORV, truncus arteriosus and TGA. In the head, neck and thorax the findings are microcephaly, micrognathia, thickened nuchal translucency, isolated cleft palate, bifid uvula and thymus aplasia. Renal anomalies (uni or bilateral hydronephrosis), polyhydramnios and IUGR are also detected. The prognosis depends on the severity of the cardiac defects and absence or presence of T cell immunodeficiency of thymus hypoplasia [12]. Variable levels of mental retardation and learning disabilities are present. Seizures may occur due to hypocalcemia. The prognosis is guarded if

associated with hypoparathyroidism. The risk of recurrence is 50% if one parent is affected, and less than 1% for a de novo occurrence.

Achondroplasia

This is the most common skeletal dysplasia, and is characterized by rhizomelic limb shortening. It occurs in 0.5 to 1.5 per 10,000 births. This autosomal dominant condition is caused by mutation in the fibroblast growth factor receptor-3 (FGFR-3) located on the short arm of chromosome 4 [13]. In inherited homozygous cases it is a lethal condition, while if heterozygous it is non-lethal. In 80% to 90% of cases, it is thought to occur due to fresh mutation. Achondroplasia is correlated with advanced paternal age. In homozygous cases, ultrasound features are long bone shortening seen early in the 2nd trimester. The femoral length is below the 3rd percentile compared to the biparietal diameter, with progressive shortening. In heterozygous cases, shortening of femur becomes apparent later at 22-24weeks. Third trimester features are megalocephaly, frontal bossing, low nasal bridge, shortening of femur and humerus, trident hand (short fingers of similar lengths) and widening of the femoral proximal diaphysis–metaphysis angle [12, 13]. The prognosis for achondroplasia is normal intellectual development, but spinal problems may occur due to spinal stenosis, kyphosis and spinal cord compression [12].

Cornelia de Lange syndrome

Cornelia de Lange syndrome is characterised by facial and limb malformations, prenatal and postnatal growth restriction and developmental delay. The incidence is 1 in 10,000 live births and it is caused by mutations in the autosomal genes NIPBL, RAD21, and SMC3 or the X-linked genes HDAC8 and SMC1A [13]. Most cases are caused by de novo mutations in NIPBL. Among the ultrasound findings are early onset IUGR, brachycephaly, micrognathia, micromelia, ulnar dysplasia with abnormal contractures of upper limbs, syndactyly and oligodactyly. This condition results in severe growth failure, mental impairment and behavioural problems [12].

Tuberous Sclerosis

This is a syndrome characterised by hamartomatous lesions in multiple sites such as the brain, skin, heart and kidneys. It occurs in 0.3 to 1 in 10,000 live births. It follows autosomal dominant inheritance with a large proportion being sporadic new mutations. Defects occur on 2 genes; TSC1 (chromosome 9) producing the protein hamartin and TSC2 (chromosome 16) producing the protein tuberin. Among the ultrasound findings are cardiac rhabdomyoma causing rhythm disruptions (Wolff-Parkinson-White syndrome, supraventricular tachycardia, paroxysmal arrhythmias), obstructions and regurgitations - which may rarely lead to heart failure and hydrops. Brain lesions detected are periventricular and basal ganglia nodules. Others such as fibroangiomatous skin lesions, cystic bone changes and renal angiomyolipomas have not yet been reported on prenatal sonogram [12, 13]. Due to the highly variable presentation of the disease, the accurate prediction of outcome is difficult. Many affected individuals have seizures and mental retardation. Some develop brain tumours and most cardiac tumours regress after birth. Abnormalities in the kidneys, eyes and heart may require treatment [13].

Meckel-Gruber Syndrome

Meckel-Gruber syndrome is characterised by a triad of posterior encephalocele, postaxial polydactyly and dysplastic cystic kidneys. It occurs in 0.2 to 0.7 per 10,000 live births and is lethal. It is an autosomal recessive condition with high genetic heterogeneity. Ultrasound findings of the CNS include occipital encephalocele, ventriculomegaly, Arnold-Chiari malformation, Dandy Walker abnormalities, cerebellar hypoplasia and microcephaly. There may be cystic dysplastic kidneys, enlarged and hyperechogenic kidneys and postaxial polydactyly [12, 13]. The recurrence risk is 25%.

Thanatophoric dysplasia

The name originates from the Greek "*Thanatophoros*" meaning 'death bearing' – and is the commonest lethal skeletal dysplasia. It is characterized by bowed, short long bones, flat vertebral bodies, a narrow chest and a large head with a prominent forehead. It occurs in 0.24 to 0.69 per 10,000 births. It follows autosomal dominant inheritance and the majority of cases

are caused by new mutations in the FGFR3 gene. Ultrasound findings in Type I dysplasia are bowed 'telephone receiver' femurs, with no cloverleaf shaped skull. In Type II a cloverleaf shaped skull is seen along with short and straight long bones. Both types have narrow short ribs and chest, polyhydramnios in late second and third trimester, ACC, ventriculomegaly and hydronephrosis. It is lethal due to pulmonary hypoplasia [12].

Beckwith-Wiedemann Syndrome (BWS)

Beckwith-Wiedemann syndrome is characterised by the classical triad of macrosomia, omphalocele and macroglossia. It occurs at a rate of 1 in 14,000 live births. It is caused by genetic and epigenetic disturbances in the 11p15 imprinted region and in most cases there is no relevant family history. The presence of exomphalos without liver as a content and with normal karyotype clinches the diagnosis of BWS [13]. Visceromegaly is observed with echogenic and large kidneys, hepatomegaly and enlarged testes. Macroglossia and small groove earlobe crease are the facial features detected. There is macrosomia especially in 3rd trimester and polyhydramnios. Other findings are single umbilical artery, cardiac defects, diaphragmatic hernia and enlarged hydropic placenta. There is a risk of hypoglycaemia in the first few days of life, preterm delivery due to macrosomia and feeding and airway obstruction due to macroglossia. Intelligence is not affected. There is an increased risk of developing abdominal tumours such as Wilms tumour, hepatoblastoma, neuroblastoma and adrenal cortical carcinoma [12, 13]. Recurrence is very low (under 1%) in the majority of cases but can be up to 50% depending on the specific genetic aetiology.

Cri-du-chat syndrome

Cri du chat syndrome includes a characteristic high-pitched cat-like cry, dysmorphic features, as well as growth and developmental delays. There is a 1 in 15,000 to 1 in 50,000 incidence in live births. It is caused by a chromosome 5p deletions, which most commonly occurs de-novo. In 80-90% of cases, the mutations are paternal in origin, possibly arising from chromosome breakage during gamete formation in males - 10% to 15% are the result of an unbalanced parental translocation. Microcephaly, hypertelorism, micrognathia, nasal bone hypoplasia,

cerebellar abnormality, encephalocele, ventriculomegaly, thickened nuchal translucency, cystic hygroma, cardiac defects, cardiomegaly, hydrops and IUGR are the ultrasound features of this syndrome [16]. The recurrence risk is practically negligible if a de-novo defect, however in balanced translocations, the recurrence risk can be up to 18%.

Smith-Lemli-Optiz syndrome

This is the first known genetic syndrome with a metabolic etiology. It is characterised by limb, genitourinary, cardiac and CNS abnormalities. There are 2 types, with Type II being lethal despite both having similar features. It occurs in 0.25 - 0.5 per 10,000 births and involves an autosomal recessive defect affecting the cholesterol pathway - there is deficiency of 7-dehydrocholesterol reductase (DHCR7) resulting in accumulation of 7-dehydrocholesterol (7DHC). Type I may have some residual activity of DHCR7, thus being less severe in nature. Prenatal diagnosis via CVS or amniocentesis shows elevated levels of 7DHC, which is usually undetectable [13]. Ultrasound findings are microcephaly, ACC, hydrocephalus, heart defects (VSD, ASD), syndactyly of second and third toes, postaxial polydactyly, clenched hands, valgus deformity of feet, genital abnormalities such as hypospadias, cryptorchidism, and ambiguous genitalia [12, 13]. Neonatal death occurs in severe forms of the syndrome. Survivors have failure to thrive, mental deficiency and behavioural problems.

Fraser syndrome

Fraser syndrome is a rare genetic syndrome with abnormalities occurring in the head, lungs, kidneys and limbs. The incidence is 0.04 per 10,000 live births and 1 per 10,000 stillbirths. It is an autosomal recessive condition with about 50% of the cases caused by mutations in the FRAS1 gene on chromosome 4q21. Ultrasound findings of the head include cryptophthalmos, microcephaly, hydrocephalus, neural tube defects, facial cleft, hypertelorism, nose and ear abnormalities. The lungs are enlarged and hyperechogenic (due to tracheal or laryngeal atresia). Other findings include renal agenesis, ambigious genitalia, syndactyly, ascites, umbilical hernia and oligohydramnios [12, 13]. This condition is lethal if laryngeal atresia and renal agenesis are present. It has a recurrence risk of 25%.

X-linked Hydrocephalus syndrome (L1 syndrome)

Also known as X-linked aqueductal stenosis, this condition is described by the acronym MASA (mental retardation, adducted thumbs, shuffling gait and aphasia). The incidence is 1 in 25,000 to 60,000 males. It is an X-linked recessive disorder with mutation of the L1CAM gene [15]. Ultrasound findings include ventriculomegaly of lateral ventricles with normal 4th ventricle, ACC, macrocephaly and adducted thumbs. Intellectual impairment, seizures, speech problems, and spasticity of lower limbs are variable, depending on the severity of the hydrocephalus [12]. The recurrence rate is 50% for a male offspring.

Ellis-van Creveld syndrome (Chondroectodermal dysplasia)

This is a rare autosomal recessive condition with high preponderance among the Amish community characterised by disproportionate short extremities, polydactyly and cardiac defects. The incidence is 1 in 60,000 births in the general population and 5 in 1,000 births among the Amish population. It is caused by mutations of genes EVC1 and EVC2 on chromosome 4 (4p16). The ultrasound findings are short long bones, narrow thorax with short ribs, postaxial polydactyly, cardiac defects (ASD, VSD, AVSD) and thickened NT [12, 13]. Up to half of affected infants die in the neonatal period due to pulmonary complications. Survivors have normal intelligence but short stature [13].

Holt-Oram Syndrome

Holt-Oram syndrome is characterised by congenital heart disease and upper limb skeletal anomalies. The inheritance of this condition is autosomal dominant with 100% penetrance for upper limb malformations. Mutations occurs in TBX5 and TBX3 genes on chromosome 12q24 [13]. Ultrasound findings include ASD, VSD, PDA, endocardial cushion defect, hypoplastic left ventricle and conduction defects of the heart. There is also radial aplasia resulting in triphalangeal thumb or club hand, absent thumb, phocomelia of upper limb and syndactyly [12, 13]. Cardiac and/or orthopaedic surgical corrections may be required in cases of this syndrome.

The recurrence risk is 50% if there is an affected parent but most cases are caused by de novo mutations [13].

Apert syndrome

Apert syndrome, also known as acrocephalosyndactyly, is a developmental deformity characterized by craniofacial and limb malformations accompanied by variable mental retardation in 50% of the cases. It is a rare condition occurring in 1 in 70,000 to 100,000 live births. It is an autosomal dominant disorder, though most cases are a result of de novo mutation. There is correlation with advanced paternal age and mutations occur in the FGFR2 gene [15]. Ultrasound features in the cranium include brachycephaly, acrocephaly, frontal bossing and hypertelorism due to craniosynostosis of the coronal suture. ACC and ventriculomegaly are detected in the brain. Other findings include VSD, pulmonary stenosis, overriding aorta, hydronephrosis, cystic renal dysplasia, cryptorchidism and polyhydramnios due to decreased fetal swallowing [12, 13]. Apert's results in varying degrees of mental retardation, though some with this condition may have normal intelligence. Early decompression of the craniosynostosis will be required. Respiratory problems due to high airways obstruction needing tracheostomy, and difficulty in using hands are the other problems encountered. The recurrence risk is 50% unless due to a de novo mutation.

Asphyxiating Thoracic Dysplasia (Jeune Syndrome)

Jeune syndrome is a skeletal dysplasia characterised by a small thorax, varying degrees of rhizomelic brachymelia, polydactyly, pelvic abnormalities and renal anomalies. The incidence is 1 in 100,000 to 130,000 live births. It is a genetically heterogeneous autosomal recessive condition with many cases being caused by mutations in the IFT80 (3q25) and DYNC2H1 (11q21) genes. Ultrasound findings show a very narrow chest in both AP diameter and width, with short horizontal ribs, short long bones and polydactyly [12]. A family history of previously affected pregnancy is helpful in diagnosis. It is usually a lethal condition due to respiratory failure at birth. However, there have been reports of survivors who possibly have a milder form of the disease.

