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REVIEW ARTICLE

Neck

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ABSTRACT

Cystic hygroma (CH) is the most frequently seen fetal neck mass on the first-trimester ultrasound (US). Overall prognosis is poor with a high association with chromosomal and structural anomalies. When diagnosed prenatally, fetal karyotyping and detailed US evaluation should be offered. Prenatal and postnatal surgical or nonsurgical treatment options are available. Fetal goiter (FG) and fetal thyroid masses are rare fetal conditions and may occur as part of a hypothyroid, hyperthyroid, or euthyroid state. Screening for FGs should be carried out in pregnancies of mothers with thyroid disease. If a FG is detected, a detailed US examination should be performed. Congenital high airway obstruction syndrome (CHAOS) is characterized by bilaterally enlarged lungs, flat or inverted diaphragms, dilated tracheobronchial tree, and massive ascites. It is usually a lethal abnormality. Fetuses with suspected CHAOS should be referred to a fetal medicine center able to perform *ex utero* intrapartum treatment (EXIT) delivery. Neck teratomas are associated with high mortality rates. Prenatal US diagnosis of cervical teratoma can be made at 15 and 16 weeks of gestation. Planning of delivery in a tertiary center allows the performance of EXIT. Lymphangioma of the neck usually diagnosed in late pregnancy could be traditionally referred to as CH, but there is a different prenatal history and outcome.

Keywords: Congenital high airway obstruction syndrome, Cystic hygroma, Goiter, Lymphangioma, Teratoma.

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EMBRYOLOGY AND DEVELOPMENT OF THE NECK STRUCTURES

Human embryos include four pairs of well-defined pharyngeal arches. The pharyngeal arches form in craniocaudal succession: 1st arch on day 22nd; 2nd and 3rd arches sequentially on day 24th; 4th arch on day 29th.[1]

Pharyngeal arches consist of a mesenchymal core – mesoderm and neural crest cells – that is covered on the outside with ectoderm and lined on the inside with endoderm.[1]

Each arch contains a central cartilaginous skeletal element, striated muscle rudiments, innervated by an arch-specific cranial nerve, and an aortic arch artery.[1]

Arterial blood reaches the head via paired vertebral arteries that form from anastomoses among intersegmental arteries and through the common carotid arteries. The common carotid arteries branch to form the internal and external carotid arteries. The common carotids and the roots of the internal carotids are derived from the 3rd arch arteries, whereas distal portions of the internal carotids are derived from the cranial extensions of the paired dorsal aortae. The endothelium of the head vasculature and aortic arch arteries is derived from the mesoderm.[1,2]

The external pharyngeal clefts or grooves between the arches remain separated from the apposed, internal pharyngeal pouches by thin pharyngeal membranes. These membranes are initially two-layered, consisting of ectoderm and endoderm, later being infiltrated by mesenchymal cells.[1,2]

All of the pharyngeal pouches give rise to adult structures. These are the tubotympanic recess, the palatine tonsils, the inferior parathyroid glands, and the ultimobranchial body. The parathyroids, thymus primordia, and ultimobranchial bodies separate from the lining of the pharynx and migrate to their definitive locations within the neck and thorax.[1]

The parathyroid glands and the ultimobranchial bodies migrate inferiorly to become embedded in the posterior wall of the thyroid gland. The two parathyroids exchange position as they migrate: Parathyroid III becomes the inferior parathyroid, whereas parathyroid IV becomes the superior parathyroid.[1-3]

The thyroid primordium first forms late in the 4th week and appears as a small, solid mass of endoderm proliferating at the apex of the foramen cecum on the developing tongue. The thyroid primordium descends through the tissues of the neck at the end of a slender thyroglossal duct. The thyroglossal duct breaks down by the end of the 5th week, and the isolated thyroid, consisting of lateral lobes connected by a well-defined isthmus, continues to descend reaching its final position just inferior to the cricoid cartilage by the 7th week.[1,2]

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Lymphatic channels arise by vasculogenesis and angiogenesis from venous precursor cells. Lymphangiogenesis begins with the formation of bilateral sprouts from the anterior cardinal veins at about day 42 of development. These sprouts eventually form a pair of enlargements, the jugular lymphatic sacs, which will collect fluid from the lymphatic vessels of the upper limbs, upper trunk, head, and neck. In the 6th week, four additional lymphatic sacs develop to collect lymph from the trunk and the lower extremities: The retroperitoneal lymphatic sac, cisterna chili, and paired posterior lymphatic sacs associated with the junctions of the external and internal iliac veins.[1,4,5]

NECK ANOMALIES

Cystic Hygroma (CH)

Cystic hygroma is a congenital lymphatic malformation. It is the most frequently observed fetal neck pathology on prenatal ultrasound (US).[6]

Cystic hygroma refers to the finding of marked skin thickening extending along the entire length of the fetus at early US examination.[7]

Cystic hygroma represents not a tumor, but an anomaly of the lymphatic drainage into the venous system, which leads to the accumulation of lymph in the jugular lymphatic sacs of the cervical region.[8]

Based on the presence of septations, it can be classified into septated or nonseptated.[6]

However, with the improving resolution and the increasing quality of the image offered by advances of US machines, it has become clear that all nuchal translucencies have visible septations.[9]

Prevalence, Incidence, and Epidemiology

The true incidence of CH remains unknown. It has been reported to be 1:6,000 at birth and 1:750 among spontaneous abortions.[6] More recent data from the first- and second-trimester evaluation of risk (FASTER) trial showed a prevalence of 1:285 in first-trimester pregnancies.[8]

It is, therefore, likely that in busy clinical practice performing routine first-trimester US, septated CH will be encountered frequently[7,10,11] (Table 1).

Cystic hygroma is normally caused by aberrant development of lymphatic vessels, as a consequence of an abnormal or absent connection with the venous system, leading to lymphatic stasis and enlargement of the jugular sacs.[6,12]

Abnormal lymphatic development in the fetal neck could lead to distension of the jugular venous sacs, an accumulation of fluid in the nuchal region, and retrograde increases in venous pressure.[13]

Table 1: Cystic hygroma incidence

Author/study	*Incidence*
Arigita M, Bennasar M, Bienvenido P. In: Copel J, D'Alton M, Gratacos E, Platt L, Tutschek B, Feltovich H, Odibo A, editors. Obstetric imaging; 2012	1:285 FASTER trial
Bianchi DW, Crombleholme TM, D'Alton ME, Malone FD. Fetology-diagnosis and management of the fetal patient. 2nd ed. 2010	1:285 Unselected pregnancies in the United States First-trimester ultrasonography
Breathnach FM, Malone FD. In: Rodeck CH, Whittle MJ, editors. Fetal medicine – basic science and clinical practice. 2nd ed. 2009[83]	1:285 Unselected population Aneuploidy confirmed in 50% of the cases 40% trisomy 21
Chen CP, Liu FF, Jan SW, et al. 1996[84]	1:750 Spontaneous abortions

This hypothesis is supported by the observation that reversed or absent ductus venosus flow during atrial contraction is observed in these fetuses. Eventual recanalization or formation of collaterals may explain the transient nature of abnormal ductus venosus waveforms and nuchal edema.[13]

Condition, Etiology, and Pathophysiology

Cystic hygroma is seen frequently in the first trimester, affecting about one in 300 pregnancies.[7]

Cystic hygroma is also frequently associated with other malformations and chromosomal abnormalities in approximately 75% of the cases[6] (Table 2).

