OGI

Obstetric & Gynecological Imaging

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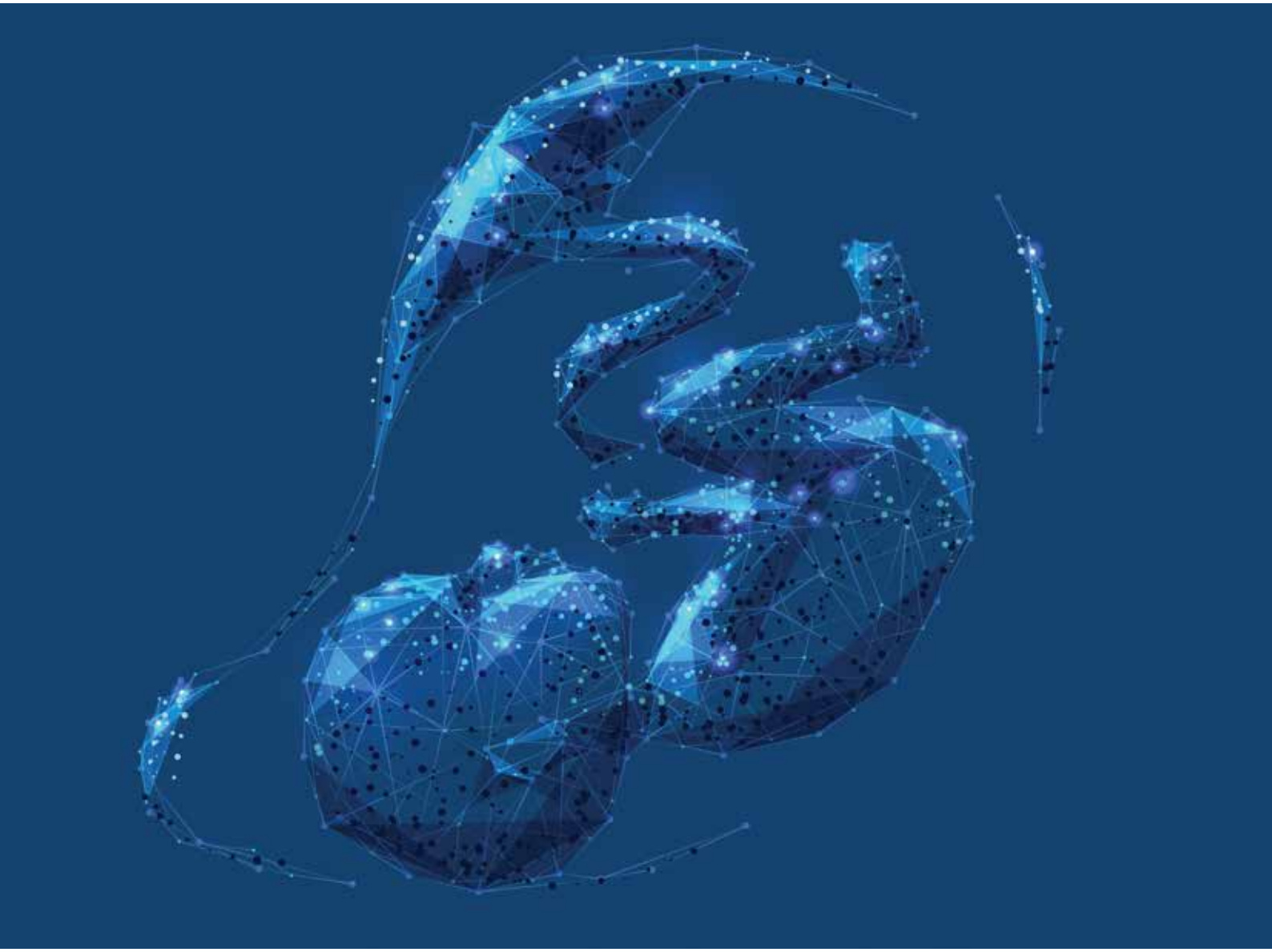

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Hellenic Society For Ultrasound In Obstetrics & Gynecology

Hellenic Society For Ultrasound
In Obstetrics & Gynecology

ARTIFICIAL INTELLIGENCE

Voluson SWIFT

Voluson™ SWIFT is changing everything with powerful AI tools for obstetric imaging. Enhance efficiency and improve consistency with SonoLyst, a suite of AI tools that automatically identify fetal anatomy seen on standard views. Using SonoCNS an Edison AI deep learning technology simplifies assessment of the fetal brain.

gehealthcare.com

This Changes Everything

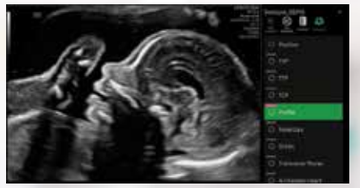
Introducing SonoLyst

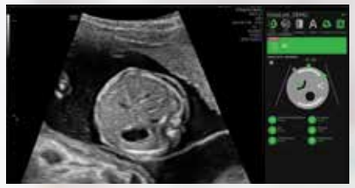
Optimize workflow by more than 70% with AI **

Includes the 20 views recommended by ISUOG mid-term practice guidelines

SonoLystIR

Simply scan then freeze and SonoLystIR (Image Recognition) does the rest. SonoLystIR identifies the anatomy visualized, checks it off the list and can initiate annotations or measurements. Confirm, and data is entered into the Scan Assistant checklist and report.





SonoLystX

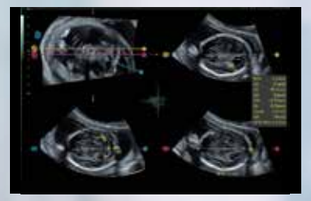
Build and refine your skills with SonoLystX your virtual, on-board ultrasound expert. Using AI the system compares the image or view acquired to standard criteria accepted by experts to ensure it meets the accepted clinical standards. Ideal for teaching and training, progress can be monitored for quality assurance to ensure the highest quality imaging standards and consistency.

Edison

SonoCNS an Edison AI Application

"Central nervous system (CNS) malformations are one of the most common congenital abnormalities"

SonoCNS helps properly align and display recommended views and measurements of the fetal brain.



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*SonoLyst incorporates the AI technology of Intelligent Ultrasound
**Comparison performed using GE's Voluson SWIFT vs. Voluson P8

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CASE REPORT

A case report of an ovarian ectopic pregnancy. A diagnostic dilemma

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ABSTRACT

Ovarian ectopic pregnancy (OEP) is a rare entity. It accounts for 3% of all ectopic pregnancies. We present a case of a nulliparous 27-year-old woman admitted to the hospital with lower abdominal pain. Clinical examination, laboratory values and imaging suggested ruptured ectopic pregnancy. The diagnosis of ruptured ovarian ectopic pregnancy was established during exploratory laparotomy, which was confirmed by the histopathological examination.