Walker-Warburg syndrome / Lissencephaly type II

Walker-Warburg syndrome is characterised by severe ocular (cataracts, retinal detachments, micro-ophthalmia) and central nervous system (lissencephaly, hydrocephalus) anomalies. The acronym associated with this condition is HARDE, which stands for hydrocephalus, agyria, retinal dysplasia and encephalocele [12]. The incidence rate is not known. It is a genetically heterogeneous autosomal recessive condition. Ultrasound findings include agyria or lissencephaly, ventriculomegaly, occipital encephalocele, Dandy Walker malformation, microcephaly, ACC, micropthalmia, cataracts, cleft lip and genital anomalies [12, 13]. Death usually occurs within 1st year of life. There is a 25% chance of recurrence [12].

Camptomelic dysplasia

This is a congenital disorder, which is usually lethal, characterised by shortening and abnormal curvature of long bones, especially the lower extremities. The incidence is 0.2 per 100,000 live births with a male to female ratio of 2:1. Inheritance is autosomal dominant with most cases being caused by de novo mutations in the SOX9 gene on 17q24. Sex reversal can occur in genotypic male fetuses that lack the H-Y antigen, which give the phenotypic sex ratio of male to female as 1:2.3 [13]. Ultrasound reveals hypoplastic scapula and fibula and severe bowing of the femur and tibia, which may mimic fractures. Other findings include narrow and bell shaped chest, hypoplasia of midthoracic vertebral bodies, scoliosis, short limbs, talipes equinovarus, a flat and small face, low nasal bridge, hypertelorism, micrognathia, cleft palate, high forehead with prominent occiput, large biparietal diameter, ventriculomegaly and ambiguous genitalia in males. Cardiac defects and renal anomalies such as large kidneys, hydronephrosis, IUGR and polyhydramnios are also seen [12, 13]. Most affected infants die due to respiratory complications during the neonatal period or in the first year of life [12].

Short Rib-Polydactyly Syndrome

This is a heterogeneous group of autosomal recessive disorders. Ultrasound findings include short ribs, severe micromelia, narrow and constricted thorax, protuberant abdomen,

polydactyly, cystic kidneys, brain anomalies, facial clefts and genital anomalies. It is a lethal condition with a recurrence risk of 25% [13].

Pallister-Killian syndrome (tetrasomy 12p)

This is a rare polymalformative complex syndrome with tissue specific distribution of the mosaic 12p, which is found in skin fibroblast but not in peripheral blood [12]. It is rare, and more commonly seen in offspring of women of advanced age. Genetically it is a tetrasomy 12p. Ultrasound findings are diaphragmatic hernia, rhizomelic limb shortening, hypertelorism, prefrontal edema, syndactyly, clinodactyly, cardiac abnormalities, hydrops and urogenital abnormalities [12]. The prognosis is poor with severe mental retardation. There is a low risk of recurrence.

Klippel-Trenaunay-Weber Syndrome

This rare syndrome is characterised by multiple hemangiomas and unilateral limb hypertrophy due to bony and soft tissue overgrowth caused by a defect in the VG5Q gene on chromosome 5q or p11. It is almost always sporadic and is caused by somatic mutations in the PIK3CA gene on 3q26 [13]. Ultrasound findings include multiple cutaneous hemangiomas such as abnormal cutaneous contours and diffuse microcystic changes of the subcutaneous tissue with some calcification. Cardiac decompenstation may occur if the hemangiomas are multiple and large, leading to high output failure. Usually, these lesions regress in size with time. If detected prenatally, the disease is more severe and prognosis poor if associated with cardiac failure [13]. Outcome would depend on the size and site of the hemagiomas, as cerebral hemangiomas may cause brain atrophy and seizures. Recurrence is rare in sporadic cases.

SUMMARY

Modern advancements in technology, research and scanning techniques have led to accurate and earlier detection of genetic anomalies in the fetus. It is crucial to undertake a structured and stepwise evaluation of the genetic markers of various organ systems. This would help to link the markers with the associated syndrome and come to a plausible diagnosis. As not all

genetic syndromes are amenable to diagnosis prenatally, neither are all ultrasound markers related to genetic syndromes. It is prudent to involve the geneticist, neonatologist, paediatric cardiologist, radiologist, paediatric surgeons, specialist midwife and nurse when dealing with a fetus with a possible genetic syndrome.

CONFLICT OF INTERSTS

The authors have no conflicts of interests to declare.

PRACTICE POINTS

- Recent advances have made it possible for certain syndromes to be detected by ultrasound scan in the 1st trimester.
- In the presence of multiple structural anomalies, it is important to look for a correlation to a particular genetic syndrome.
- Invasive diagnostic testing should be considered in the presence of multiple anomalies.
- A marker seen in isolation is unlikely to be of significance.
- Further imaging such as MRI complements the ultrasound scan to confirm a suspected diagnosis especially CNS lesions.

RESEARCH AGENDA

- The feasibility of cell free DNA testing in genetic syndromes other than the main trisomies.
- Value of incorporating an additional scan in early 3rd trimester as certain syndromes present late.

REFERENCES

[1] Rashmi Rao, Lawrence D. Platt, Ultrasound screening: Status of markers and efficacy of screening for structural abnormalities, Seminars in Perinatology 40 (2016) 67-78.

[2] Brankica Vasiljevic, Miroslava Gojnic and Svjetlana Maglajlic-Djukic. Ultrasound Diagnosis of Congenital Brain Anomalies. In: Dr. Alastair Sutcliffe editor. Congenital Anomalies - Case Studies and Mechanisms, 2012 ISBN:978-953-51-0075-1, InTech.

[3] O.B. Petersen, A. David, L. Thomasson, L.S. Chitty, OC240: Abnormal fetal head shape: etiology and management, Ultrasound in Obstetrics and Gynecology 2007; 30: 441.

[4] S. Delahaye, J.P. Bernard, D. R'enier, Y. Ville, Prenatal ultrasound diagnosis of fetal craniosynostosis, Ultrasound in Obstetrics and Gynecology 2003; 21: 347-353.

[5] J.C. Gillham, S. Anand, P.J. Bullen, Antenatal detection of cleft lip with or without cleft palate: incidence of associated chromosomal and structural anomalies, Ultrasound in Obstetrics and Gynecology 2009; 34: 410-415.

[6] D. Paladini, Fetal micrognathia: almost always an ominous finding, Ultrasound in Obstetrics and Gynecology 2010; 35: 377-384.

[7] Deepa R. Biyyam, Teresa Chapman, Mark R. Ferguson, Gail Deutsch, Manjiri K. Dighe, Congenital Lung Abnormalities: Embryologic Features, Prenatal Diagnosis, and Postnatal Radiologic-Pathologic Correlation, RadioGraphics 2010; 30:1721–1738.

[8] Mary Ella Pierpont, MD, PhD, Chair; Craig T. Basson, MD, PhD, FAHA; D. Woodrow Benson, Jr, MD, PhD, FAHA et al, Genetic Basis for Congenital Heart Defects: Current Knowledge A Scientific Statement From the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young Endorsed by the American Academy of Pediatrics, Circulation 2007; 115: 3015-3038.

[9] Federico Prefumo, Claudia Izzi, Fetal abdominal wall defects, Best Practice & Research Clinical Obstetrics and Gynaecology 28 (2014) 391–402.

[10] Tiran Dias, Shanthi Sairam, Shanya Kumarasiri, Ultrasound diagnosis of fetal renal abnormalities, Best Practice & Research Clinical Obstetrics and Gynaecology 28 (2014) 403–415.

[11] Santina Ermito, Angela Dinatale, Sabina Carrara, Alessandro Cavaliere, Laura Imbruglia, Stefania Recupero, Prenatal diagnosis of limb abnormalities: role of fetal ultrasonography, Journal of Prenatal Medicine 2009; 3 (2): 18-22.

[12] BR Benacerraf. Ultrasound of Fetal Syndromes. 2nd ed. Philadelphia: Churchill Livingstone Elsevier; 2008.

[13] PW Callen. Ultrasonography in Obstetrics and Gynecology. 5th ed. Philadelphia: Saunders Elsevier; 2008.

[14] Shayna N. Conner, Ryan E. Longman, Alison G. Cahill, The role of ultrasound in the diagnosis of fetal genetic syndromes, / Best Practice & Research Clinical Obstetrics and Gynaecology 28 (2014) 417–428.

[15] Genetics Home Reference, U.S. National Library of Medicine (https://ghr.nlm.nih.gov/)

[16] DW Bianchi, TM Crombleholme, ME D'Alton, FD Malone. Fetology Diagnosis & Management of the Fetal Patient. 2nd ed. New York: McGraw-Hill Medical; 2010

MULTIPLE CHOICE QUESTIONS

Question 1

The following statements are true regarding ultrasound markers:

(a) Ventriculomegaly is caused by obstruction at the cerebrospinal (CSF) fluid pathway, central nervous system (CNS) malformations, brain destruction or overproduction of CSF.

(b) Unilateral ventriculomegaly is typical of CNS malformations.

(c) The main differentiating feature between congenital pulmonary airway malformation (CPAM) and brochopulmonary sequestration (BPS) is that all CPAM have a systemic vascular supply.

(d) 80% of congenital diaphragmatic hernia (CDH) occurs on the right side.

(e) There is unlikely to be karyotype abnormality in cases with isolated cleft lip and palate.

Answers to question 1

(a) T (b) F (c) F (d) F (e) T

Explanation to the answers in question 1

(a) The ventricles of the brain are cavities filled with CSF fluid. These ventricles become enlarged when there is an obstruction to the flow of the CSF fluid. Non obstructive causes

include congenital CNS malformation, where there is failure of normal development of the brain. Brain destruction by congenital infection (CMV, toxoplasmosis), vascular malformation or mechanical insult are other etiologies. Overproduction of the CSF in conditions such as choroid plexus papilloma is another non obstructive cause of ventriculomegaly.

(b) Unilateral ventriculomegaly is typically physiological. Pathological cases occur from brain destruction due to congenital infections, vascular or mechanical insult.

(c) CPAM typically derive their blood supply from the pulmonary artery and drains via the pulmonary veins, with the exception of hybrid lesions, which have systemic blood supply.

(d) CDH occurs more commonly on the left side probably due to the earlier closure of the right pleuroperitoneal canal.

(e) There risk of karyotype abnormality in isolated cleft lip and palate is extremely low, but midline cleft is invariably associated with karyotype abnormalitie

Question 2

These statements are true regarding fetal ultrasound findings except:

(a) Exomphalos occurs due to failure of the herniated bowel to return to the abdominal cavity by 14 weeks gestation.

(b) Gastrochisis is associated with chromosomal abnormality.

(c) Bilateral renal agenesis is a lethal condition and death occurs primarily from pulmonary hypoplasia.

(d) Achondroplasia can be detected in the 1st trimester scan.

(e) Congenital talipes equinovarus (CTEV) is abnormality in the development of the foot.

Answers to the question 2

(a) F (b) F (c) T (d) F (e) F

Explanation to the answers in question 2

(a) The physiological gut herniation occurs up to 12 weeks of gestation after which, this would represent an anterior abdominal wall defect or exomphalos.

(b) Gastrochisis is not associated with chromosomal abnormality but 60% of exomphalos is associated with trisomy 18.

(c) In bilateral renal agenesis the absence in fetal urine production leads to oligo or anhydramnios which results in pulmonary hypoplasia.
(d) Achondroplasia is a late development which is not amenable to detection by scan in the 1st trimester but only in late 2nd or early 3rd trimester.
(e) CTEV is an abnormality of the ankle joint (subluxation of the talo-calcaneo-navicular joint) which occurs secondary to a neurolgical deficit resulting in underdevelopment and weakness of the muscles on the lateral side of the calf or from intrauterine crowding.