Cystic hygroma has been related to the inherited disorders and malformation syndromes in euploid fetuses and to drug intake, including alcohol, aminopterin, and trimethadione.[6,14]

There are studies suggesting that septations predict an increased likelihood of aneuploidies.[15]

On the contrary, some studies have not confirmed this affirmation.[16]

Cystic hygroma in the first trimester has clearly visible septations running transversely between the fetal skin and underlying subcutaneous tissue. It appears that the diagnosis of this finding early in pregnancy represents a completely different entity than the diagnosis of CH in later pregnancy.[7]

The latter condition is typically an isolated structural abnormality of lymphatic drainage and appears to have little or no association with chromosomal abnormality or other malformation.[6,7]

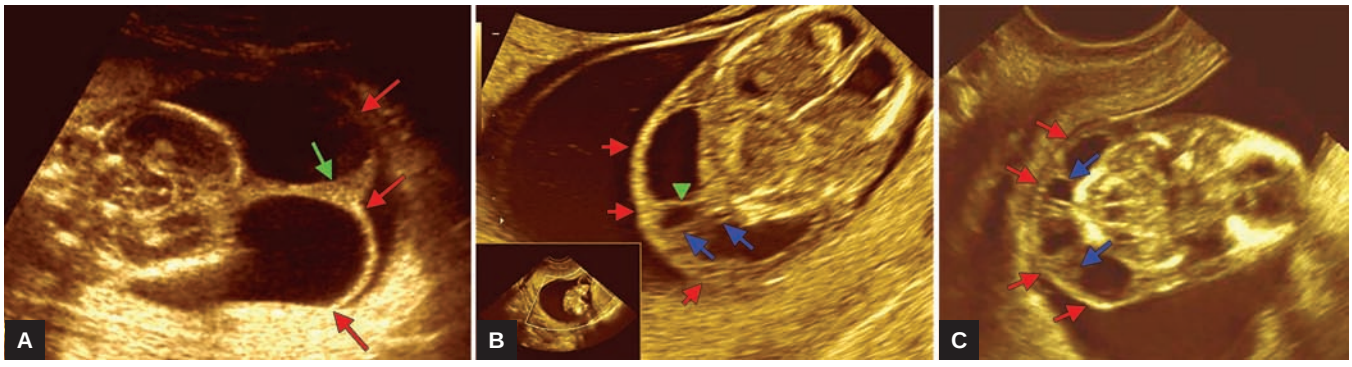
The anomaly is visible from the first trimester, and it represents the end of the spectrum of the increased nuchal translucency.[8]

On the one hand, recent studies suggest a higher prevalence of Down syndrome, but on the other hand, Turner

Table 2: Genetic and malformation syndromes associated with CH

Achondrogenesis[6,20]	Lethal skeletal dysplasia with extreme hypoplasia of the bones, micromelia, decreased ossification of the bones and hydrops
Achondroplasia[6,20]	Autosomal dominant condition with rhizomelic limb shortening, nonlethal, heterozygous type usually is not apparent until late in the second trimester
Arthrogryposis[20]	Sequence of neurologic, muscular, and connective tissue disorders, cystic nygroma, or thickened nuchal translucency
Beckwith–Wiedemann syndrome[6]	Gigantism *in utero*, macroglossia, omphalocele, renal abnormalities
Cerebrocostomandibular syndrome[20]	Autosomal recessive, micrognathia, vertebral body abnormalities, CH/nuchal thickening
CHARGE association[20]	Coloboma of the iris, heart defect, choanal atresia, IUGR, genital anomalies, ear anomalies, CH
Cornelia de Lange syndrome[20]	Facial/limb anomalies, growth restriction, mental developmental delay
Cowchock syndrome (CMTX4)[6]	A slowly progressive X-linked recessive disorder with axonal neuropathy, deafness, and cognitive impairment[21]
Cowden disease[6]	Tumor-like growths – hamartomas. Multiple hamartoma syndrome[22,23]
Cumming syndrome[6]	Autosomal recessive pattern of inheritance, cervical lymphocele (CH), renal-hepatic-pancreatic dysplasia, short gut, polysplenia, generalized lymphedema, short limbs, bowed limbs (campomelia)[24]
Cri du Chat syndrome (Deletion 5p)[20]	Abnormality of chromosome 5 characterized by microcephaly, hypertelorism, micrognathia, hydrops, IUGR, CH
Ectrodactyly–Ectodermal Dysplasia–Cleft (EEC) syndrome[20]	Autosomal dominant condition, labial clefting, ectrodactyly, genitourinary tract anomalies, CH
Fraser syndrome[6]	Cryptophthalmos, syndactyly, genital, renal, and tracheal abnormalities[20]
Fryns syndrome[6,20]	Autosomal recessive condition with diaphragmatic defects, digital and facial abnormalities, brain anomalies[20]
Hereditary lymphedema[6]	Dysfunction of the lymphatic system. Hypoplasia or aplasia of lymphatic channels. Usually segregating as an autosomal dominant trait[25]
Lymphedema–distichiasis syndrome[6]	Rare genetic multisystem disorder. Lower limb lymphedema and distichiasis. Distichiasis, which may be present at birth, is observed in 94% of affected individuals[26,27]
Multiple pterygium syndrome[6,20]	Autosomal recessive condition, multiple contractures and webbing across joints, CH, facial defects
Noonan syndrome[6,20]	Phenotypically a Turner-like syndrome, short stature, webbed neck, cardiac abnormalities, normal karyotype
Oculodentodigital syndrome[6]	Caused by mutations in the GJA1 gene. Oculodentodigital dysplasia presents with a spectrum of clinical features including craniofacial, ocular, dental, and limb anomalies[28-30]
Optiz-Frias syndrome[6]	X-linked Opitz G/BBB syndrome (XLOS) is a multiple congenital anomaly disorder, facial anomalies, hypertelorism, prominent forehead, broad nasal bridge, laryngotracheoesophageal defects, and genitourinary abnormalities[31]
Pena Shokeir syndrome[6]	Autosomal recessive condition, IUGR, multiple joint contractures, facial anomalies, pulmonary hypoplasia[20]
Pentalogy of Cantrell[6]	Ectopia cordis, omphalocele, disruption of the distal strenum, anterior diaphragm, diaphragmatic pericardium
Perlman syndrome[20]	Autosomal recessive syndrome, fetal overgrowth, macrosomia, bilaterally enlarged kidneys, renal tumors, polyhydramnios, CH
Polysplenia/asplenia syndrome[6,20]	Defects in lateralization of normal body asymmetry, severe heart defects, and anomalies of the intrathoracic and intra-abdominal viscera
Proteus syndrome[6]	Asymmetric focal overgrowth, subcutaneous tumors, lipomas, hamartomatous lymphangiomas[20]
Roberts syndrome[6]	Severe shortening of the limbs and facial anomalies[20,32]
Thrombocytopenia-absent radius (TAR) syndrome[6]	Autosomal recessive syndrome, radial aplasia, and thrombocytopenia[20]
Triploidy[20]	Complete extra set of chromosomes, lethal abnormality, early-onset IUGR, multiple anomalies
Williams syndrome[6]	Distinctive facies, congenital cardiovascular malformations, intellectual disabilities, and various other manifestations[33,34]
Zellweger syndrome[6]	Prototype of peroxisomal disorders characterized by craniofacial dysmorphism and severe neurologic abnormalities, growth restriction, gastrointestinal malformations[35]