KEY WORDS Ovarian pregnancy, ectopic pregnancy, low β-hCG, TVS imaging

Introduction

Ectopic pregnancy (EP) is defined as the implantation of the blastocyst in a location outside of the uterine cavity. The majority occur in the fallopian tube (96%), with ampulla being the most common location (70%). Isthmus ectopic pregnancy accounts for 12% and fimbrial for 11.1%. Interstitial location can be found in 2.4% of ectopic pregnancies, whereas abdominal is the rarest with 1.3% frequency. Here we present a case of ovarian ectopic pregnancy which accounts for 3.2% of all ectopic pregnancies.[1]

The diagnosis of an ectopic ovarian pregnancy is often challenging. A high index of suspicion is necessary to make an early diagnosis. The exact etiology of ovarian ectopic pregnancy is still missing, yet there are a few theories involving ovulatory dysfunction, the egg is fertilized while still within the follicle[2-4]. Most OEP seem to be secondary due to the reflux of a fertilized ovum from the fallopian tube to the ovary. Risk factors, signs and symptoms of an OEP are not sensitive or specific enough to establish a definitive diagnosis. Transvaginal Ultrasound (TVS) with the combination of beta-human chorionic gonadotropin (β-hCG) serum levels are valuable tools for the diagnosis. Transvaginal ultrasonography has a discriminatory zone of β-hCG between 1,000 and 1,500 mIU/mL.[5] An ectopic pregnancy can be suspected if the

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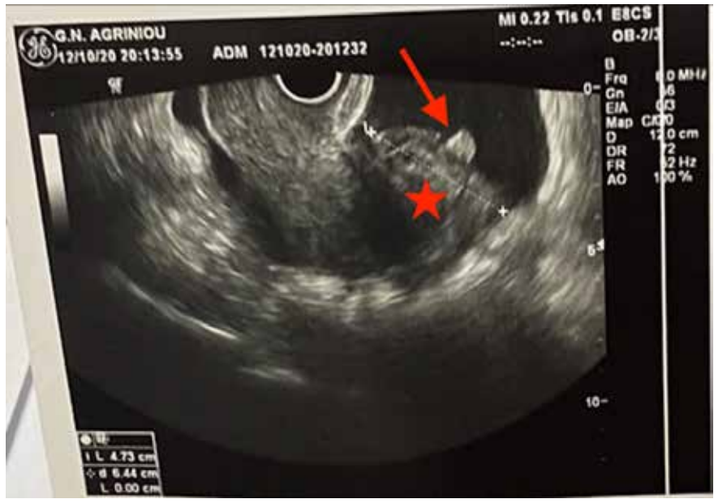

Figure 1: *TVS image, Star: Ovary, Arrow: Echogenic mass*

TVS examination does not detect an intrauterine gestational sac when the β-hCG level is higher than 1,500 mIU/mL. In our case β-hCG serum levels were lower than 1500 mIU/ml, thus a gestational sac could not be visible using a TVS, making it particularly difficult to establish a diagnosis using clinical methods.

Case

A nulliparous 27-year-old woman presented to the Emergency Department of our Hospital with sudden lower abdominal pain. She has had unremarkable past medical and surgical history. History of use of any form of contraception and she was a non-smoker. Her last menstrual period was 1 month ago and her menstruation cycle was regular. Physical examination showed a heart rate at 90 beats/min and a blood pressure of 120/78 mmHg. She had abdominal tenderness at the hypogastric area. The laboratory analysis, at the time of admission, revealed a total white blood cell count (WBC) of 14,300/mm^6, hemoglobin (Hgb) of 13.1 g/dl, hematocrit (Htc) of 40 %, positive urine pregnancy test followed by a serum test for β-hCG which was 448.87 mIU/mL.

Transvaginal sonography was performed, which showed a normal-sized uterus with no intrauterine gestational sac. However, the presence of an inconclusive echogenic mass at the outer edge of the right ovary was observed (Image 1), giving the impression of a pseudosac and a heterogeneous liquid and blood clots in the pouch of Douglas. Multiple intraovarian cysts were identified in the area of the right ovary. Her left ovary seemed to be unaffected. The combination of the ultrasound findings along with β-HCG quantification and patient's clinical status raised the suspicion of a ruptured ovarian ectopic pregnancy. Even though there was a high index of suspicion for an OEP, a ruptured corpus luteum cyst cannot be excluded since β-hCG levels, confirmed in two consecutive measurements, are relatively low. The surgical treatment of the patient was decided, due to the hemodynamic instability.

Exploratory laparotomy was performed. It revealed a hemoperitoneum of approximately 500 ml. The right ovary was 4x3 cm in size with a hemorrhagic mass on its surface (Image 2). Wedge resection was performed followed by primary repair, during which an unidentified mass was retrieved. Histological examination of the specimen revealed a ruptured ectopic ovarian pregnancy. Multiple ovarian cysts were observed underneath the rupture.

Early postoperative period was uneventful and β-hCG levels were reducing gradually reaching 39 mIU/mL three days after the operation, ruling out the possibility of a coexisting intra-uterine pregnancy. Subsequently, patient was discharged on postoperative day three. Follow up β-hCG levels were reduced to 15 mIU/mL on day 14 postoperatively.

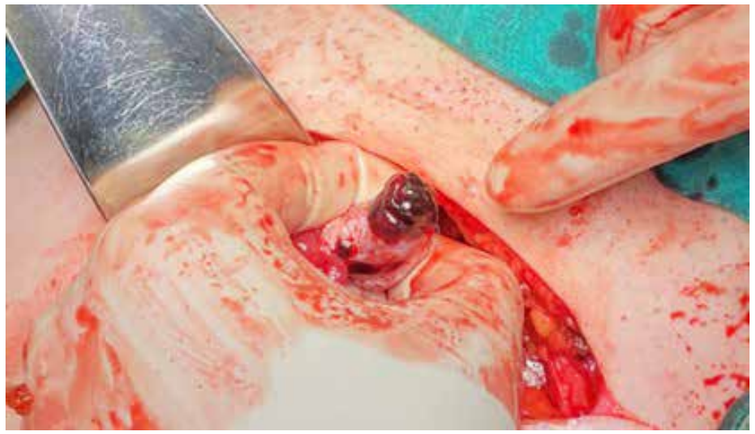

Figure 2: *Intraoperative image of a hemorrhagic mass at the outer edge of the right ovary.*

Discussion

We present a case of a nulliparous 27-year-old woman with signs of ectopic pregnancy. TVS suggested the presence of an ovarian mass and hemoperitoneum. Laparotomy revealed a ruptured ovarian mass and histology confirmed a ruptured OEP.

Several risk factors for ectopic pregnancy have been identified. The risk of EP is associated with previous EP, previous pelvic inflammatory disease and other genital infections such as Chlamydia trachomatis infection, history of infertility, in vitro fertilization and embryo transfer, previous adnexal surgery, previous appendectomy and previous use of intrauterine devices.[3] Additionally, EP risk is increased with age, smoking and spontaneous or induced abortions.[1] Our patient however had no medical or surgical history, she was a non-smoker and never used contraceptives.

Patients with ectopic pregnancy may present symptoms of a normal early pregnancy, such as interruption of the normal menstrual period, nausea, vomiting and fatigue. Furthermore, the most common clinical manifestation of ectopic pregnancy is first-trimester vaginal bleeding with or without abdominal pain.[7] Less commonly, EP presents with hypovolaemic shock secondary to acute intra-abdominal bleeding. Some women, however, can be asymptomatic.[8] In our case, the 29-year-old presented at the ER with acute lower abdominal pain.

Transvaginal Sonography (TVS) is an essential tool for a pre-operative diagnosis with an increasing degree of certainty. Ultrasonic images suggestive of OEP are a wide echogenic ring with a small internal echolucent area.[9] However, resection of ectopic pregnancy tissue followed with histological confirmation is still the gold standard for the diagnosis. In 1878 Spiegelberg established four criteria for the diagnosis of ovarian pregnancy: the fallopian tube on the affected side must be intact, the gestation sac should occupy the position of the ovary, ovary and sac must be connected to the uterus by the ovarian ligament, and ovarian tissue must be histologically present in the sac wall.[10]

Our case was unique in terms of symptomatic manifestation, risk factors and clinical indications, putting us in a diagnostic dilemma. Our patient presented with acute lower abdominal pain without vaginal bleeding. She had no risk factors for ectopic pregnancy and β-hCG serum levels were low, raising several clinical questions. The existence of 448.87 mIU/mL of β-hCG indicates a pregnancy. However, at this level, the gestational sac cannot be visualized within or outside the uterus with the use of TVS. Even though there is a high index of suspicion for an OEP, a ruptured corpus luteum cyst cannot be excluded. In our case, we proceeded to exploratory laparotomy, due to the impended hemodynamic instability of the patient.