Question 3

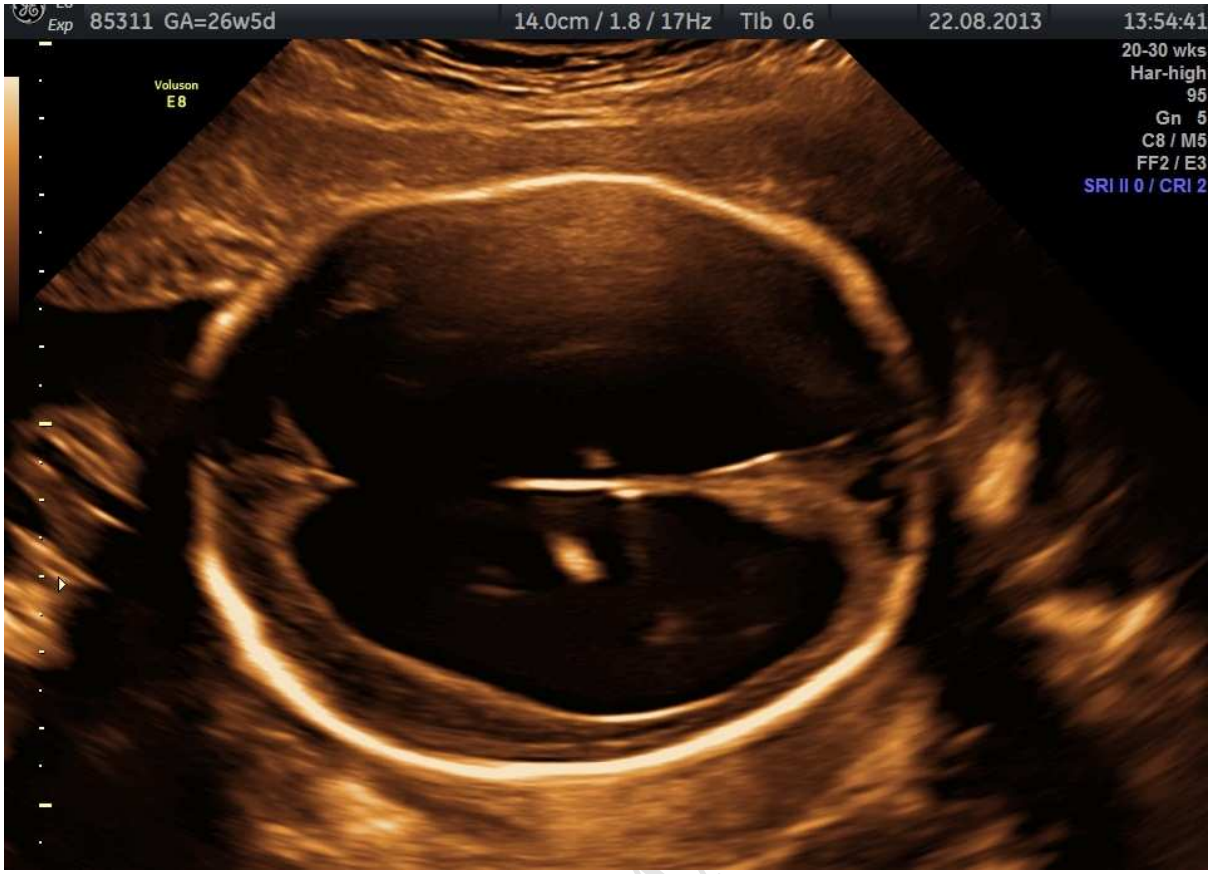
These following genetic syndromes are correctly linked with the prenatal ultrasound features:
(a) Edward syndrome – strawberry shaped head, exomphalos, clenched hands, cardiac defects, rocker bottom feet, intrauterine growth restriction and polyhydramnios.
(b) DiGeorge syndrome – conotruncal cardiac defects, thymus aplasia, cleft palate.
(c) Beckwith-Weidemann syndrome – clover leaf shaped skull, short long bones, narrow thorax and short ribs, polyhydramnios.
(d) Turner syndrome – cystic hygroma, nuchal edema, hypoplastic left heart, coarctation of aorta, short femur, non immune hydrops fetalis.
(e) Meckel Gruber syndrome – severe early onset IUGR affecting skeleton more than the head, small thin placenta.

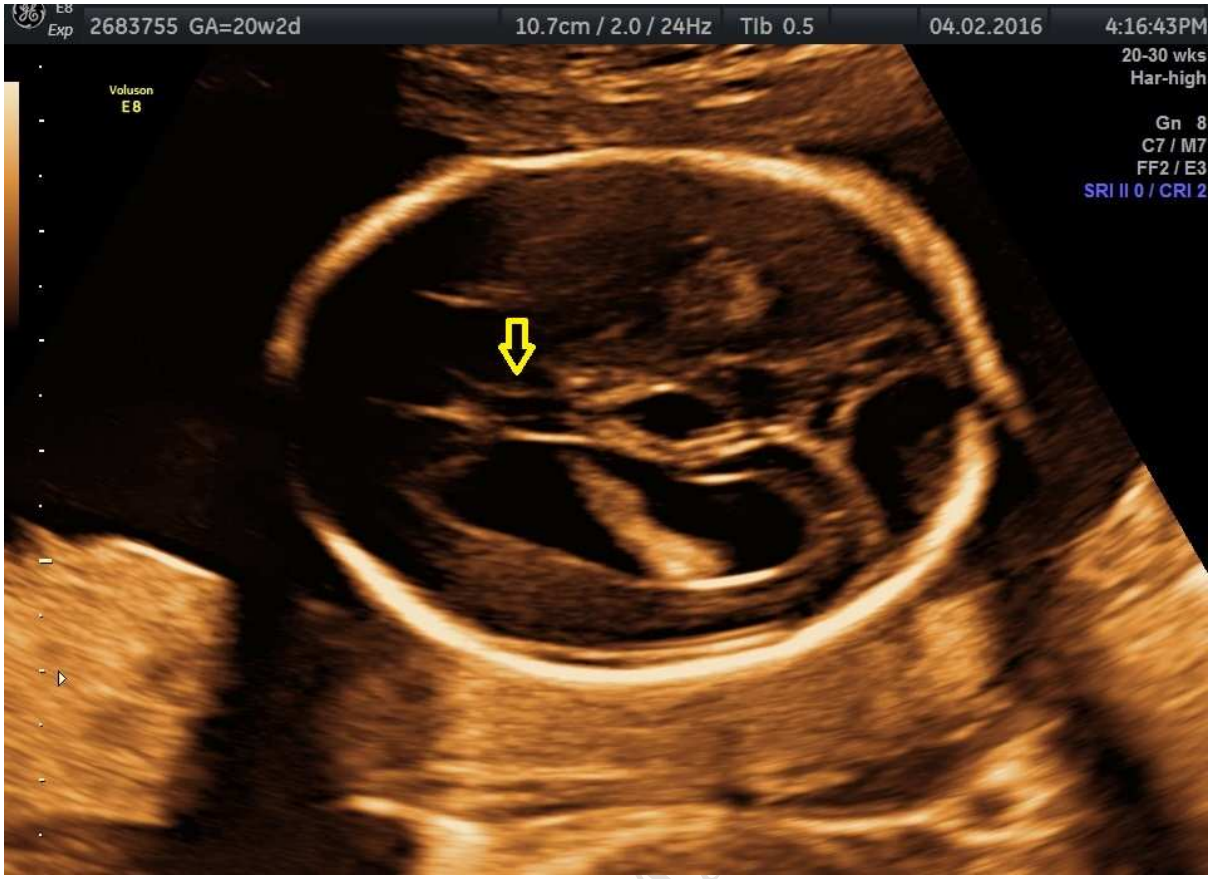
Answers to question 3

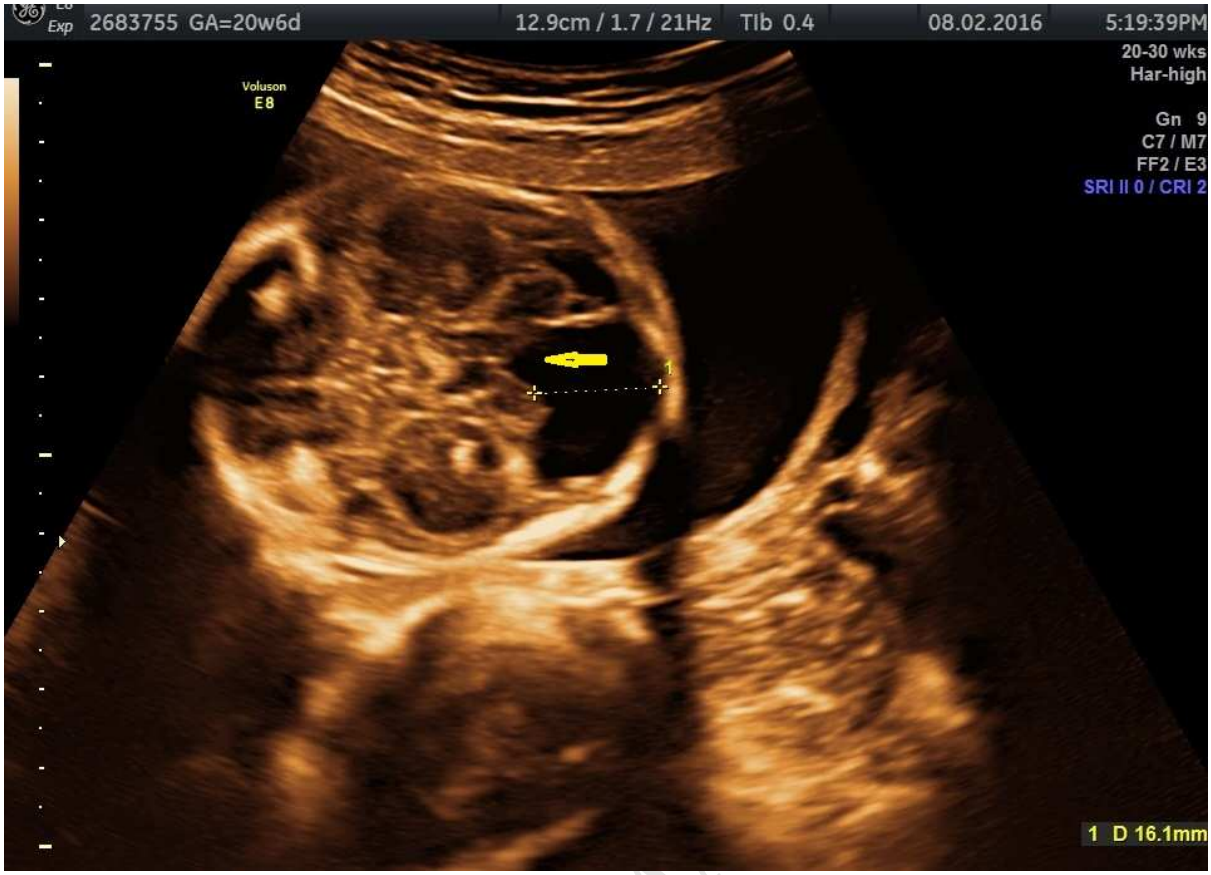
(a) T (b) T (c) F (d) T (e) F

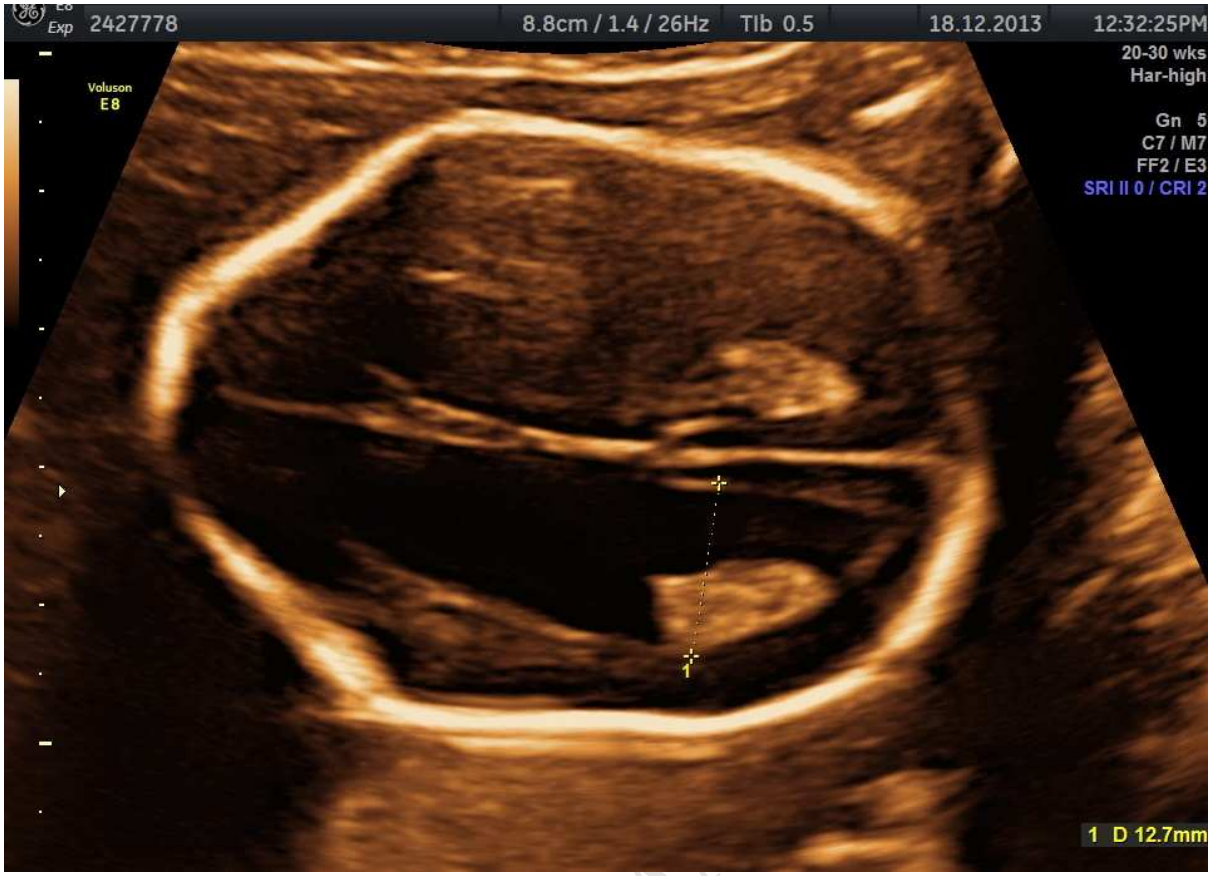
Explanation to the answers to question 3