This table is designed as a synopsis of genetic and structural abnormalities associated with CH[6,20-35]



Figs 1A to C: (A) Axial view of septated CH (red arrows) in early second-trimester US. Two separate fluid accumulations are visible, the nuchal ligament (green arrow) is spotlighted; (B) axial view of septated CH (red arrows), the nuchal ligament (green arrow), and clearly visible septations (blue thin arrows); and (C) axial view of septated CH (red arrows), typical honeycomb appearance (blue arrows), and intact calvarial bones

syndrome is the most common associated chromosomal abnormality, also affecting approximately 60% of the cases.[6]

Other chromosomal abnormalities include autosomal trisomies, Klinefelter syndrome, partial trisomies, partial monosomies, translocations, and mosaicisms.[6,7,17-19]

Diagnosis and Imaging Findings: US

Cystic hygroma typically develops late in the first trimester and is characterized by the presence of posterior and posterolateral fluid-filled cavities in the fetal neck (Figs 1A and B). These cavities are quite variable in size. Nuchal hygromas are frequently bilateral, separated by the nuchal ligament, resembling a complex mass with one or more septa in the center[6,36] (Fig. 1C).

The central sonographic criteria for diagnosing CH in the first trimester of pregnancy is the presence of a significantly enlarged nuchal translucency measurement that extends along the entire length of the fetal back and in which septations are clearly visible in the transverse section through the fetal neck.[7]

Natural history of CH may be variable. It can resolve spontaneously or progressively affect other fetal structures separate from the neck (plaura, pericardium, abdomen), leading to hydrops fetalis in 75% of the cases, resulting in fetal demise.[6,7,37]

Cystic hygroma is associated with other malformations in 60% of the cases, including cardiac defects, skeletal dysplasias, genitourinary system abnormalities, congenital diaphragmatic hernia, and central nervous system (CNS) abnormalities.[6,37]

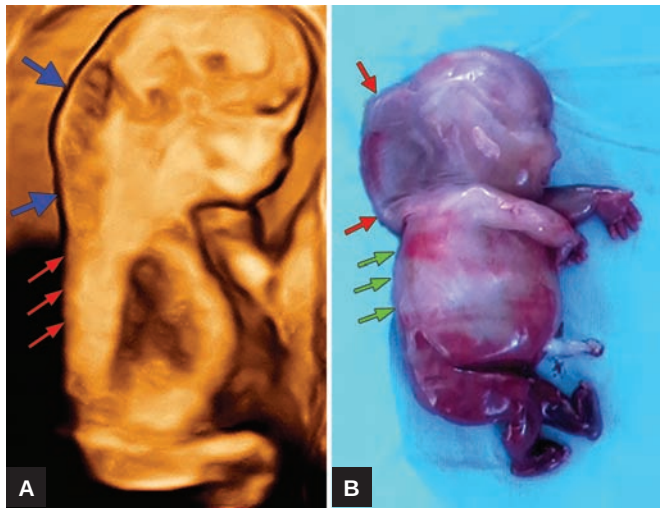
The main problem in the diagnosis of CH remains the differential diagnosis in the first trimester between the enlarged nuchal thickening and when it meets criteria to be termed CH or whether it should be considered a simple increased NT.

Ultrasound imaging – overdistension of the jugular lymphatic sacs that are located in both sides of the neck results in the formation of a cystic structure that is usually partitioned by a thick fibrous band corresponding to the nuchal ligament. Within the cystic structure, thinner septa are seen and probably represent fibrous structures of the neck or deposits of fibrin, giving to the lesion a typical honeycomb appearance[38] (Fig. 1C).

There is a correlation between increased nuchal translucency and CH. Cystic hygroma can be regarded as the most severe end of the spectrum of increased NT. Generally, when NT is in excess of 4 mm, septa are seen within it.[38]

It is argued that septations can be seen in all fetuses with increased NT, and CH should not constitute a distinct entity in the first trimester.[9]

Septated CH, using the definition as described above, can be easily identified in the first trimester. If the nuchal thickening does not extend along the entire length of the fetal back, and if transverse septations are not clearly visible, then the term nuchal translucency should be used[7] (Figs 2A and B).



Figs 2A and B: (A) Three-dimensional surface-rendered view of fetus with CH at 14 weeks of gestation. Increased dimensions of the nuchal region (blue arrows) extending along the entire length of the fetal back (red arrows); and (B) macro-image of the postabortum specimen demonstrating CH (red arrows) extending along the fetal back (green arrows) and fetal hydrops

Table 3: Differential diagnosis of CH

Occipital encephalocele and meningocele	Defect in the calvaria and the absence of gyral pattern
Hemangioma	Normally irregularly shaped, low-level echoes, and color Doppler showing vascularization
Teratoma	Located anteriorly, hyperextension of the fetal neck, and a solid or mixed-solid mass
Goiter	Bilobed mass in the anterior region
Other	Sarcoma, melanoma, brachial cleft cyst, thyroglossal duct cyst, laryngocele, fibroma, lipoma, metastases

Adapted from Arigita et al[6]

Magnetic Resonance Imaging

In late pregnancy, magnetic resonance imaging (MRI) can be useful in prenatal evaluation of airway access and extension of the lymphatic abnormalities to plan an adequate delivery and perinatal management.[6,39]

Differential diagnosis of CH is spotlighted in Table 3.

Management, Outcome, and Recurrence Risk

Cystic hygroma is the most frequently seen fetal neck mass on first-trimester US. Overall prognosis is poor with a high association with chromosomal and structural defects and progression to hydrops and fetal demise[6,7,38] (Table 4).

Recurrence risk for CH associated with fetal aneuploidies should be provided based on the individual chromosomal abnormality. For cases of fetal trisomy, recurrence risk is generally about 1%; the maternal age-related risk is even higher. For cases with Turner syndrome, there is no significant increased risk of recurrence beyond the general population risk. Similarly, the risk of recurrence in cases with cardiac malformations should be individualized[6,7,38]

Fetal Goiter and Fetal Thyroid Masses

Fetal goiter (FG) or thyromegaly is a diffuse enlargement of the fetal thyroid gland. Goiter in the fetus can occur as part of a hypothyroid, hyperthyroid, or euthyroid state.[7]

It is defined on US as a thyroid circumference or diameter greater than the 95th centile for gestational age. It is frequently associated with maternal thyroid dysfunction, generally hypothyroidism.[40,41]

Goiter associated with fetal hypothyroidism can be caused by transplacental passage of antithyroid medications being used by a mother with hyperthyroidism, iodine deficiency or intoxication, transplacental passage of antithyroid antibodies, congenital metabolic disorders of thyroid hormone synthesis, or hypothalamic–pituitary hypothyroidism.[7,42]