TVS is the most frequent tool used for the differential diagnosis of ectopic pregnancy[11]. Taking into consideration the dilemma presented in our case, amendment of diagnostic modalities could be of value in the future research.

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Conclusion

An ovarian ectopic pregnancy is a rare entity in everyday clinical practice. We present a case of a nulliparous 27-year-old woman with no medical history with a ruptured ovarian ectopic pregnancy. The diagnosis was established with histopathological examination of the surgical specimen.

The diagnosis of ovarian EP may be challenging. High suspicion along with a systemic and robust approach of clinical information (symptoms and imaging), will aid in order to minimize diagnostic dilemmas and guide further surgical management. ■

Conflict of Interest

None declared

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CASE REPORT

Fetal Ovarian Cyst: A case report

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ABSTRACT

Introduction: Fetal ovarian cysts are common intra-abdominal cystic masses diagnosed prenatally in female fetuses. The etiology of these cysts is still unknown but an increase in fetal gonadotropin levels is thought to be a possible mechanism.

Case Presentation: We present the case of a 31-year-old nulliparous woman who was diagnosed with a possible fetal ovarian cyst during the routine growth scan at 36+3 weeks of gestation. The scan revealed a unilocular, anechoic mass without a solid component, in the lower abdomen of a female fetus, measuring 60x50x44mm.

Conclusion: Careful evaluation of the fetal abdomen from the second trimester ultrasound and in every routine growth scan is essential for the timely and accurate diagnosis of abdominal cysts. Ultrasound is the gold standard imaging technique during the antenatal period. The prenatal detection of ovarian cysts allows close monitoring of the evolution of the cyst and proper postnatal management of possible complications.

KEY WORDS Fetal ovarian cyst; abdomen cyst; prenatal diagnosis

Introduction

Ovarian cysts are the most common intra-abdominal cystic masses diagnosed prenatally in female fetuses [1]; the etiology of these cysts is unknown but an increase in fetal gonadotropin levels usually related to placental hyperproduction in cases of diabetes mellitus, rhesus isoimmunization and fetal hypothyroidism is thought to be the possible mechanism [2]. They are usually diagnosed after 26 weeks of gestation and in the majority of cases they are unilateral and unilocular, while they may sometimes contain a "daughter cyst" [1]. Ovarian cysts usually disappear after birth, while during pregnancy, torsion and rupture of the ovarian cyst may occur, a challenging situation to manage without a definite treatment plan existing antenatally and postnatally. The main goal is to preserve ovarian function in the highest level possible [3]. In large ovarian cysts (>6cm in diameter) due to compression of the bowel, polyhydramnios may occur

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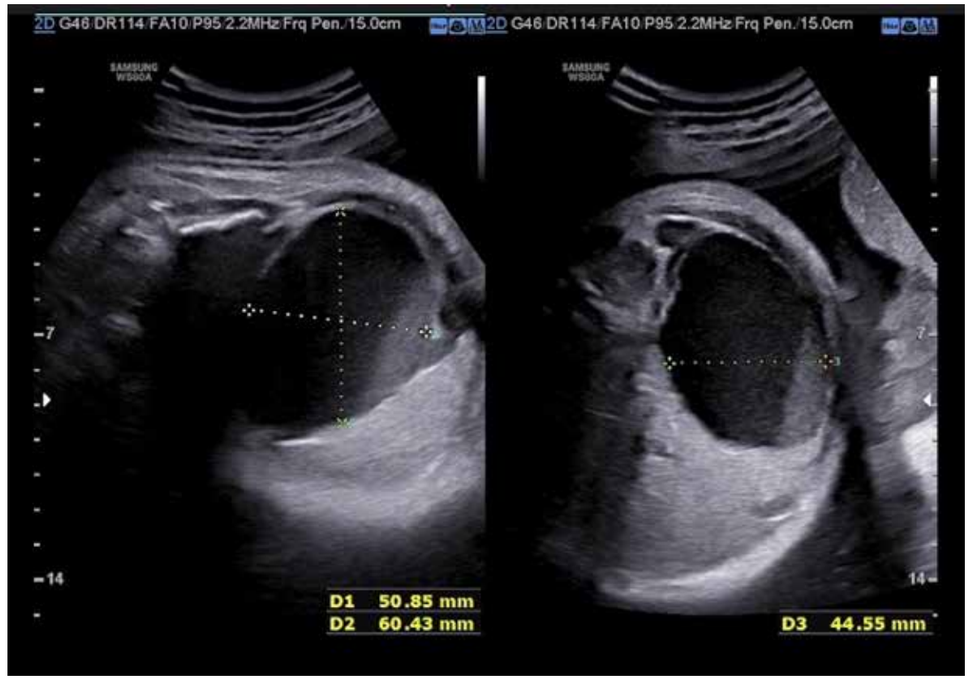

Figure 1. *Fetal ovarian cyst – transabdominal scan*

[4]. We repost a case of a fetal ovarian cyst that led to an uneventful outcome.

Case presentation

A 31-year-old nulliparous woman with spontaneous conception, normal BMI (23kg/m^2), with unremarkable medical history, non-smoker and uncomplicated pregnancy, underwent a routine growth scan at 36^{+3} weeks of gestation. The scan revealed a 60x50x44mm cyst in the lower abdomen of the female fetus. The cyst was unilocular, anechoic with no solid component (Figure 1). Further examination showed no fetal abnormalities, pleural effusion or ascites.

The differential diagnosis included ovarian cyst, duplicated intestinal tract, hydroureter, megacystis, liver and splenic cyst. The kidneys and the bladder appeared normal during the scan, with an ovarian cyst appearing as the most probable diagnosis as the cystic mass appeared on the left side of the upper fetal pelvis and the previous antenatal scans did not show any abnormality. A follow-up appointment in two weeks was arranged.

At 38^{+5} weeks of gestation, the pregnant woman was admitted to the labor ward with preterm rupture of membranes and she delivered vaginally a female neonate weighing 3,340g and an Apgar score of 8 and 9 at the 1st and 5th minute, respectively. The neonatologists performed an ultrasound scan and the diagnosis of ovarian cyst was confirmed. After appropriate counselling to the parents, they decided not to intervene immediately and proceed with another scan in six weeks. In the follow-up scan revealed the ovarian cyst had resolved spontaneously.

Discussion

We described a case of a fetal ovarian cyst with spontaneous resolution during the first six weeks of life. The incidence of fetal ovarian cysts is estimated at 1 in 2,000-3,000 pregnancies [5]. These cysts are usually detected in the third trimester of pregnancy, with the earliest described at 19 weeks of gestation [6]. Most ovarian cysts are less than 5cm and disappear within the first few months of life.

Ultrasound is the gold standard imaging method in the perinatal period, while magnetic resonance imaging may provide supplemental findings like tissue contrast [7]. The "daughter cyst sign", a sonographic clue for the diagnosis of ovarian cysts, is a single, round, anechoic structure attached to the cystic wall, with a sensitivity and specificity of 82% and 100% respectively [8].

Fetal ovarian cysts are classified into two groups. The first group, includes unilocular, ulilateral, anechoic, round, <5cm in diameter, thin-walled cysts while the second "complex" group, includes thick-walled masses with hyperechogenic components and intra-cystic septations [7]. During the prenatal period, ultrasonographic examination to detect any structural changes in size, appearance and complications, is useful in establishing the prognosis.

Most fetal ovarian cysts are small and have no complications; complications that may occur include torsion, rupture, hemorrhage, pleural effusion, ascites and polyhydramnios [4, 9, 10]. Hemorrhage and torsion may cause damage to the ovary. The most serious complication is torsion, seen in 38-55% of cases antenatally and 50-78% during the neonatal period [11]. Possible signs of torsion are fetal tachycardia related to peritoneal irritation, while hemorrhage within the cyst is usually found in association with torsion. Finally, pleural effusion, ascites and polyhydramnios are the result of intestinal obstruction due to large ovarian cysts [4].