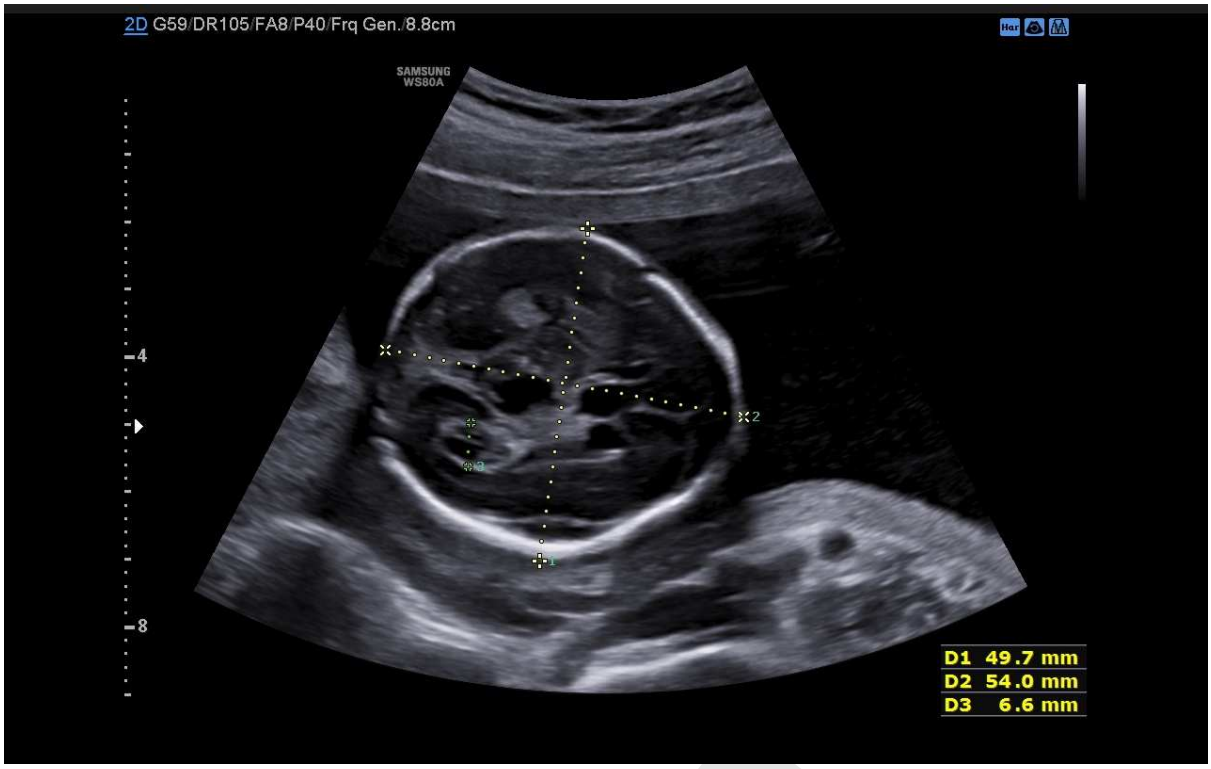
(c) Beckwith-Weidemann syndrome is characterised by triad of macrosomia, macroglossia and exomphalos. The stem answer in the question are features of thanatophoric skeletal dysplasia.
(e) Meckel Gruber syndrome presents with occipital encephalocele, multicyctic dysplastic kidneys and postaxial polydactyly. The stem answer in the question are features of triploidy of maternal origin.