Prevalence, Incidence, and Epidemiology

The prevalence of goitrous hypothyroidism is 1:30,000–1:50,000 live births in Europe and North America.[41] Hypothyroid goiter is more common than hyperthyroid goiter.[7] Iodine deficiency is still considered a major health problem worldwide.[40] However, only a small fraction of the estimated prevalence will be diagnosed prenatally with FG.[7]

Condition, Etiology, and Pathophysiology

In the euthyroid fetus, the main potential problem associated with goiter is the obstruction of trachea or esophagus as the goiter enlarges with pregnancy progression. On the one hand, this may lead to polyhydramnios and, on the other hand, to hyperextension of the fetal neck.[7,43]

Congenital goiters are most commonly diagnosed in mothers with known thyroid disease, usually Graves' disease. Graves' disease is a common cause of hyperthyroidism, i.e., present in 0.2% of pregnant women.[41,44] Fetuses of mothers with thyroid disease are especially susceptible to develop congenital hyperthyroid goiter owing to the passage of antibodies against the thyroid-stimulating hormone (TSH) receptor also called thyroid-stimulating immunoglobulin, found in 1% of children born from mothers with Graves' disease. Fetuses can also develop congenital goitrous hypothyroidism because of the transplacental passage of propylthiouracil, or occasionally inhibitory immunoglobulins.[41,45]

Table 4: Management of CH in the first trimester

Step 1	First-trimester diagnosis of CH	Counseling regarding fetal aneuploidy (50%)[7]	Diagnostic testing – chorionic villus sampling[7]
Step 2	Chorionic villus sampling – no evidence for aneuploidy	Counseling regarding fetal residual risk of major structural malformation (50%). Most likely malformations are cardiac and skeletal[7]	Comprehensive fetal US anatomic survey Fetal echocardiography Serial assessment of fetal status 16–20 weeks of gestation*
Step 3	Fetal evaluation confirms a structurally normal fetus	Counseling of a 95% likelihood of normal short-term pediatric outcome. A residual risk of 5% for abnormal pediatric outcome should be described[7]	Long-term outcome – minimal data avilable[6,7]

*Early fetal anatomic evaluations can be performed using a combined approach, starting with an abdominal survey and assessing details through high-resolution transvaginal ultrasound; experienced ultrasonographers can detect many major malformations in the first trimester. Fetal echocardiography may be attempted as early as the first trimester. According to the quality of image and the US findings, fetal heart may be reassessed at 14, 16, 18, or 20 weeks.

Fetal goiter associated with hyperthyroidism may result in significant fetal changes including tachycardia, cardiac hypertrophy, hydrops, intrauterine growth restriction (IUGR), fetal death, intellectual impairment, and preterm birth.[7] Congenital goitrous hyperthyroidism is most frequently caused by maternal antibodies or dyshormonogenesis.[41]

When considering all cases of congenital goitrous hypothyroidism, almost 80% are due to thyroid dysgenesis and may be related to somatic mutations in the TSH receptor. Nearly 15% of cases are due to dyshormonogenesis or transplacental passage of TSH receptor-blocking antibodies.[45] Dyshormonogenesis is the most frequent cause in the absence of maternal thyroid disease or iodine deficiency; it is frequently caused by recessively inherited biochemical defects in one or more steps in the pathway, leading to the normal synthesis of thyroid hormones[41,45] (Table 5).

Fetal goiter secondary to hypothyroidism may result in fetal bradycardia, heart block, or cardiomegaly.[7]

Fetal goiter as a result of the enlarged thyroid gland, progressing to a global thyroid mass, can be detected by a dedicated US evaluation of the fetal neck or by the complications that it may cause.

Sonographic screening for FG may be difficult because of problems in accurately identifying the fetal thyroid during early gestation.[7]

Diagnosis and Imaging Findings: US

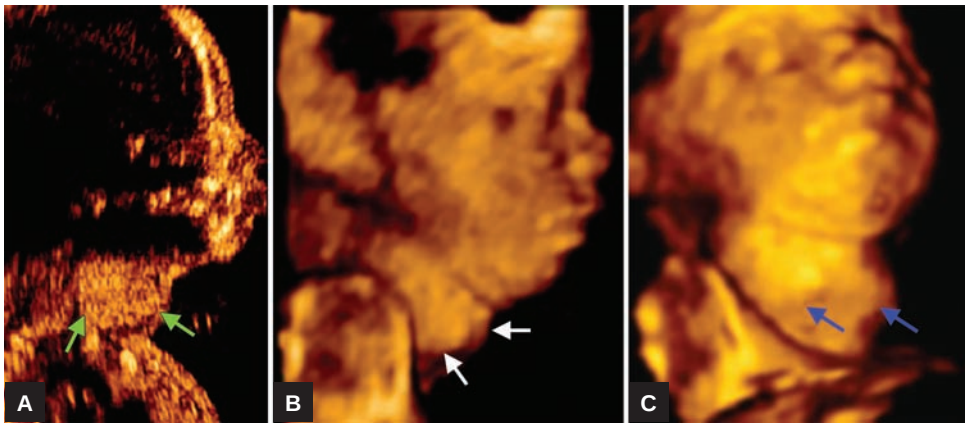
The classic US findings of FG spotlight a homogeneous, echogenic, symmetric mass in the anterior fetal neck, and sometimes with some lobulation[7] (Fig. 3A).

When FG is suspected, the transverse width and circumference of the thyroid gland should be measured. The diagnosis should be made when these measurements are above the 95th centile based on the nomograms for gestational age. Some US signs can be helpful in determining whether FG is associated with hypothyroidism or hyperthyroidism[38,41] (Table 6).

Table 5: Fetal complications of the goiter and thyroid masses

A. Fetal complications by compression and the mass effect[41]	
Esophageal obstruction	– can cause polyhydramnios – risk of preterm delivery
Tracheal obstruction	– can cause perinatal asphyxia – need for intubation – *Ex utero* intrapartum treatment
Neck hyperextension	– consequent fetal dystocia
B. Fetal complications consequent to thyroid dysfunction[7,41]	
Fetal hyperthyroidism	– IUGR – tachycardia – cardiac hypertrophy – intrauterine death by cardiac failure – accelerated bone maturation – thyrotoxicosis – hepatosplenomegaly – craniosynostosis with intellectual impairment – hydrops – preterm birth
Fetal hypothyroidism or untreated congenital hypothyroidism	– bradycardia – heart block – cardiomegaly – impaired motor and intellectual development in the later stages of life in some affected infants – the degree of neurologic impairment has been related to the severity of fetal hypothyroidism as assessed by the age at diagnosis, the lower serum thyroxine concentrations, and the delay in postnatal treatment – an early diagnosis should be made – subsequent treatment should be promptly started before potentially irreversible neurologic damage occurs secondary to insufficient thyroid hormone levels

The fetal neck is often maintained in a state of hyperextension, and the trachea and esophagus may be compressed or displaced. Later in pregnancy, as swallowing becomes more difficult, polyhydramnios may be induced[43] (Fig. 3C).