There is insufficient data to guide the clinician on the optimal perinatal management of ovarian cysts. Prenatal or postnatal aspiration, ultrasonographic monitoring and neonatal surgery have been proposed, as the main objective is to preserve the ovarian parenchyma [12-14]. The Fetal Medicine Foundation states that if the cyst diameter is more than 6 cm, aspiration of the cyst should be considered, in order to prevent compilations such as distension of the fetal abdomen and disruption of the fetal heart function [1]. Regarding the mode of delivery, unless an obstetric indication is present, vaginal delivery is recommended [1, 15]. Postnatally, the majority of cysts resolve spontaneously, however, surgery may be necessary in cases with torsion, suspicion of neoplastic tumor or abdominal distension due to large cysts.

In conclusion, fetal ovarian cysts represent a non-life-threatening condition, they are usually small in size, uncomplicated and resolve spontaneously. Large cysts can be associated with complications and thus ultrasound scans every 4 weeks to monitor the evolution of the cyst may be advisable [1]. ■

Conflict of interest

The authors declare no conflict of interest.

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Acknowledgments

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PICTORIAL ESSAY

Fetal kidneys: normal sonographic appearance and red flags

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The images below demonstrate the minimum sections that should be obtained in order to assess the fetal urinary system, according to the ISUOG guidelines. At the 20+2 planes approach for the routine anatomy scan, plane 13 refers to the kidneys.

The 20 + 2 planes

Anatomical area	Plane	Description
Abdomen	11	Transverse section of abdomen with stomach & umbilical vein*
	12	Transverse section of abdomen at cord insertion
	13	Transverse section(s) of left kidney & pelvis, right kidney & pelvis
Pelvis	14	Transverse section of pelvis, bladder, both umbilical arteries
Limbs	15	Femur diaphysis length*
	16	3 bones of both legs, both feet & normal relationships to both legs
	17	3 bones of both arms, both hands & normal relationships to both arms
Face	18	Coronal view of upper lip, nose & nostrils
	19	Both orbits, both lenses
	20	Median facial profile
Overview 2	Sweep 2	Transverse sweep of body from neck to sacrum, one vertebra at a time

Requirements from each plane

Plane	Description	Structures to be evaluated[2,3,4]	Measurement & criteria for referral	Abnormalities that can be excluded from the normal appearances of the section
13	Transverse section of left kidney & pelvis, right kidney & pelvis	Both kidneys & pelves	Refer if one or both renal pelves >7 mm AP	Bilateral renal agenesis Renal pelvic dilatation (upper limit of normal = 7 mm AP) Cystic renal dysplasia (unilateral/bilateral)
14	Transverse section of pelvis, bladder, both umbilical arteries	Bladder & umbilical arteries, genitalia*		2 vessel cord Lower urinary tract obstruction

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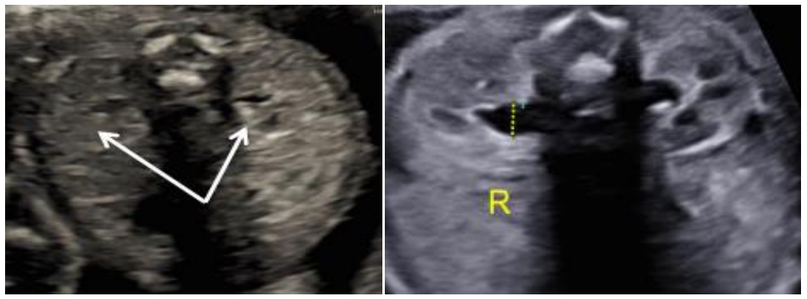
The main section that is always required is the spine up transverse section where both renal pelvises can be clearly seen and measured (antero-posterior diameter, AP). Measurement above 7mm is an indication for referral for further evaluation and follow-up by a specialist. Fetal kidneys are usually spotted via their pelvises.

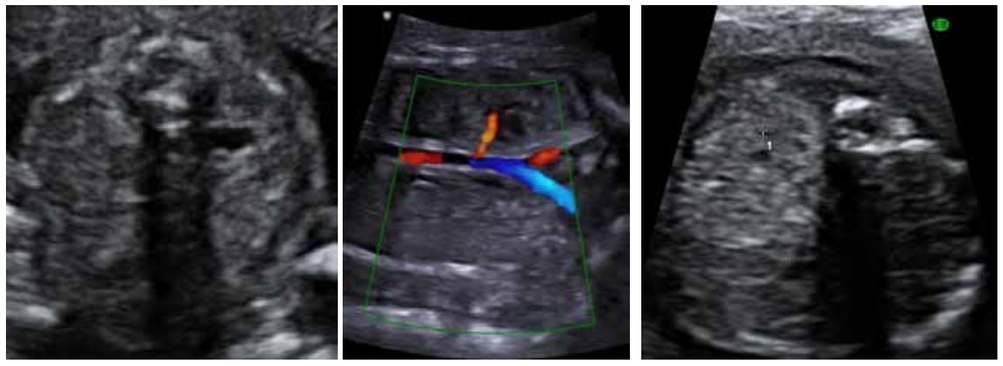


The correct measurement of the renal pelvis includes the inner to inner placement of the calipers at the most clear section.

The main structural abnormalities that are diagnosed or excluded are renal agenesis (bilateral or unilateral), hydronephrosis, cystic renal dysplasia.

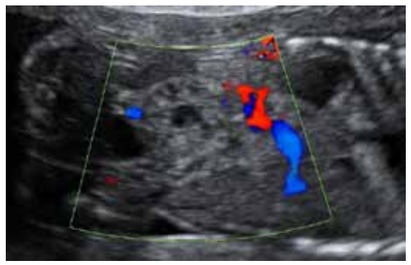
Renal agenesis red flags

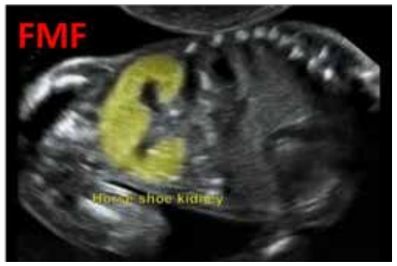
1. Failure to visualize one or both fetal kidneys
2. The adrenal gland appears rounder than normal and fills the renal fossa in what has been termed the "lying down" adrenal sign
3. Color Doppler demonstrates single or no renal arteries (horizontal coronal view)
4. In bilateral renal agenesis (Potter sequence) the fetal bladder is empty and cannot be clearly visualized
5. In case of single renal agenesis compensatory hypertrophy of the contralateral kidney can be detected



Renal ectopia red flags

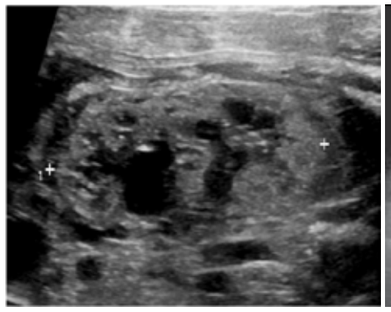
1. Failure to visualize one or both fetal kidneys at the normal renal fossa
2. The adrenal gland appears rounder than normal and fills the renal fossa in what has been termed the "lying down" adrenal sign
3. Kidney structure visualized in the fetal pelvis
4. Color Doppler demonstrates single or no renal arteries (horizontal coronal view), vascular supply may be seen branching from the abdominal aorta in a more acute angle, oblique and caudally oriented, or directly from the iliac arteries
5. A horseshoe kidney may be demonstrated at the coronal or transverse planes (renal tissue crossing the mid-line due to fusion of the lower poles of both kidneys in front of the descending aorta)