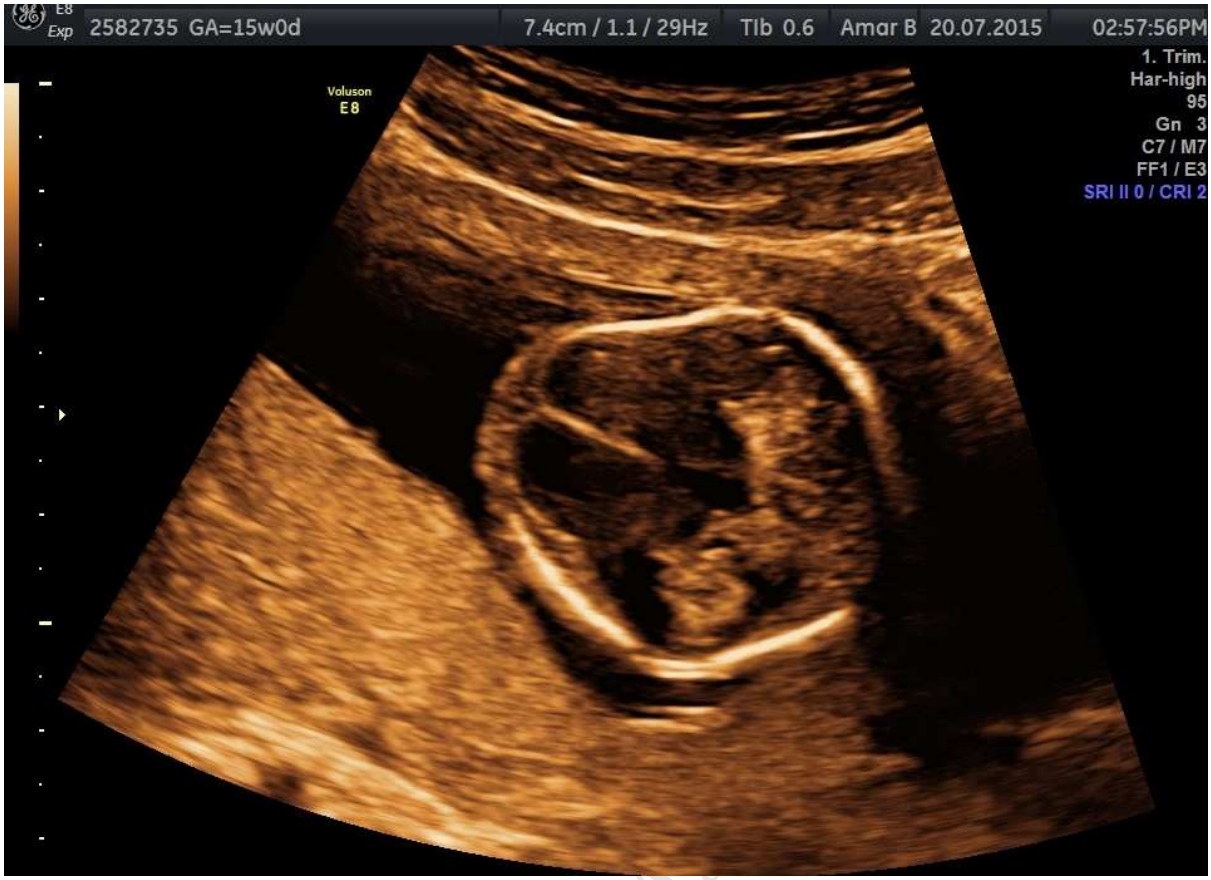


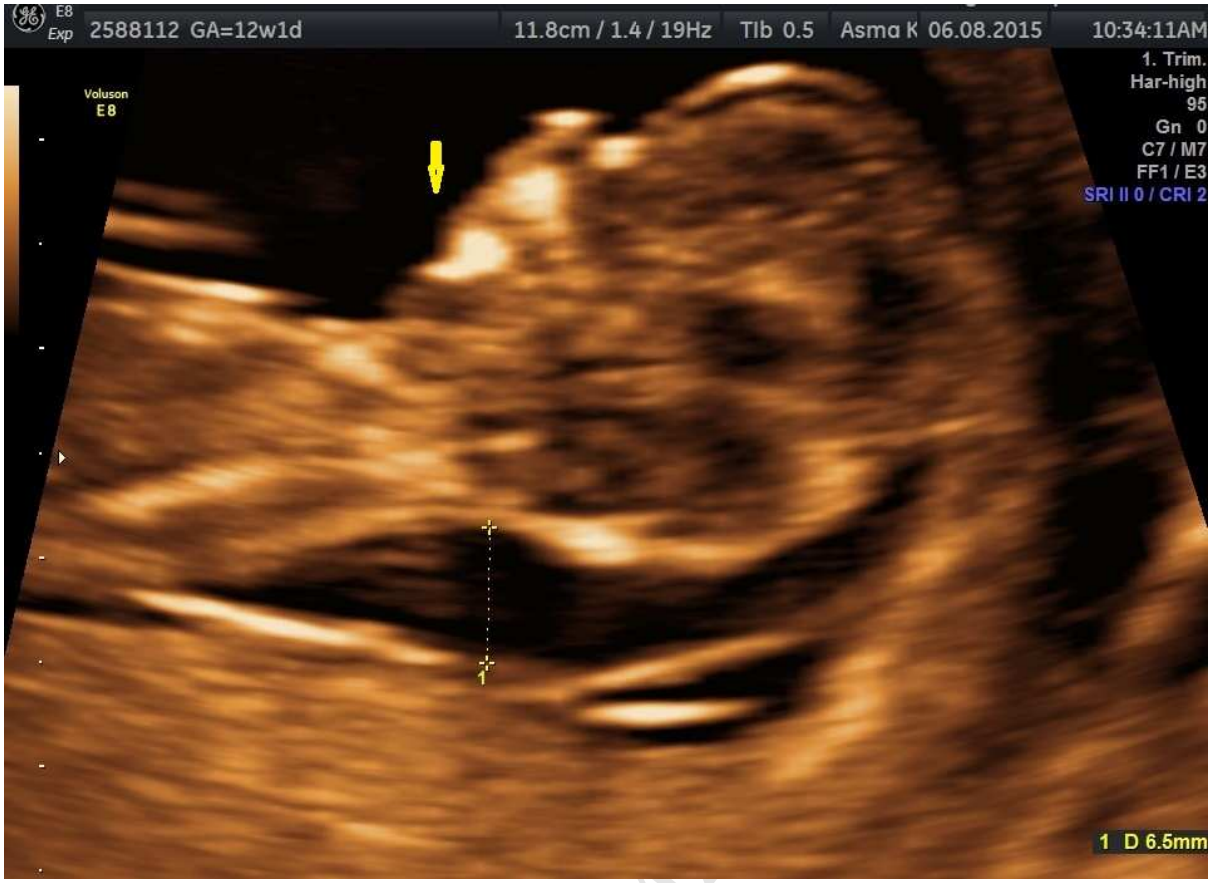


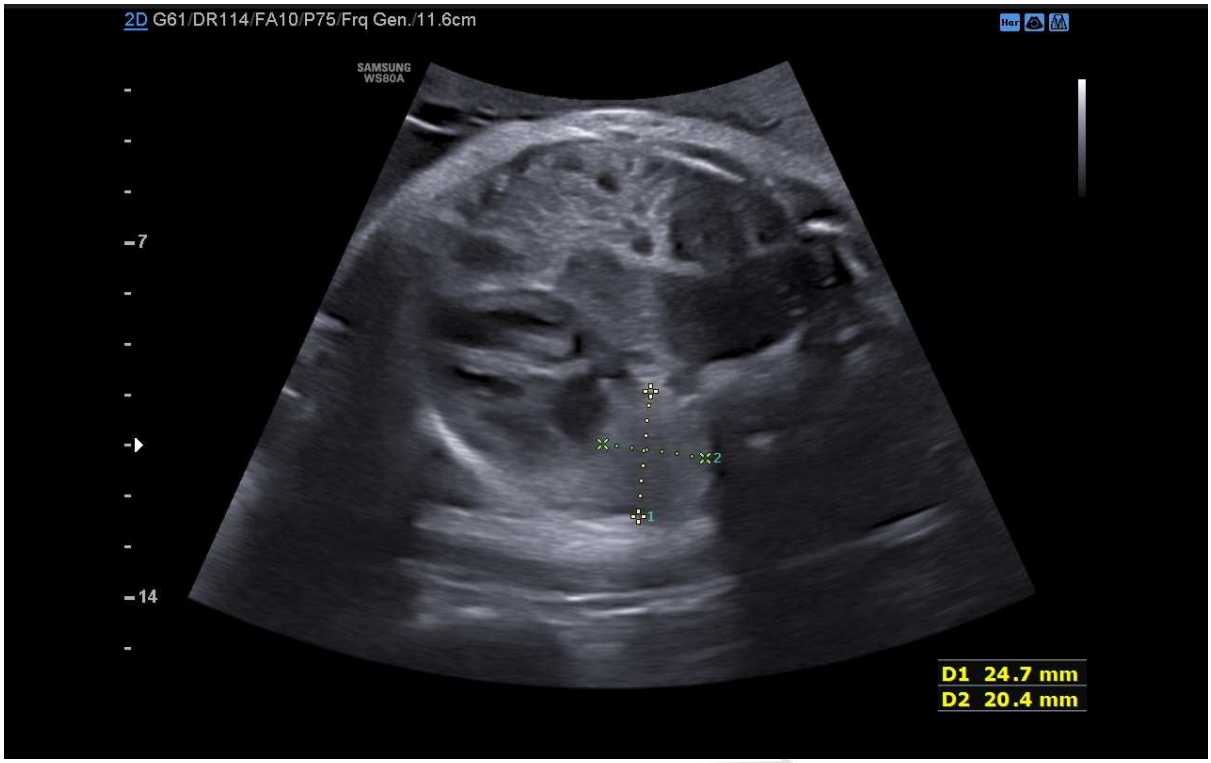


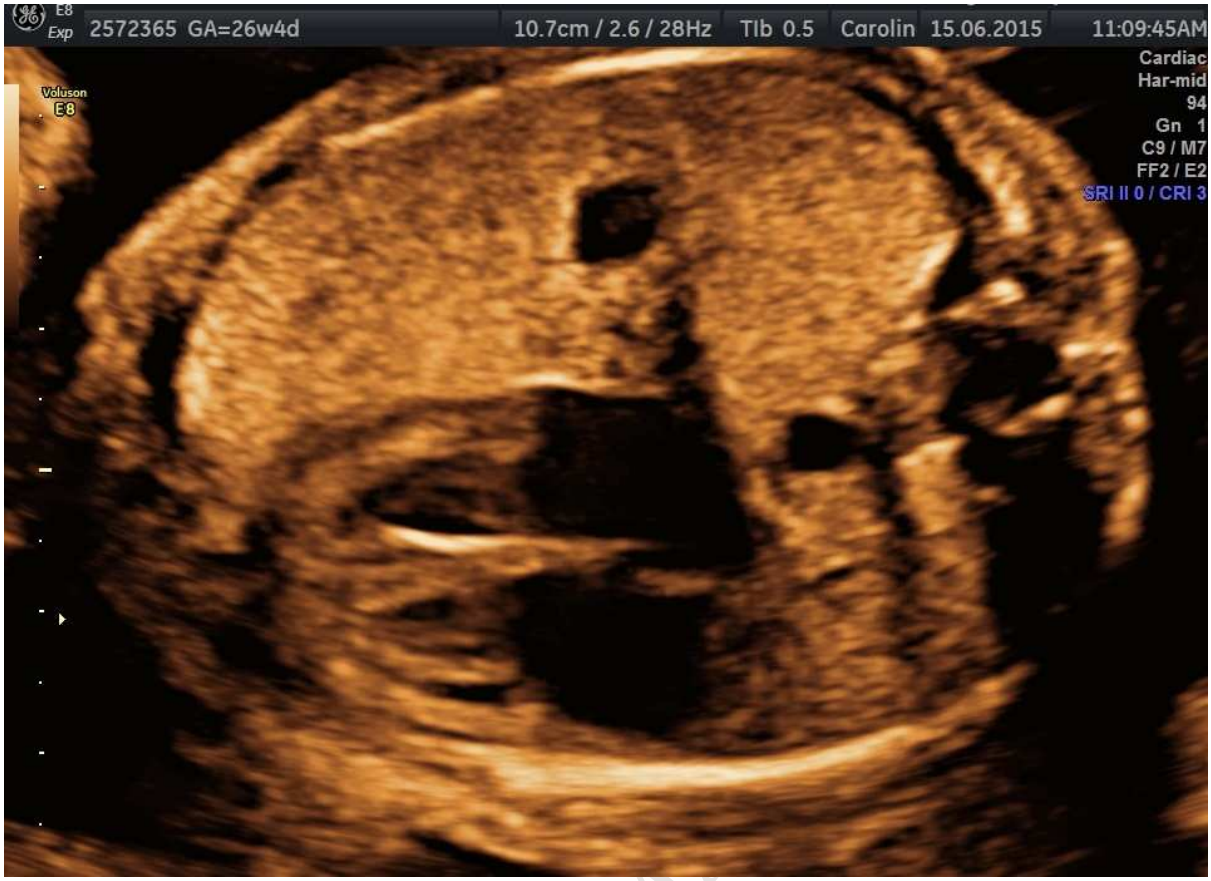


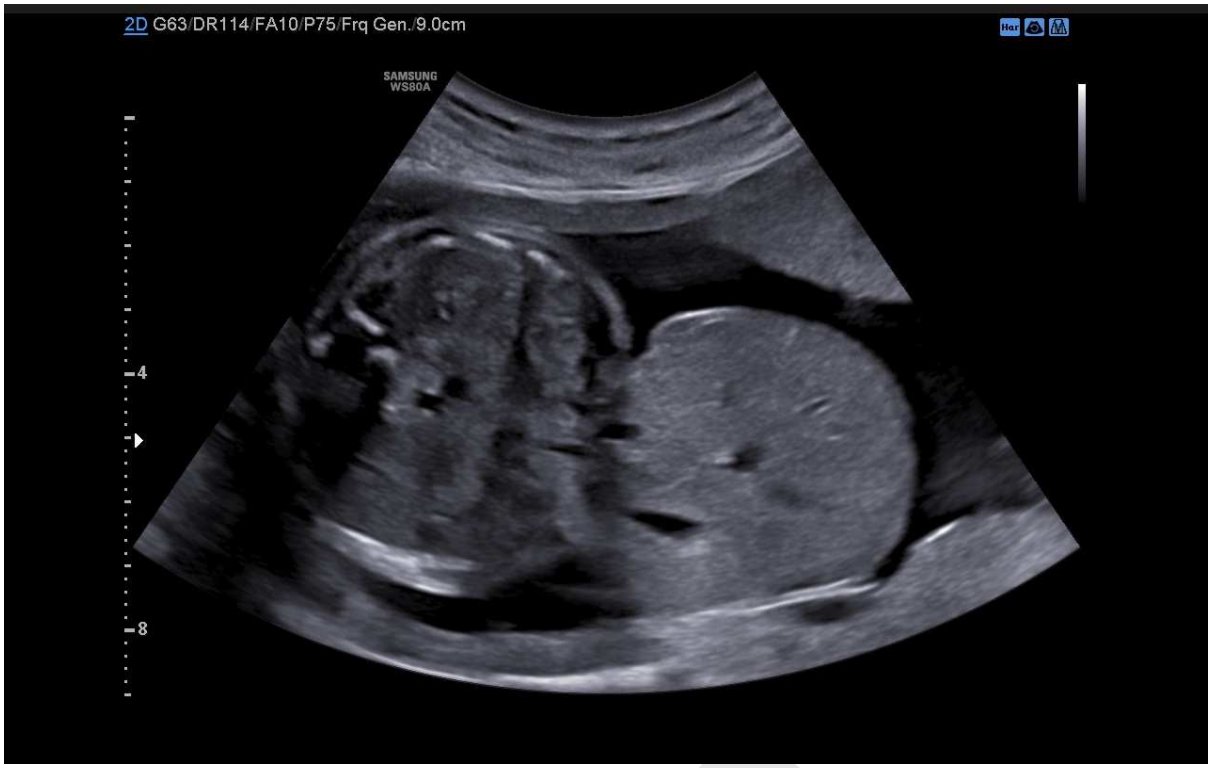


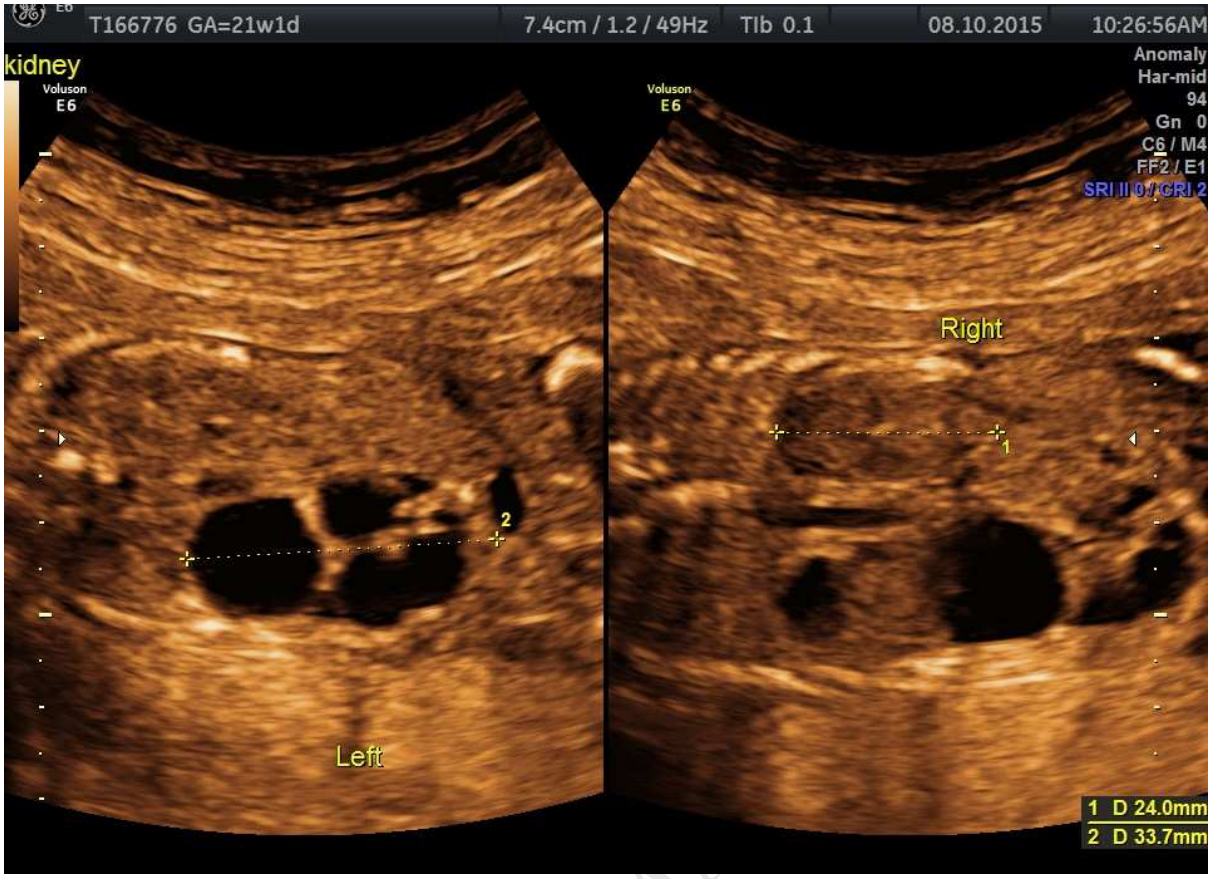


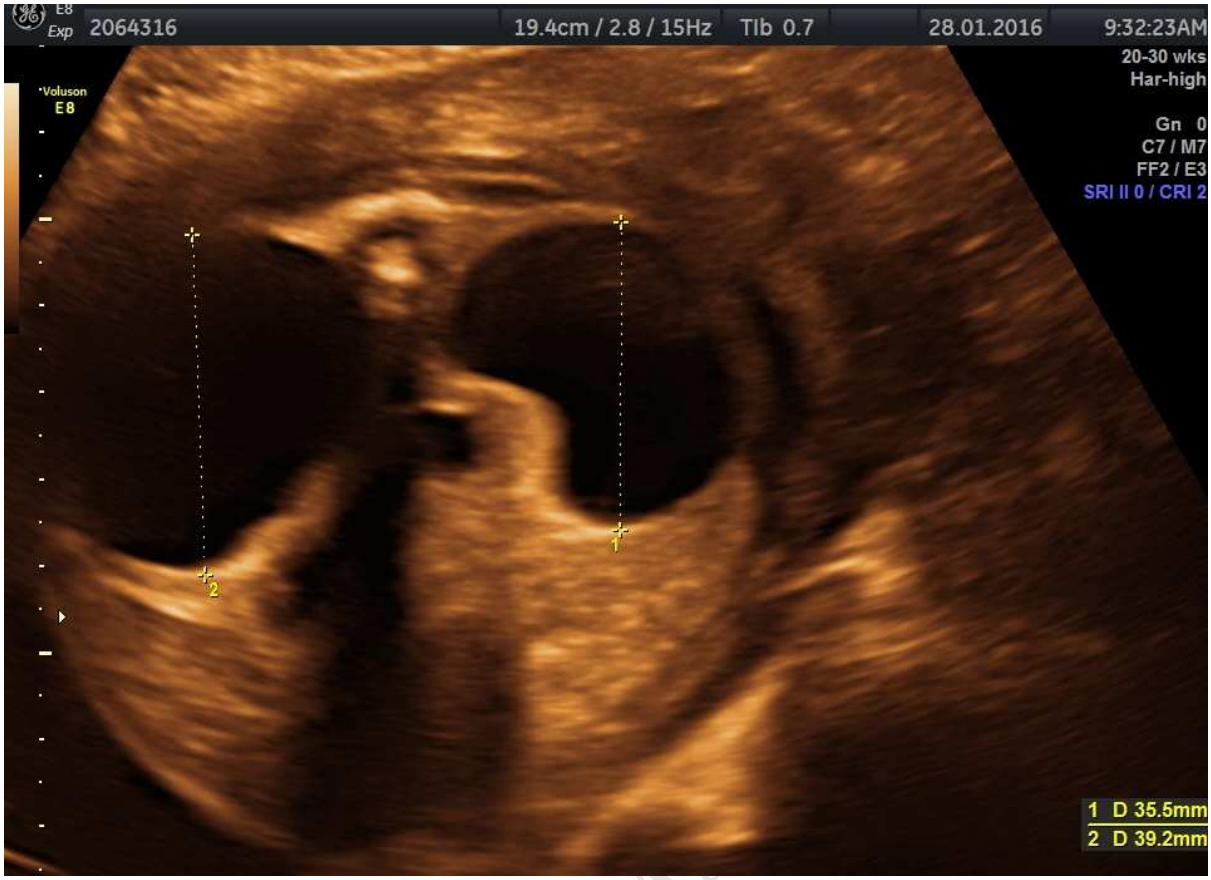