Figs 3A to C: (A) Fetal goiter in sagittal view (green arrows). Homogeneous, echogenic mass in the anterior fetal neck; and (B, C) three-dimensional imaging of a FG. Surface rendering demonstrating the appearance of the thyroid mass (white arrows), sometimes with some lobulation (blue arrows)

Table 6: Indirect US signs of fetal thyroid dysfunction

Bone maturation[41,44]	Accelerated bone maturation is defined as the presence of distal femoral ossification before 31 weeks of gestation and is frequently present in hyperthyroidism
	Delayed bone maturation is defined as the absence of this center after 33 weeks of gestation and is more frequently present in hypothyroidism
Fetal tachycardia[41]	Fetal tachycardia, defined as a continuous heart rate greater than 160 beats/min, is an indirect sign of hyperthyroidism
Fetal movements[41,44]	Hypothyroid fetuses showed more frequently increased jerky movements which were absent in cases of hyperthyroidism
Polyhydramnios[41]	When FG is suspected, the amniotic fluid should be always evaluated using the amniotic fluid index because of the potential compression of the fetal esophagus. Polyhydramnios is related to goiter volume rather than etiology. When polyhydramnios is present, cervical length should be measured

Adapted, completed and revised from Sanz-Cortéz et al[41]

Color Doppler US showing a high-flow pattern confirms the diagnosis of FG but does not imply fetal hyperthyroidism, as hypothyroid FGs may also have increased vascularity. Color Doppler of the thyroid may show peripheral vascularization that reflects a hypertrophic but inactive thyroid gland, more commonly present in hypothyroid goiters.

The disappearance or reduction of the mass or the Doppler signal may be associated with improvement in fetal thyroid status.[41,44]

Three-dimensional US in fetal thyroid masses is helpful (Figs 3B and C) and may facilitate the mother's understanding of FG, which may obtain better treatment compliance. Three-dimensional US also could be useful in assessing the reduction in size and volume of FG after treatment.[41]

Magnetic Resonance Imaging

A complementary imaging mode to study fetal thyroid masses and its use has been reported in cases of goitrous hypothyroidism during pregnancy. Magnetic resonance imaging of congenital hypothyroid goiters shows a T1 and T2 signal hyperintensity. Fetal MRI can be beneficial in assessing the compromise and compression of the esophagus and trachea and when neonatal intubation may seem unavoidable.[7,41]

Differential diagnosis of FG is marked out in Table 7.

Table 7: Differential diagnosis of FG and thyroid masses

Thyroglossal duct cysts[7,41]	– the most common congenital anomaly of thyroid development
	– persistence of the thyroglossal duct
	– usually disappears by the 8th week of gestation
	– accumulation of fluid can result in a ductal cyst
	– can be located anywhere from the base of the tongue to the thyroid isthmus
	– it can be anechoic, hypoechoic, or complex
Thyroid teratomas[7,41]	– they can be solid, semicystic, or multiloculated
	– derive from the embryonic thyroid anlage
	– fetal thyroid teratomas generally are considered benign tumors
Ectopic thymus[7,41]	– aberrant migration of the thymus causes the ectopic presence of remnants anywhere in the mediastinum, base of the skull, tracheal bifurcation, or cervical region
	– ectopic thymus is rarely symptomatic
Branchial cleft cysts[7,41]	– result from incomplete involution of the branchial apparatus
	– lack of any solid elements or septations
Other conditions[7,41]	– CH, lymphangiomas or hemangiomas, and cervical neruroblastomas, cervical meningocele

Adapted, completed and revised from Bianchi DW et al,[7] Sanz-Cortéz et al[41]

Management, Outcome, and Recurrence Risk

Fetal goiters are rare. They are associated more frequently with fetal hypothyroidism and less frequently with fetal hyperthyroidism. Prenatal euthyroid goiters can also exist. Screening for FGs should be carried out in pregnancies of mothers with thyroid disease, especially Graves' disease. If a FG is detected, a detailed US examination should be performed looking for signs of either hyperthyroidism or hypothyroidism. If the neck mass is large enough to compress the esophagus, polyhydramnios may be present, and a preterm delivery could occur. If there is tracheal occlusion, there is a risk of neonatal asphyxia, and the need for intubation should be anticipated. When a FG is detected, fetal thyroid function should be assessed, preferentially by cordocentesis. If there is congenital hypothyroidism, intra-amniotic instillation of LT-4 is the preferred treatment option, although the dosage and the intervals of administration are not standardized. The main objective of intrauterine treatment for FGs is to decrease the mass size and secondarily to normalize thyroid function.[38,41,44]

Recurrence of FG in subsequent pregnancies is a significant circumstance when a mother has thyroid dysfunction. A total of 2 to 12% of all infants of mothers with Graves' disease will have hypo- or hyperthyroidism.

Overall, the recurrence risk in such circumstances is 25%.[7,38,41,44]

Congenital High Airway Obstruction Syndrome

Congenital high airway obstruction syndrome (CHAOS) is a rare fetal anomaly that is associated with mortality in about 80 to 100% of cases. Congenital high airway obstruction syndrome is an exceedingly rare condition consisting of complete intrinsic obstruction of the fetal upper airway that can be located at the level of the larynx, trachea, or bronchi. As a result of the obstruction, the fetal lungs are completely expanded secondary to retention of bronchial secretions, leading to tracheobronchial dilatation and pulmonary developmental impairment.[46]

Congenital high airway obstruction syndrome is a clinical entity manifested by the presence of extremely large echogenic fetal lungs, flattened or inverted diaphragm, dilated tracheobronchial tree, ascites, other manifestations of nonimmune hydrops, due to complete obstruction of the fetal airway.[7,47]

When fetal hydrops and complete airway obstruction are associated, CHAOS is lethal without intervention.

In one-third of the cases, there is a spontaneous perforation of the laryngeal or tracheal atresia, resulting in the resolution of the hydrops.[7]

The airway obstruction may be generated by laryngeal atresia, tracheal atresia, or laryngeal cyst, and the fetal clinical presentation is quite the same. Congenital high airway obstruction syndrome can be bilateral or unilateral (bronchial atresia). The incidence is unknown as the disease is very rare.[7,46,48,49]

Condition, Etiology, and Pathophysiology

Isolated CHAOS is a sporadic fetal malformation with low risk of chromosomal anomalies, but CHAOS also can be present within a syndrome. A significantly high proportion of cases can be associated with Fraser syndrome[46,50] (Table 8).