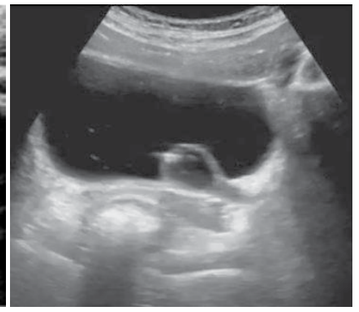




Duplex ureters red flags

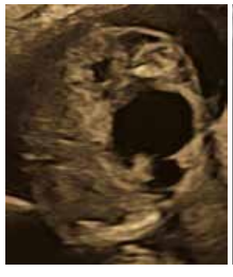
1. Double renal pelvises, non communicating, one or both dilated
2. Ureterocele

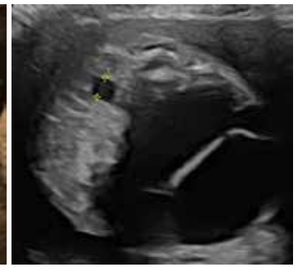




Hydronephrosis red flags

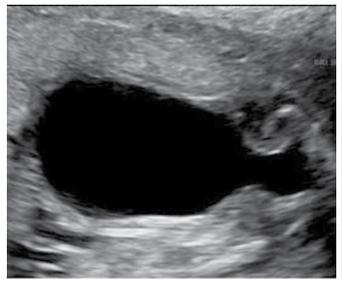
1. In case of a uretero-pelvic junction obstruction, there is pelvicalyceal dilatation without ureteral dilatation
2. Normal or slightly increased AFI
3. Pelvicalyceal communication (vs MCDK)
4. In severe cases, renal cortex thinning (calyces cannot be distinguished)

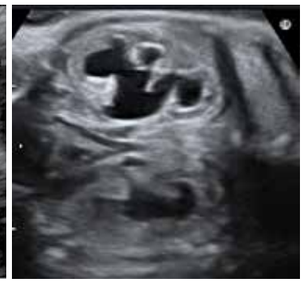




Lower urinary tract obstruction red flags

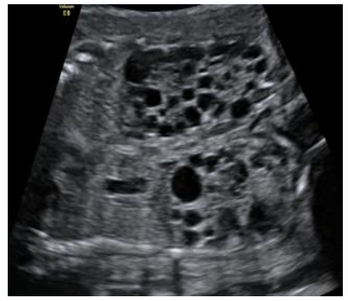
1. Reduced AFI
2. Dialated, thick-walled (>2mm) bladder
3. "Key hole" sign
4. In severe cases there is also ureter dilatation and subsequently renal hydronephrosis

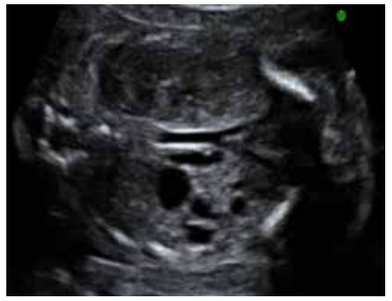




Multicystic dysplastic kidney (MCDK)

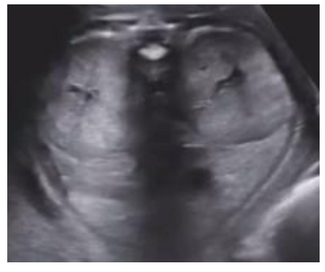
1. Kidney with polycystic appearance or totally replaced by multiple irregular cysts of variable size with intervening hyperechogenic stroma
2. Renal cysts non communicating with renal pelvis (vs hydronephrosis)
3. Renal pelvis usually not visible
4. Echogenic renal cortex





Polycystic kidneys red flags

1. Symmetrically enlarged and hyperechogenic kidneys (when cysts are relatively small in size)
2. Kidneys are generally larger in autosomal recessive form of the disease
3. Renal pelvises cannot be visualised in autosomal recessive form of the disease and there is gradual onset of oligohydramnios from the second trimester (small bladder)
4. Difficulty to differentiate renal cortex to renal stroma ■



CASE REPORT

Ventricular and Great Artery Disproportion during routine Fetal Heart Imaging Evaluation and Management / Technical Report

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ABSTRACT

Size discrepancy (disproportion) between left and right cardiac chambers (atria, ventricles) and /or great arteries is easily identified during routine mid-gestational ultrasound screening (basic fetal heart imaging), representing a referral indication for detailed fetal echocardiogram to rule out the presence of fetal congenital heart disease. In the present review the appropriate imaging technique to avoid foreshortening of ventricular chambers during basic fetal heart imaging, non-cardiac causes of heart chamber disproportion as well as common congenital heart defects associated with chamber and artery disproportion during routine ultrasound fetal imaging are presented.

KEY WORDS Fetal ovarian cyst; abdomen cyst; prenatal diagnosis

Clinical examples

Case 1. Great artery and ventricular disproportion with right ventricular and pulmonary artery dominance over left ventricle and aorta, respectively, was diagnosed during routine sonographic evaluation in a female fetus at 34 wks of gestation. After birth the neonate had signs of diminished femoral pulses, the clinical suspicion of aorta isthmus stenosis (coarctation) has been confirmed by echocardiography. Surgical treatment followed within the first month of life.

Case 2. Pronounced great artery and ventricular disproportion, with diminutive non-apex forming left ventricle, associated hypoplasia of mitral valve, aortic valve, aorta ascendens and transverse aortic arch, detected during routine "extended basic" fetal heart sonographic evaluation at mid-gestation (19weeks). Fetal caryotype was normal, while the diagnosis of hypoplastic left heart syndrome was confirmed following referral for fetal echocardiogram, family was informed about the guarded long-term prognosis and the need for three cardiosurgical procedures after birth followed by increased probability of heart transplantation later in life.

Case 3. Ventricular disproportion, with right ventricular dominance, mild disproportion of great arteries (pulmonary artery dominance) associated with a central septal wall defect (atrial and ventricular) in 4-chamber view and the presence of a common atrioventricular valve. Fetal echocardiogram followed confirming the diagnosis of unbalanced atrioventricular septal defect (AVSD), trisomy 21 has been detected following amniocentesis.

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Definition

Disproportion is defined as an obvious size difference when comparing two structures. The Greek terms dys-analogy (abnormal proportions) or a-symmetry (lack of symmetry) express also the visual size imbalance among structures. The evaluation of disproportion most commonly is subjective (qualitative), expressing the visual impression of the observer when comparing two structures. However for the confirmation of the subjective visual impression exact measurement of each structure size and estimation of the size ratio is needed (objective assessment)

The subjective evaluation for the presence –or absence-of symmetry between fetal heart structures is a fundamental part of the routine fetal heart imaging during mid-gestation sonographic evaluation of fetal anatomic surveillance. Due to the contribution of both fetal circulations to the combined cardiac output (connected at atria level with foramen ovale and arterial level with the ductus arteriosus), the left and right fetal heart structures are visually equally in size. The documentation of symmetry between left and right fetal heart structures is mandatory to be documented both for the atria and ventricles, evaluated at 4 chamber view during "basic" fetal heart imaging, as well as for the great arteries, evaluated at 3 vessel/ 3 vessel-trachea view during "extended" basic fetal heart imaging. The absence of symmetry between left and right fetal heart structures, when imaging errors are excluded, is indicative of imbalance in fetal heart loading and /or growth.

According to current guidelines for the performance of routine sonographic fetal heart evaluation (1) as an essential element of midgestation sonographic fetal anatomy surveillance, the sonographer should evaluate the integrity of fetal cardiovascular system, based on the detailed evaluation of five consecutive transverse views of fetal thorax, from upper abdomen included up to mediastinum. These include the 1) upper abdomen, 2) four chamber (4CH), 3) left ventricular outflow tract (LVOT), 4) Right ventricular outflow tract (RVOT), 5) 3 vessel view (3V) and 6) 3 vessel and trachea (3V-T) view.