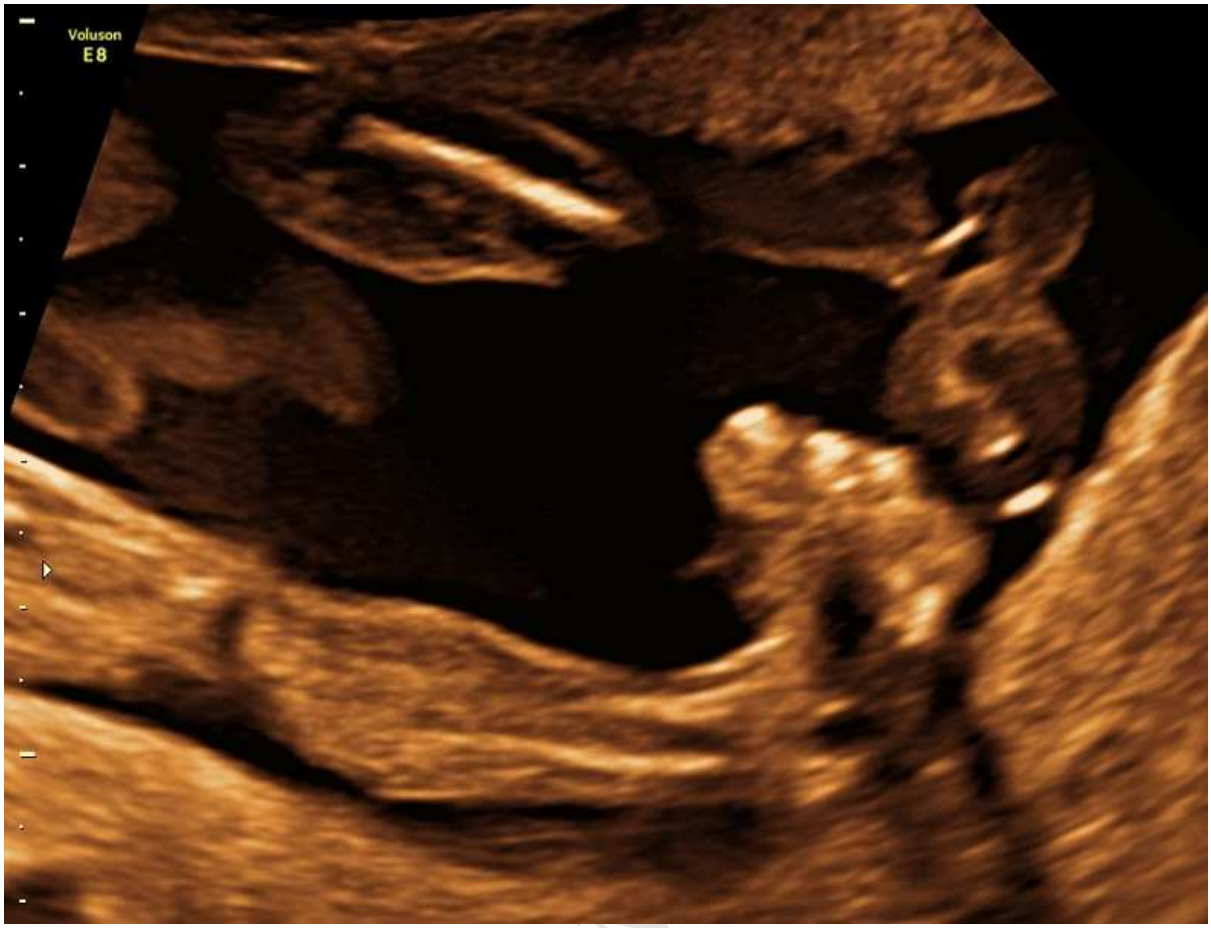


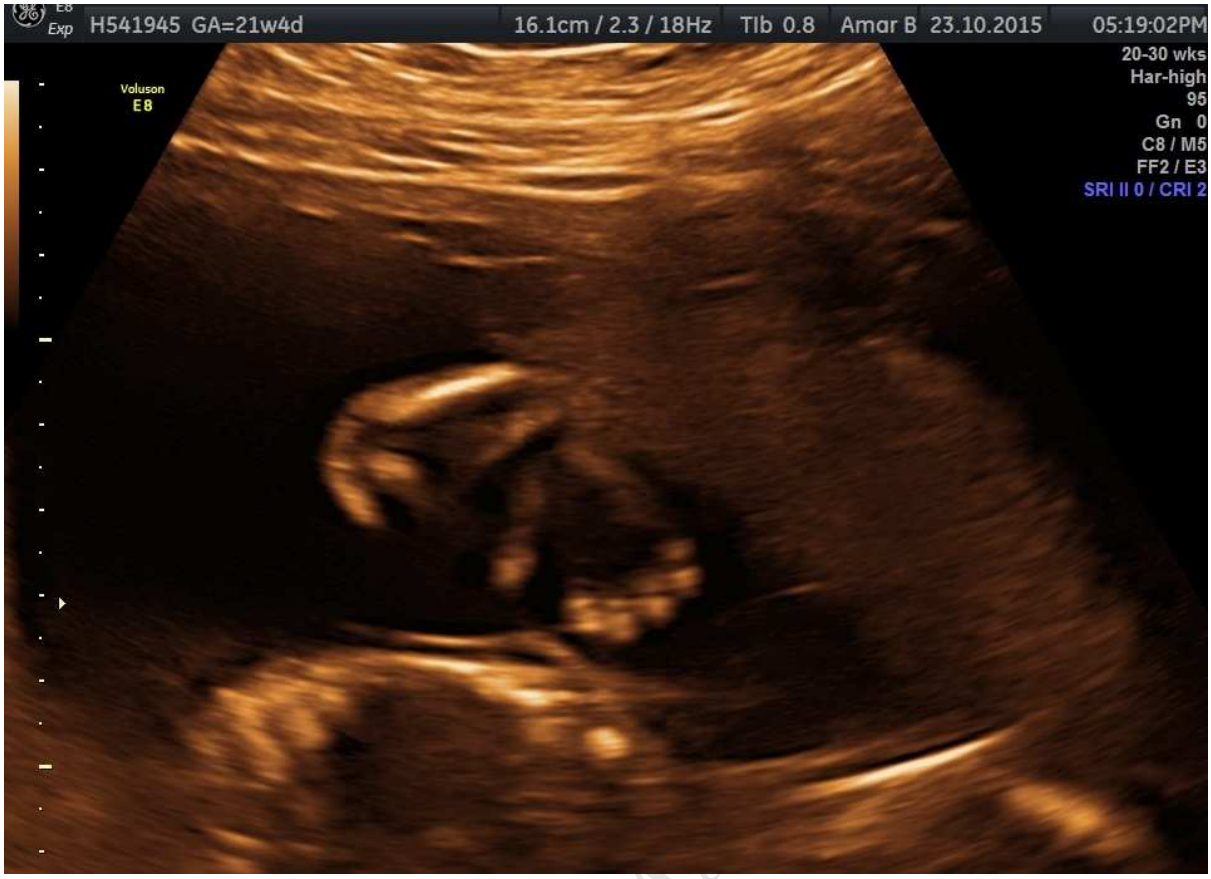


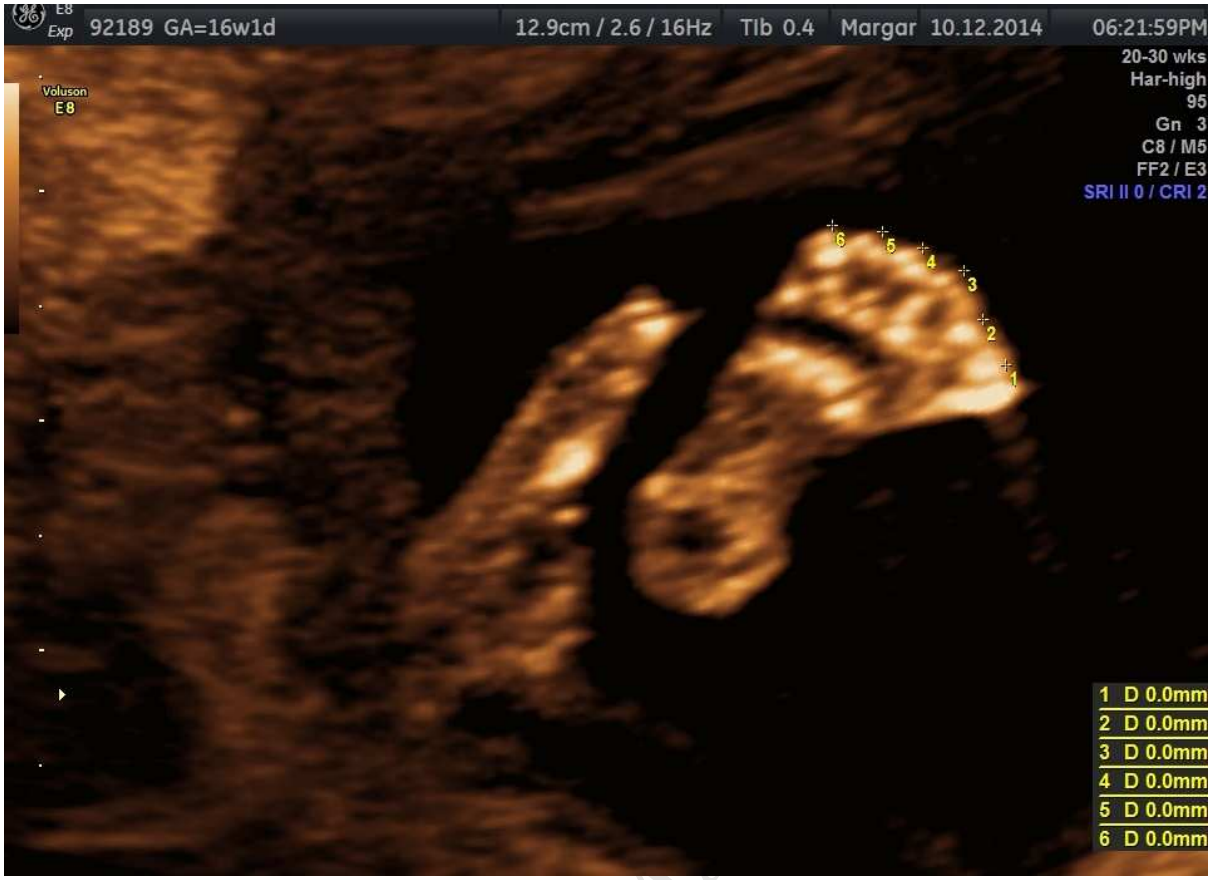


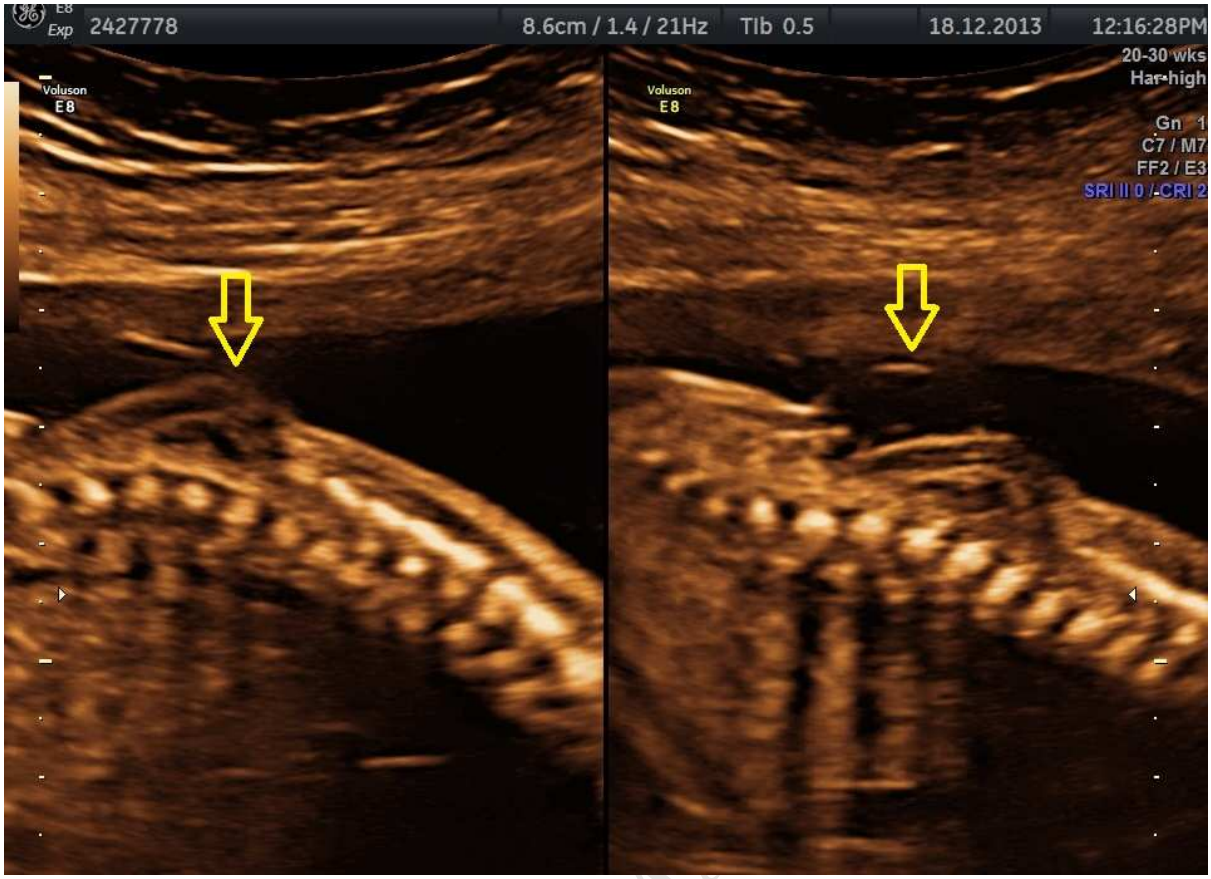


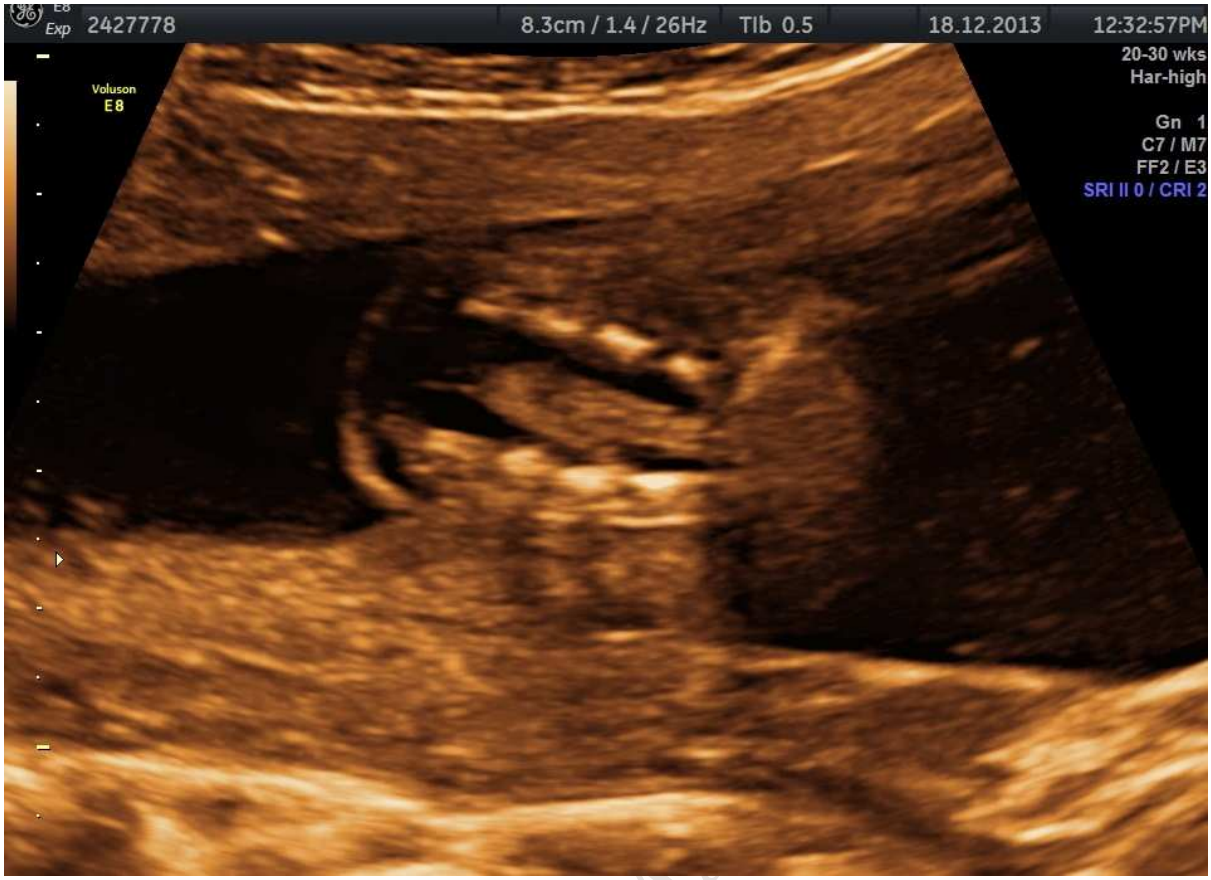


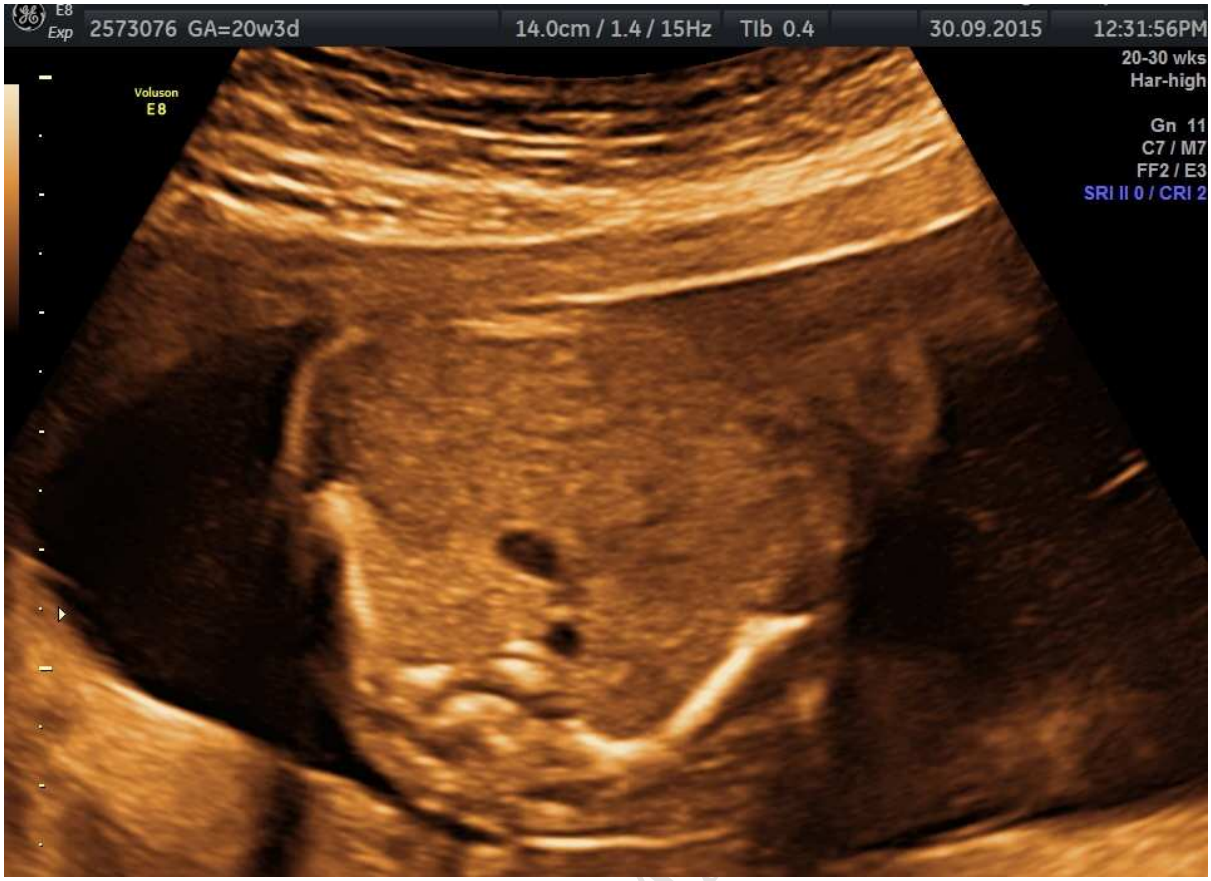


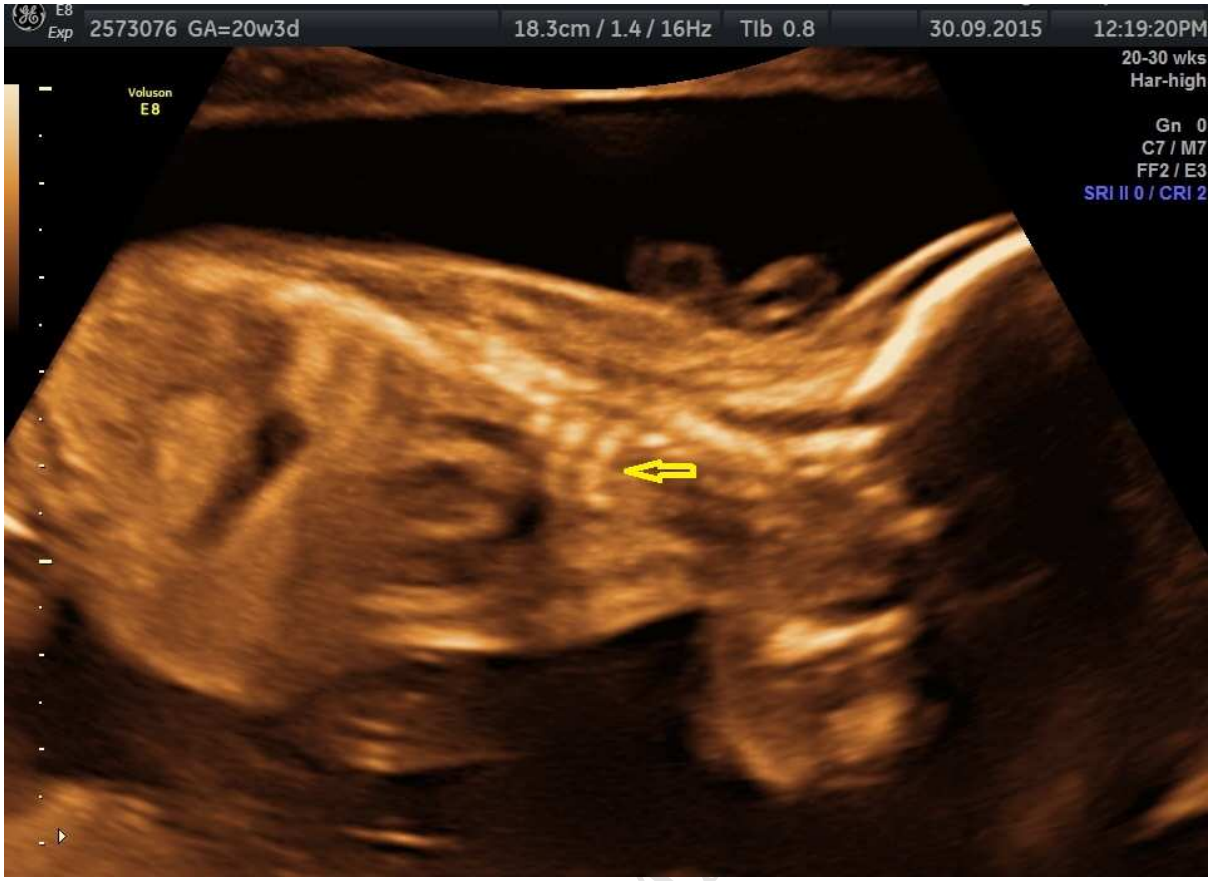


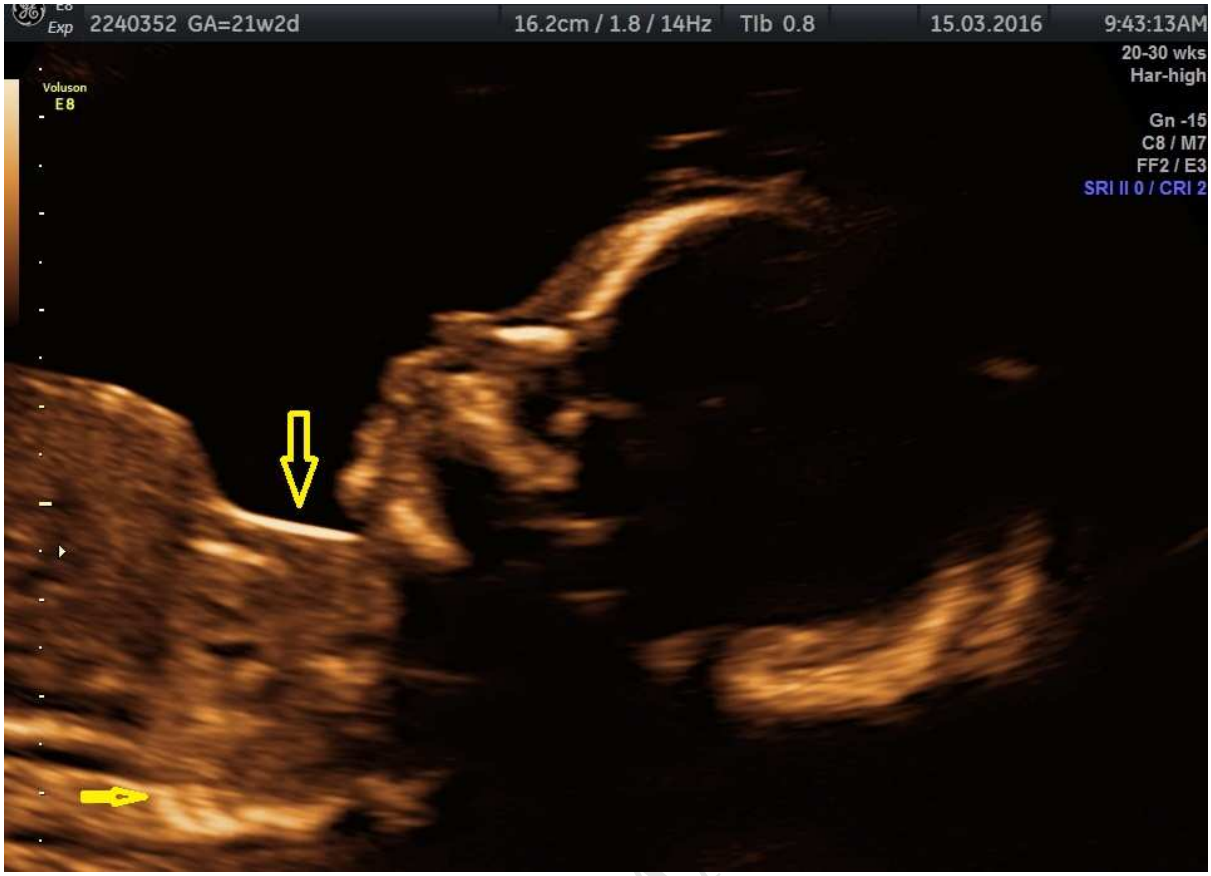