Moreover, other conditions may induce an extrinsic obstruction of the tracheobronchial tree, such as lymphatic congenital malformations, cervical teratoma, or vascular rings, such as double aortic arch or aberrant right subclavian artery.[46,51]

Congenital high airway obstruction syndrome is characterized by retention of bronchial and alveolar secretions resulting in elevated intratracheal pressure and a significant increment in the amount of fluid within the lungs and tracheobronchial tree, leading to severely increased lung volume and tracheal dilatation. The massively enlarged lungs deform the fetal thorax inducing a regression in the diaphragmatic convexity and a mediastinal shift. These findings can be detected on US in the first trimester of pregnancy.[46,52]

Table 8: Congenital high airway obstruction syndrome-associated anomalies or syndromes

Anomalies associated with CHAOS[7]	Fraser syndrome – cryptophthalmos, syndactyly, genital abnormalities, abnormalities of the ears, nose abnormalities, urinary tract hypoplasia or agenesis, laryngeal stenosis or atresia, microcephaly, hydrocephalus, facial cleft, neural tube defect, ascites, hypertelorism
	Cardiac anomalies
	Esophageal atresia
	Syndactyly
	Tracheoesophageal fistula
	Hydrocephalus malformation of the aqueduct of Sylvius
	Vertebral anomalies
	Absent radius
	Bronchotracheal fistula
	Uterine anomalies
	Imperforate anus
	Anophthalmia
	Genitourinary anomalies

Adapted, completed and revised from Bianchi et al[7]

The diagnosis is usually made on examination of the fetal thorax, which is typically characterized by hyperexpanded and hyperechoic lungs, flattened diaphragms, and dilated airways below the level of the obstruction.[46,53]

Diagnosis and Imaging Findings: US

Ultrasound shows signs related to complete airway obstruction. In a transverse view and at the level of the four-chamber view of the fetal heart, the lungs appear severely enlarged and highly hyperechoic. Secondary to the exceedingly high intrathoracic pressure and the degree of pulmonary expansion, the heart is squeezed into the middle of the fetal mediastinum between the lungs and shows a reduction of the cardiac angle. The sagittal and coronal views of the fetal thorax reveal two pathognomonic signs: Flattening or inversion of the diaphragmatic convexity and greatly dilated airways filled with bronchial secretions with an anechoic appearance, which allows observation of the entire tracheobronchial tree as a bronchogram. The dilated trachea and bronchi are better displayed with a coronal view of the fetal chest.[46,51,54]

In addition, the absence of flow in the trachea during fetal breathing or swallowing can be shown using color Doppler US. Extrapulmonary signs include nonimmune hydrops fetalis and placentomegaly secondary to cardiac failure or impeding venous return, or both, and polyhydramnios secondary to esophageal compression.[46,48,49]

Magnetic Resonance Imaging

Magnetic resonance imaging findings of CHAOS include confirmation of dilated airways below the level

of obstruction, increased lung signal intensity, and large lung volumes with flattened or inverted hemidiaphragms. Differential diagnosis between unilateral CHAOS and congenital cystic adenomatoid malformation can be challenging by US, and MRI can be useful in differentiating among congenital lung lesions. Magnetic resonance imaging also may help to exclude additional congenital malformations and other conditions associated with extrinsic compression of the tracheobronchial tree, such as adjacent tumors. Magnetic resonance imaging may play an important role in better identification of the level of obstruction, particularly in unilateral cases.[7,46,55-58]

Differential Diagnosis of CHAOS

The main diagnosis mistaken for CHAOS is cystic adenomatoid malformation. Congenital cystic adenomatoid malformation is usually lobar, not involving the entire lung, and very few of the cases are bilateral.[7] Congenital high airway obstruction syndrome may be a part or a morbid association with Fraser syndrome.

Management, Outcome, and Recurrence Risk

Congenital high airway obstruction syndrome is usually a lethal abnormality, especially in the presence of hydrops. Fetuses with suspected CHAOS should be referred to a fetal medicine center with teams able to perform *ex utero* intrapartum treatment (EXIT) delivery. Perinatal mortality is 100% without intervention. Preliminary studies reported that fetuses with CHAOS could benefit from *in utero* fetal therapy. Further studies are required.[46] Most cases of CHAOS occur sporadically and are isolated malformations without a known risk of recurrence. When Fraser syndrome is associated, there is a 25% risk of recurrence.[7,46,59]

Neck Teratoma

Cervical teratomas are rare tumors that vary in size and generally consist of a mixture of cystic and solid components, frequently with internal calcifications.[38]

Teratomas are the most common histologic type of fetal tumors that are rather rare. The neck is the most common location after the sacrococcygeal region for teratomas. The tissues found in fetal and infant teratomas are essentially the same regardless of the site of origin. A neck teratoma may be associated with neonatal mortality in 80 to 100% of the cases if delivery is not managed properly. *Ex utero* intrapartum treatment and intensive neonatal care are essential to improve outcome.[60]

Fetal cervical teratoma is a normally benign tumor in the neck composed of multiple tissues derived from all three germ layers of the embryonic disk (ectoderm, mesoderm, and endoderm) and is derived from primordial germ cells, with a high potential of growing in excess[1,60] (Figs 4A and B).

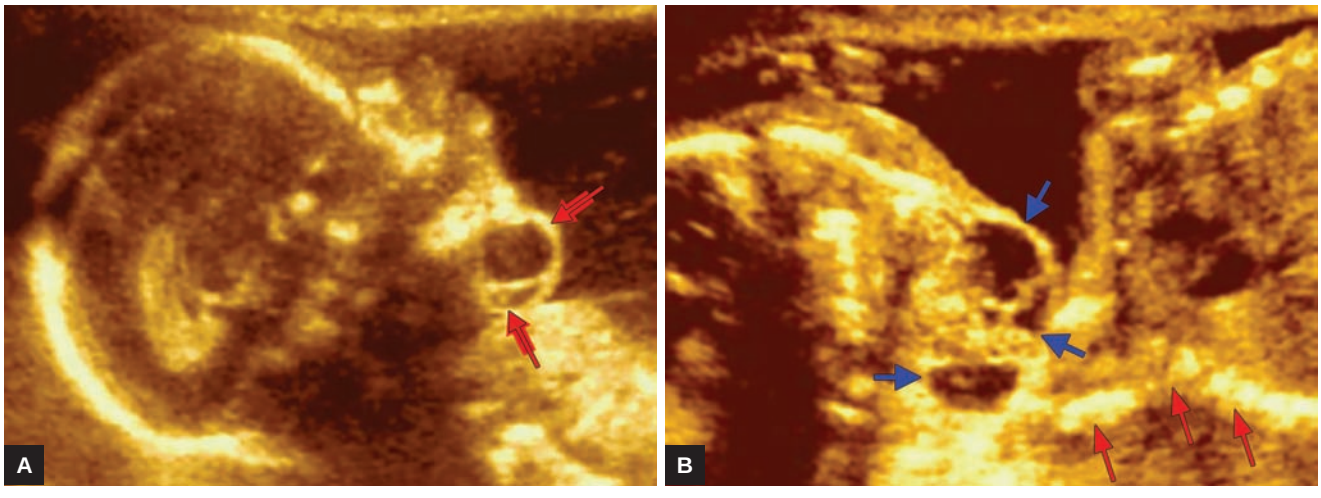
Some of these tumors may be malignant or may develop malignancies later into adult life.