Disproportion during routine fetal heart imaging

The presence of symmetry between left and right fetal heart chambers is an essential element of a normal four chamber view (Figure 1): 1) two atria, approximately equal in size, should be documented. They are differentiated as left and right atrium not only from their relative position (the left atrium being the most posterior fetal heart chamber, anterior to the spine, the right atrium being more anterior and rightward relative to the left atrium) but also due to distinct anatomic landmarks: pulmonary veins enter into the left atrium, while the foramen ovale flap projects into the left atrium. 2) two ventricles, approximately equal in size, should be also documented. Similarly they are differentiated as left and right ventricle not only based on their relative position (the right ventricle is the most anterior fetal heart chamber just behind the fetal sternum, the left ventricle posterior and leftward from the left ventricle, with the intraventricular septum having a normal angle of 45 degrees relative to the anteroposterior fetal thorax axis) but also due to distinct anatomic features: the right ventricle atrioventricular valve (tricuspid) offset is more close to the fetal apex compared to the left ventricle atrioventricular valve (mitral), the right ventricle has a muscular band close to its apex (moderator band). (1-4)

The presence of symmetry between the great arteries can be already assessed in their proximal parts, as they originate from the corresponding ventricles in a "cross-over" fashion (LVOT and RVOT views) as the proximal aorta has a rightward (towards right shoulder) and the proximal pulmonary artery a straight backward direction (towards left paravertebral area).

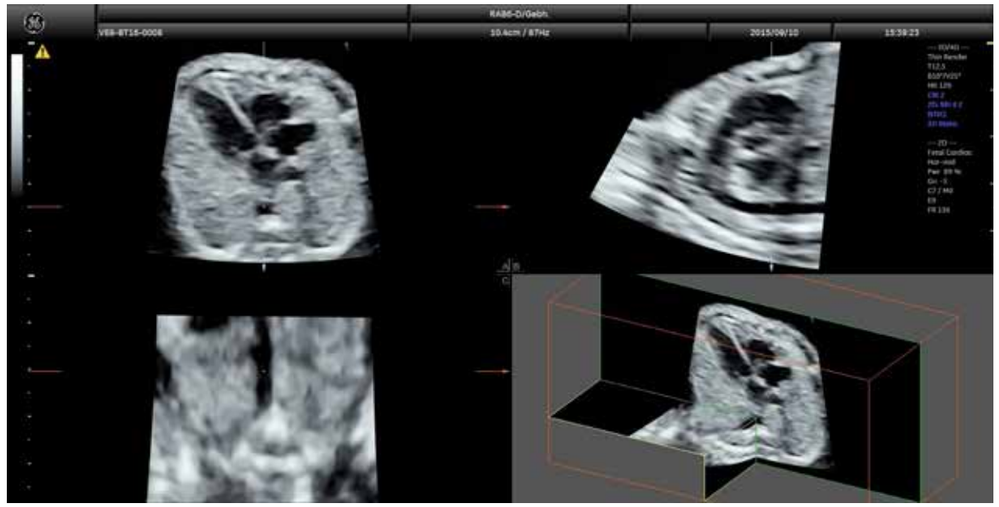

Figure 1. *Appropriate transverse plane for routine fetal heart imaging: 4 chamber view*
STIC volume reconstruction, demonstrating the recommended 4 chamber view transverse plane (upper left, original acquisition plane A), acquired by scanning the fetal thorax perpendicular to the fetal spine-aorta (upper right, reconstructed plane B), which are visualized at a large segment (lower left, reconstructed plane C). Author's personal archive

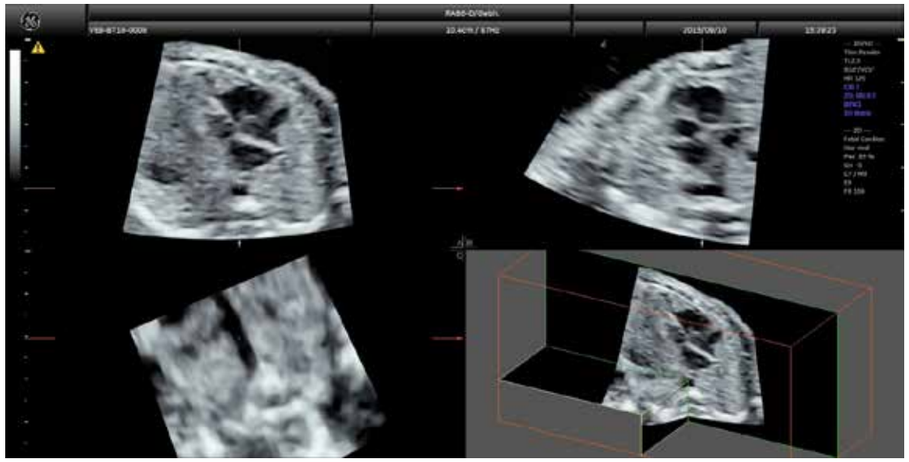

Figure 2. *Pseudo-disproportion due to misalignment of 4-Chamber view plane*
STIC volume reconstruction, demonstrating ventricular pseudo-disproportion (RV>LV) obtained by a non-perfect transverse fetal thorax view (upper left, original acquisition plane A), acquired by scanning the fetal thorax perpendicular to the fetal spine-aorta (upper right, reconstructed plane B), which are although not visualized at a large segment (lower left, reconstructed plane C) due to incomplete rotation of the probe to the transverse plane. Author's personal archive

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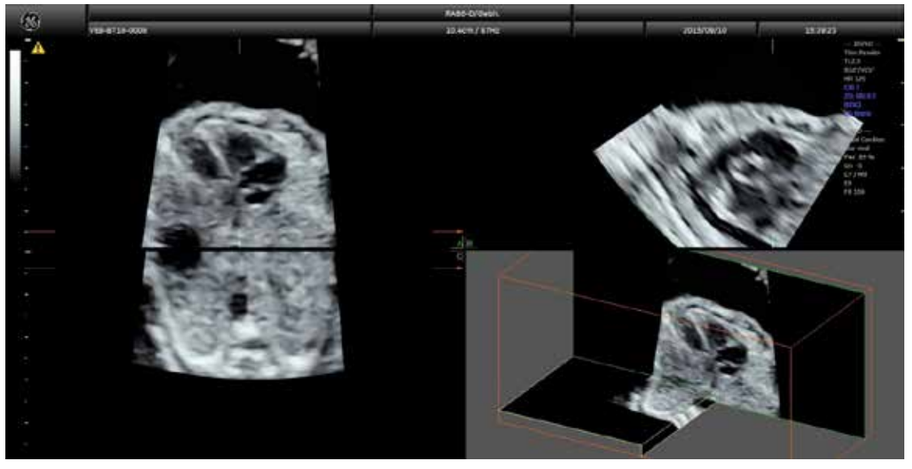

Figure 3. *Pseudo-disproportion due to misalignment of 4-Chamber view plane*
STIC volume reconstruction, demonstrating ventricular pseudo-disproportion (RV>LV) obtained by a non-perfect transverse fetal thorax view (upper left, original acquisition plane A), acquired by scanning the fetal thorax oblique to the fetal spine-aorta (upper right, reconstructed plane B), due to unfavorable fetal position. Author's personal archive

The assessment of symmetry in the distal parts of the great arteries (transverse aorta compared to distal pulmonary artery –ductus arteriosus) is evaluated at the more superior mediastinal views, namely at the 3 vessel view and 3 vessel-trachea view. In the 3 vessel view, from right to left are visualized the cross section of the right superior vena cava, the transverse aortic arch (with a leftward now direction), and the pulmonary artery – ductus arteriosus (straight backward direction). In the 3V trachea view, both great arteries (aorta and ductus arteriosus) confluence at the left of the trachea (named the V sign), where the aorta descendent accepts their combined flow. In the 3 vessel view a mild asymmetry of the vascular structures is expected representing a normal finding, with the superior vena cava being of smaller diameter compared to aorta, which is relative smaller than the pulmonary artery-ductus arteriosus. It should be emphasized that the presence of cross-over of the great arteries and a V sign at their confluence at the left of the trachea is not sufficient to identify the artery originating from the left ventricle as aorta, and the one originating of the right ventricle as the pulmonary artery: the distinct anatomic features of each vessel should be also demonstrated for their correct characterization (the pulmonary artery giving branches –bifurcation very close to its proximal part, the aorta's branches originate much more distally).