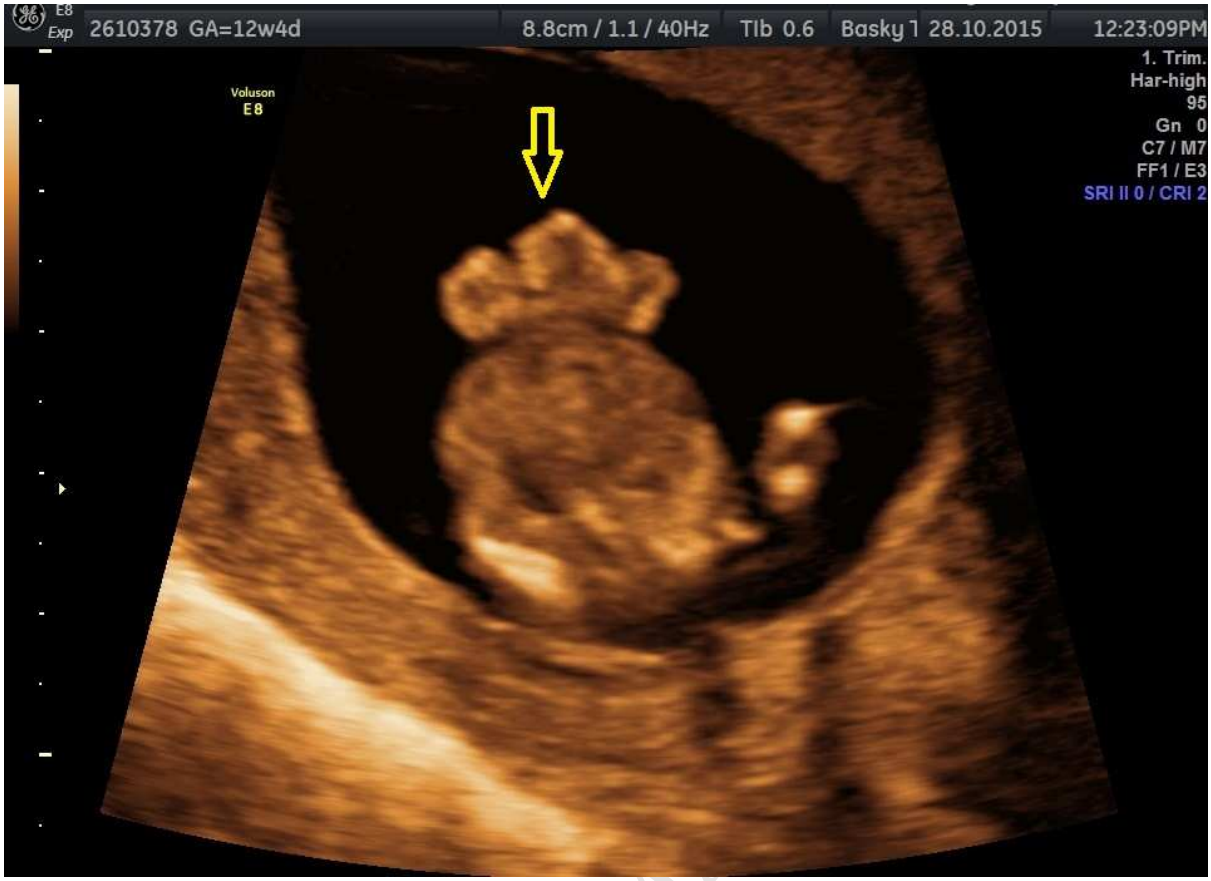


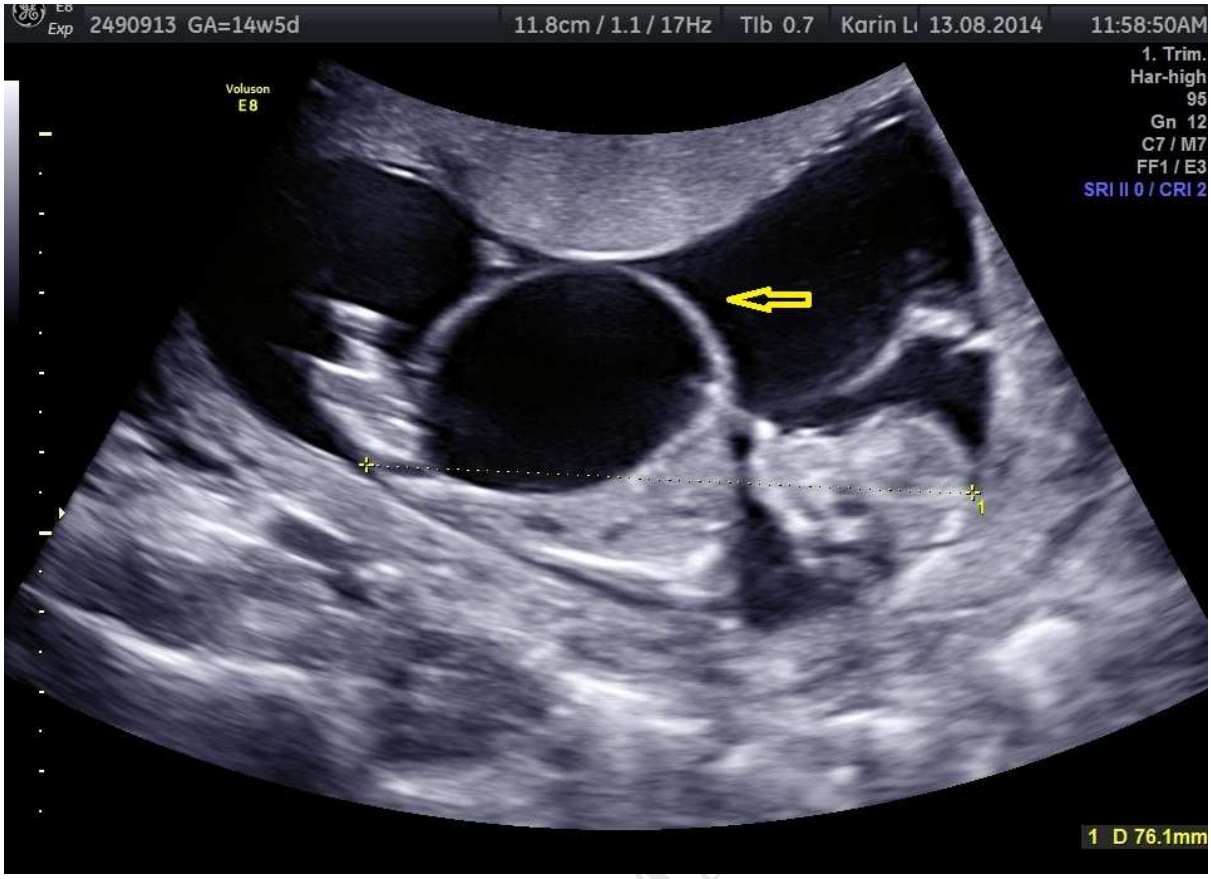












HIGHLIGHTS

- Prenatal diagnosis is a rapidly evolving speciality.
- Nuchal translucency (NT) measurement was one of the main advances with regards to first trimester screening
- Many other additional abnormalities are now amenable to detection earlier in the 1st trimester
- There is now widespread availability of non-invasive prenatal testing
- There are specific markers on ultrasound that can be linked to certain genetic syndromes
- A structured and stepwise approach is needed to identify and reach a possible diagnosis