Cervical teratomas are found in about 1:20,000 to 1:40,000 live births, accounting for 3 to 6% of all neonatal teratomas. The presentation is sporadic, without an apparent relationship to race, maternal age, parity, or fetal sex.[60-62]

Condition, Etiology, and Pathophysiology

In fetuses, tumors may result from failure of developing tissues to undergo normal cytodifferentiation and maturation.[60,63]

The pluripotency of teratomas is exhibited by the fact that they can give rise to a variety of definitive anatomic structures.[1]



Figs 4A and B: (A) Sagittal view of a neck teratoma (red arrows), significant distortion in the neck contour, predominantly cystic, well-encapsulated mass; and (B) neck teratoma located in the anterolateral region (blue arrows). The tumor is large and bulky, producing mass effect and extended position of the neck (red arrows)

The development of fetal tumors does not match the same processes as tumors observed in adults. Cervical teratomas may originate from the palate, nasopharynx, or thyrocervical area. They are usually closely related to, but do not arise from, the thyroid gland. Mature or immature neuroglial tissues are the most frequent component, but cartilage, respiratory epithelium, and ependymal-lined cysts are common. Malignancy is extremely rare. Immature elements present do not express the biologic behavior.[1,60]

Conventional anatomic US scan, usually in the second trimester, may diagnose the neck teratoma. With large masses, obstruction of the airways and esophagus leads frequently to polyhydramnios. The diagnosis may be as early as the first trimester.

Diagnosis and Imaging Findings: US

Targeting the diagnosis as early as the first trimester, this is not most often possible. However, diagnosis of a teratoma can be made early in the pregnancy (15–16 weeks of gestation), but the tumor is usually detected on routine second-trimester screening for fetal abnormalities (18–23 weeks of gestation) or targeted US scan after initial diagnosis of polyhydramnios (Figs 4A and B).

The key sign is the distortion in neck contour by the presence of an asymmetric, unilateral, and well-encapsulated mass. The tumor is usually large and bulky, with mixed echostructure of cystic and solid components. Echogenic foci of calcifications are present in about half of all cases. Located anterior to the neck, the tumor may produce a mass effect on surrounding tissues from the ear to the jaw or extend into the mediastinum. Large tumors result in severe hyperextension of the fetal head. Polyhydramnios is considered an indication of severity. It is related to tumor size and reflects impaired swallowing by mouth obstruction or esophageal compression[60,62,64] (Figs 5A and B).

The risk of chromosomal anomalies or nonchromosomal syndromes is low, but various associated anomalies have been reported, including trisomy 13, hypoplastic left ventricle, and CNS anomalies. The protocol should include detailed fetal US, echocardiography, neurosonogram, and fetal caryotype.[60,65,66]

Tumor vascularization and characteristics could be assessed by color Doppler, power or high-definition modes.

Three-dimensional US may enhance the accuracy of prenatal diagnosis and provide additional detailed information on aspects related to location, extension, and intracranial spread.[60]

Magnetic Resonance Imaging

Magnetic resonance imaging may provide additional information about tumor location calcifications, extension, facial involvement, and intracranial spread.[60]

Magnetic resonance imaging can estimate lung volumes and is helpful in predicting the presence of pulmonary hypoplasia complicating fetal cervical teratoma.[67]

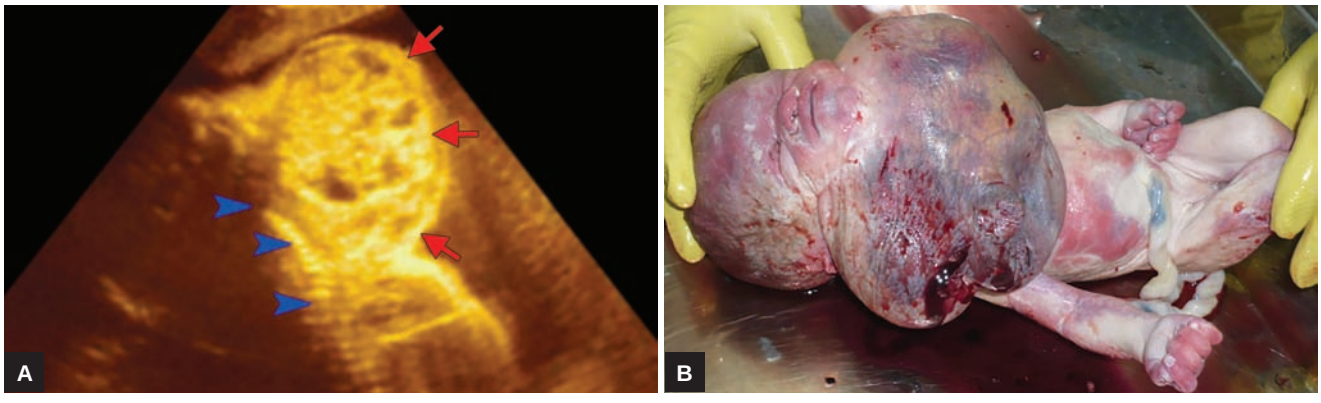
It also allows evaluation of the relationship of the mass to the trachea, information of critical importance in planning delivery, normally by EXIT, and postnatal surgery.[60,68-70]

Fetal MRI performed during pregnancy for investigation of fetal neck masses detected on US gives compatible results observed in the neonate after birth and maintains adequate findings for follow-up and planning of treatment.[39]

Differential diagnosis of the neck teratoma is marked out in Table 9.

Management, Outcome, and Recurrence Risk

Cervical teratomas are associated with high mortality rates. Prenatal US diagnosis of cervical teratoma can be made at 15 to 16 weeks of gestation. Tracheal and esophageal obstruction can lead to polyhydramnios or to airway compromise in the newborn. No direct fetal treatment is



Figs 5A and B: (A) Two-dimensional sonogram in sagittal view demonstrating a massive neck teratoma (red arrows), severe mass effect, and hyperextended position of the neck (blue arrows), especially with solid component; and (B) macro-image demonstrating the immediate postnatal condition; (*Courtesy*: Crîngu Ionescu MD)

Table 9: Differential diagnosis of the neck teratoma

Lymphangioma	Large, unilateral, multiloculated, predominantly cystic tumor often with intrathoracic extension, complicated by hydrops[60]
CH	Posteriorly located, septated cystic tumors, relatively characteristic
Goiter	Homogeneous, echogenic, symmetric mass in the anterior neck
Other neck masses	Amniotic band syndrome, solid thyroid tumors, thyroglossal duct cyst, branchial cleft cyst, laryngocele, parotid tumor, neuroblastoma, hemangioma, hamartoma, lipoma, fibroma[20,60]

available, but management often requires amnioreduction secondary to polyhydramnios and risk of preterm labor. Delivery must be planned with EXIT in a tertiary care center, to reduce the risk of serious complications, which can occur even in apparently successful resuscitations and include brain damage or death associated with severe pulmonary hypoplasia.[60,71-73]

Early resection is the treatment of choice. Delaying surgery can result in further complications, including retention of secretions, atelectasis, and pneumonia owing to interference with swallowing.[60,74]

Because, the thyroid and parathyroid glands may be removed or affected by tumor excision, the risk of permanent hypothyroidism must be considered. Malignancy risk is very low.[60,75]

A novel fetoscopic procedure targeting to ensure extrauterine tracheal permeability by means of a fetal endoscopic tracheal intubation (FETI) before delivery has been reported by Cruz-Martinez and Puerto .[76] The procedure consisted of a percutaneous fetal tracheoscopy under maternal epidural anesthesia using an 11-Fr exchange catheter covering the fetoscope that allowed a conduit to introduce a 3.0-mm intrauterine orotracheal cannula under US guidance. After FETI, a conventional cesarean section was performed uneventfully with no need for an EXIT procedure. This report is the first to illustrate that in cases with large neck tumors involving fetal airways, FETI is feasible and could potentially replace an EXIT procedure by allowing prenatal airway control.