Pseudo-disproportion.

This term is suggested as most appropriate in the present review, to describe the visual impression of fetal heart chamber disproportion when such a disproportion does not really exist, a finding based solely due to imaging related limitations (Figures 2,3). Pseudo-disproportion is a common referral indication for fetal echocardiography, especially in cases where the fetal position is unfavorable, combining a twisting and bending fetal projection, or when there is a failure to obtain a perfect transverse cut of the fetal thorax, due to unfavorable fetal spine projection relative to any available ultrasound probe angle placed on the maternal abdominal area.

An ideal 4 chamber view should be obtained at a perfect transverse fetal thorax sonographic plane (Figure 1). First we have to evaluate whether the sonographic plane is appropriate (perfect transverse) and then to validate fetal heart chamber symmetry. The correct imaging plane should be perpendicular (at 90 degrees) to the axis of the fetal spine: This can be accomplished by first vis-

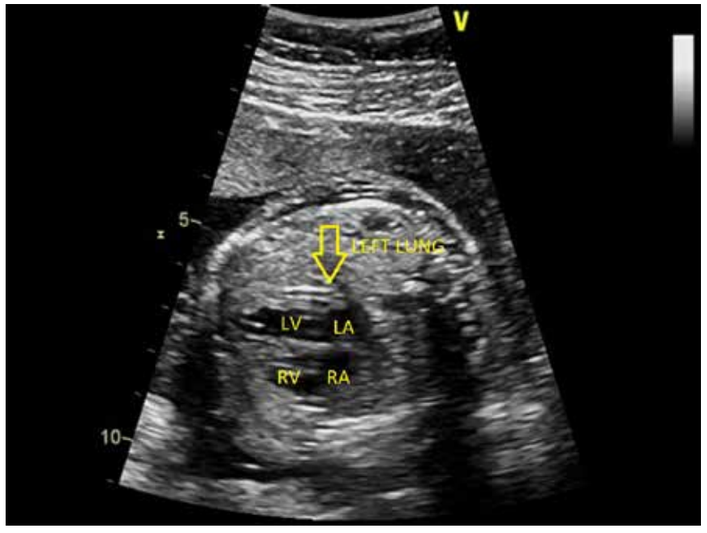

Figure 4. *Fetal Heart Disproportion due to external fetal heart compression*
External compression by left lung mass (CCAM) resulting into rightward displacement of fetal heart, abnormal heart axis and mild disproportion (LV<RV) of ventricles in 4 chamber view. Author's personal archive

ualizing the fetal spine in a sagittal view (where the full length of the thoracic spine is in view), first by moving / angling our probe to the maternal abdomen so as the fetal spine lies parallel to our probe interface, then carefully rotating the probe (while keeping the same insonation angle relative to spine) at 90 degrees, and adapting our transverse plane to the recommended fetal heart imaging plane by sliding the probe towards the fetal head or abdomen, as needed. In cases where the fetal projection is a combination of twist and bending it could be impossible to have a perfect transverse view, as indicated by the imaging of multiple rib cuts in the one side of the fetal thorax compared to the other. Care therefore should be taken to comment on the present of fetal heart chamber symmetry or not, when a perfect transverse imaging plane was not or cannot be acquired. Repeating the scan at a later point and referring the case for fetal echocardiography in case of persistent fetal chamber disproportion despite repeated imaging efforts, is recommended.

Non-cardiac causes of disproportion.

Fetal heart position, size and symmetry within the fetal thorax can be affected by non-cardiac conditions resulting in heart compression or translocation within the fetal thorax (Figure 4). The normal fetal heart imaging in 4 chamber view is characterized by a) both stomach and heart being at the left side of the fetus b) heart occupies one third or thoracic area (cardiothoracic area ratio < 0.33), c) the majority of fetal heart area lies in the left chest and d) the cardiac axis (apex) points to the left, with an angle of 45 degrees (± 20 degrees) between the anteroposterior thorax line (sternum to spine) and the line crossing the fetal intraventricular septum. In case of fetal heart chamber disproportion associated with any abnormalities of the above normal 4-chamber view features, including abnormal fetal heart position within the fetal thorax, abnormal fetal heart size or abnormal fetal heart axis care should be taken to rule out non-cardiac causes resulting into fetal heart compression including congenital diaphragmatic hernia, fetal lung malformations with mass effect on adjacent structures (lung sequestration, cystic adenomatous malformation, lung cysts), lung hypoplasia and fetal thorax deformities

Disproportion due to loading conditions.

Provided that pseudo-disproportion and non cardiac causes of disproportion have been excluded, differences in loading conditions between left and right fetal heart

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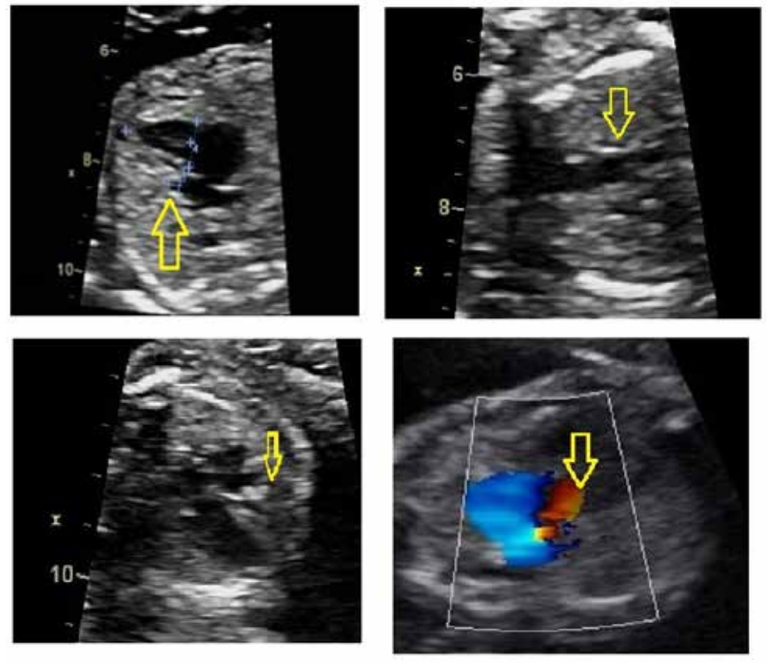