Neck teratoma is considered to be a spontaneous malformation such that risk of recurrence in subsequent pregnancies would not be anticipated.[77]

Lymphangioma and Hemangioma of the Neck

Lymphangioma and hemangioma represent a specific type of vascular malformation most often seen in the soft tissue of the neck, axilla, thorax, and lower extremities.

Lymphangioma of the neck usually diagnosed in late pregnancy could be traditionally referred to as CH, but there is a different prenatal history and outcome.[7]

Lymphangioma is a benign type of vascular abnormality composed predominantly of dilated cystic lymphatics characterized by localized or diffuse malformations of lymphatic channels that can be described as microcystic, macrocystic, or both.[7,78]

Hemangiomas are the result of vascular endothelial proliferation. They have a predilection for the head and neck, although they can occur anywhere in the skin, mucous membranes, or internal organs. Hemangiomas range in size from a few millimeters to many centimeters in diameter. They may be superficial, deep, or combined.[78]

In contrast with the first-trimester diagnosed CH, in which 60% are chromosomal abnormalities and are often associated with other structural defects, isolated CH presenting during the third trimester, often with previously normal sonographic studies earlier in gestation, is usually located anteriorly or anterolaterally in the anterior cervical triangle.[7,79]

These 2 groups of fetuses appear to have lymphangiomas of differing origin, pathophysiology, natural history, and prognosis[7] (Table 10).

Isolated CH presenting late in gestation appears to be a completely different entity. These cases had CH located in the anterior and lateral regions of the neck and were not generally associated with other anomalies or hydrops.[79]

Diagnosis and Imaging Findings: US

Ultrasound is the modality of choice for detecting fetal lymphedema and lymphatic or vascular malformations. Fluid-filled cystic spaces divided by fine septae are commonly observed in the nuchal region and anterior or posterior triangles of the neck.

Table 10: Abnormalities associated with lymphangioma and hemangioma

Chromosomal and nonchromosomal abnormalities associated with CH in late pregnancy[7]	*Chromosomal*
	45×, Trisomy 18, 13, 21, 13q deletion, 18p deletion, Partial 11q:22q trisomy, Trisomy 22 mosaicism
	Nonchromosomal
	Noonan syndrome
	Klippel-Trenaunay-Weber syndrome
	Hennekam syndrome
	Prader-Willi syndrome
	Aagenaes syndrome
	Fetal alcohol syndrome
	Lymphedema–distichiasis syndrome
	PHACE syndrome
	Congenital diaphragmatic hernia

Adapted, completed and revised from Bianchi et al[7]

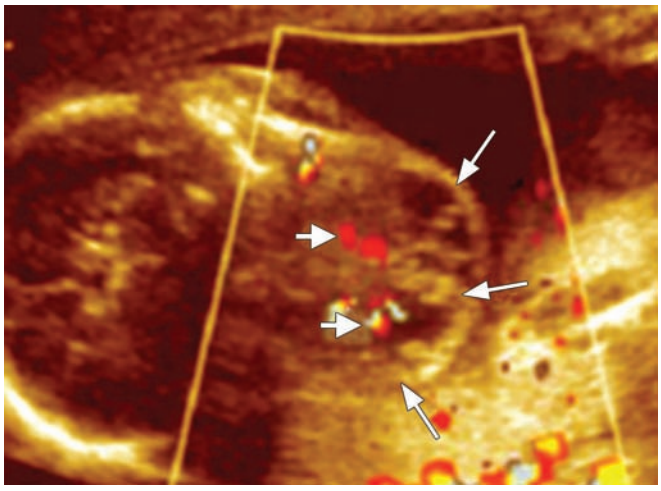


Fig. 6: Axial view of a neck hemangioma (white thin arrows). Mixed solid and cystic tumor with important vascularization – color Doppler (white thick arrows)

In order to differentiate CH from other entities, it is important to exclude a bony defect in the skull or vertebral column as would be seen with enephalocele.[7,38]

Both hemangiomas and lymphangiomas may be large size tumors, which makes the prenatal diagnosis easy. There are reports of first-trimester detection.[80,81]

Hemangiomas are solid or mixed solid and cystic tumors, with important vascularization (Fig. 6). Due to the low velocity of the blood flow, power Doppler may be more useful than color Doppler. Even though the lesion is benign, it may be fatal in cases with large tumors where congestive heart failure and hydrops may occur.[80,81]

Classic signs of association in US diagnosis of lymphangiomas and hemangiomas are generalized fetal edema, fetal hydrops, cystic neck mass, pleural effusion, and pericardial effusion.[82]

It is important to mention that the diagnosis can be missed, even with large lesions, when severe oligohydramnios is present. Cystic hygroma can be mistaken for pockets of amniotic fluid. Serial US examinations every 3 and 4 weeks in the second and third trimesters are useful to evaluate the lesion size and progression, to clarify issues regarding timing and mode of delivery, and to search for findings that are associated with a poor outcome, such as progression of fetal hydrops or the development of oligohydramnios or polyhydramnios.[7,38,82]

Magnetic Resonance Imaging

Magnetic resonance imaging may be helpful in distinguishing CH from cervical teratoma. Nuchal edema is usually without septae except the midline nuchal ligament and is a few millimeters in thickness.[7] Magnetic resonance imaging may also be helpful for assessing the extent of infiltration of the cysts into surrounding structures and in determining the extent of the disease.[82]

Table 11: Differential diagnosis of lymphangioma and hemangioma

Nuchal edema	Septations are absent. Tumescent fetal cervical region
Encephalocele and other neural tube defects	Skull or vertebral column defects (+) hydrocephalus
Cystic teratoma	Difficult diagnosis MRI Teratomas have a more complex sonographic appearance – solid and cystic structure
Branchial cleft cysts	Lack of any solid elements or separations. Good prognosis after surgery
Laryngocele	Well-defined fluid-filled lesion related to the paraglottic space, which has continuity with the laryngeal ventricle
Transient cervical cyst	In soft tissues, superficial to sternocleidomastoid muscle
Multiple aneuploidies and genetic syndromes	Characteristic appearance

Differential diagnosis of lymphangioma and hemangioma is highlighted in Table 11.

Management, Outcome, and Recurrence Risk

Detailed sonographic examination should be performed in a center with expertise in fetal US. Management depends on the presence/absence of nonimmune hydrops, chromosomal abnormalities, or structural anomalies. Genetic amniocentesis is recommended in all cases of CH, and molecular genetics may provide a definitive diagnosis. Prenatal care involves serial US scans. In the presence of severe associated anomalies or chromosomal abnormality prior to 24 weeks, elective termination may be offered. An isolated CH diagnosed in the third trimester has a much more favorable prognosis, and attention should be focused on site and mode of delivery. Delivery should occur in a tertiary center with ability to perform EXIT and manage a difficult neonatal airway. Depending on the diagnosis, the neonate may require a multidisciplinary approach for management of complications. Cystic hygroma with normal karyotype can be inherited as an autosomal recessive transmission.[7,38,82]

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