Figure 5. *Ventricular and Great Artery disproportion due to Critical Fetal Congenital Heart Disease*
Severe hypoplasia of left atrium-diminutive left ventricle (upper left) and aorta (upper right) in Hypoplastic Left Heart Syndrome; Hypoplasia and hypertrophy of right ventricle (lower left) with retrograde flow in hypoplastic pulmonary artery (lower right) in Pulmonary Atresia-Intact Ventricular Septum (arrows). Author's personal archive

chambers have to be also excluded. In contrast to postnatal circulation, where the two circulations (pulmonary, systemic) are connected in series (all systemic venous blood return will pass through the right heart chambers into pulmonary circulation, then to left heart chambers, systemic arteries and back to right heart), in the fetus the two circulations are connected in parallel (communicating in the atrial level-foramen ovale and arterial level-ductus arteriosus, both with right to left shunt) (5). On contrast to postnatal circulation where the left ventricle (LV) is the dominant pump, in the fetus the right ventricle (RV) is dominant, contributing about 60% of combined fetal cardiac output. RV filling is based mainly on inferior and inferior vena cava flow (deoxygenated venous blood) while it pumps relative deoxygenated blood through the ductus arteriosus (DA) into the fetal aorta descendens and placenta (fetal lungs receive very low perfusion). LV filling is based mainly on the highly oxygenated blood, of umbilical vein-ductus venosus (DV), entering preferentially into the left atrium through the foramen ovale intraatrial communication. LV pumps the highly oxygenated blood into aorta ascendens and fetal brain, the remaining passing through the narrowest part of the aorta (isthmus) to the aorta descendens (which receives also the flow from the ductus arteriosus). Different loading conditions (in terms of filling –preload and resistance against which the ventricles have to work-afterload) can result in ventricular disproportion, including cavity size and / or wall thickness. A typical example of ventricular disproportion due to differential loading conditions is ductus arteriosus (DA) constriction, associated with significant afterload increase for the RV, resulting into RV dilation and RV/LV disproportion. Careful inspection of DA flow pattern and size can allow for the appropriate diagnosis, as ventricular disproportion at late gestation is also associated with the possibility of congenital heart

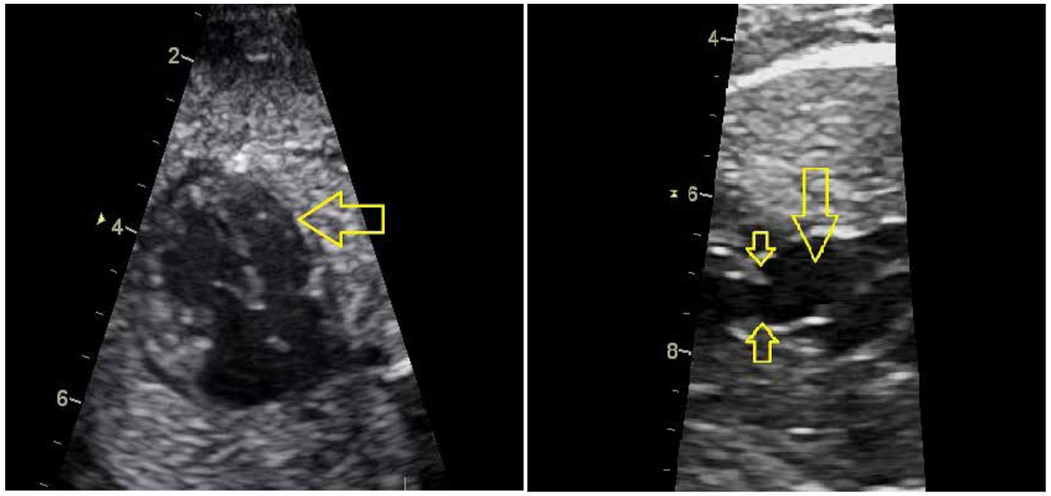

Figure 6. *Ventricular and Great Artery disproportion due to Mild-Moderate Fetal Congenital Heart Disease*
Mild Ventricular disproportion (LV <RV) in atrioventricular septal defect (AVSD) (left); Mild Great Artery disproportion (PA>AO) in valvar pulmonary stenosis associated with systolic doming of thickened pulmonary valve leaflets (smaller arrows) (right). Author's personal archive.

disease (especially aortic isthmus stenosis / coarctation of the aorta). Avoidance or discontinuation of administration of prostaglandin inhibitors (NSAIDs) to the pregnant woman with DA constriction can result in recovery of normal DA flow pattern and ventricular disproportion (6). Other causes of non-congenital heart disease associated ventricular disproportion include restrictive flow in the foramen ovale (in animal models resulting into hypoplastic left heart syndrome), increased placenta flow vascular resistance etc. Cases of fetal anemia or high flow states (hyperdynamic circulation associated with AV malformations) can lead to increased fetal heart size with relative balanced ventricular size.

Disproportion due to congenital heart disease.

Provided that pseudo-disproportion and fetal heart compression and loading imbalances have been excluded, the possibility that fetal heart artery chamber and /or great artery disproportion is due to fetal congenital heart disease (CHD) is very high (7). There is an immediate referral indication for fetal echocardiogram by an expert fetal cardiologist, with referral indication "abnormal fetal heart views during anomaly scan, suspected fetal congenital heart disease" (2-4). The detailed description of all CHD types associated with ventricular and /or great artery disproportion is out of the scope of this review, as CHD forms associated with disproportion are numerous with a great variability of the presence and extent of disproportion observed also within any given CHD form (for example tetralogy of Fallow can be associated with various degrees of pulmonary hypoplasia) as well as within the same subject with advancing gestational age (dynamic evolution of CHD forms during pregnancy) (5). As general rule, the more pronounced the disproportion and the earlier in gestation when the disproportion is detected, the more guarded the final prognosis of the fetus regarding the possibility of a final complete bi-ventricular repair might be. An example of extreme disproportion (RV> LV) with diminutive left heart structures (LV, Aorta) at times hardly to detect at all represents the hypoplastic left heart syndrome (HLHS, one of the most severe CHD forms) (Figure 5). Similar findings regarding the right ventricle can be observed in pulmonary atresia with intact ventricular septum, characterized by extreme hypertrophied, diminutive right ventricle (Figure 5). Ventricular and great artery disproportion can be observed in cases of aortic isthmus stenosis (coarctation) at times

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associated with long segment aortic arch hypoplasia (7). Cases of aortic and pulmonary artery valve stenosis, especially if not critical, can be associated with postenotic dilation of the corresponding artery, resulting in great artery disproportion (Figure 6). Atrial and ventricular disproportion is a common finding in complex congenital heart disease associated with malformation of atrioventricular valves (including tricuspid valve atresia with ventricular septum defect, Ebstein malformation of tricuspid valve characterized by a massively enlarged right atrium and some forms of atrioventricular septal defect –non balanced AVSD forms, Figure 6).

In every case of fetal heart chamber / artery disproportion during the routine mid-gestational anomaly scan, not explained due to fetal position, external fetal heart compression or loading imbalance, there is an immediate referral indication for fetal echocardiogram (2-4). This will confirm the finding of disproportion, provide indexed values (to gestational age or fetal body size) of cardiac structures (confirming which of the compared structures and at what extend deviate from normative values) (8-11), confirm or detect of associated fetal heart malformations (atrial, ventricular septum defects, abnormalities of inflow and outflow valves). Application of advanced imaging fetal heart imaging can be helpful (12,13). Counselling of the family regarding defect-specific postnatal treatment and long term prognosis will follow (14), as well as recommendation for fetal karyotyping including heart defect specific defects –such as Di George etc, in case where karyotyping has not already been performed.

Summary

Training in the acquisition of the recommended fetal heart views during routine fetal heart imaging is crucial for the early detection of fetal CHD, as most cases do not have an indication for fetal echocardiogram, representing a specialized evaluation reserved for specific indications. Fetal heart chamber and /or great artery disproportion is an easily detected abnormality of the recommended views of the fetal heart during routine mid-trimester ultrasound scan screening. Provided that the finding is not due to fetal unfavorable position, external fetal heart compression or loading conditions, there is an immediate referral indication for fetal echocardiography, as the risk of fetal congenital heart disease is high. ■

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ORIGINAL ARTICLE

Antithrombotic therapy during in vitro fertilization (ivf)

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ABSTRACT

The use of antithrombotic agents during IVF is widely considered for the prevention and treatment of thrombotic complications, but also for their possible beneficial effects on pregnancy outcome. Women who develop OHSS are recommended to receive LMWH for at least 3 months. An assessement of thrombotic risk should be offered to all women undergoing IVF
Heparin emerges as a promising agent in IVF, not only for its antithrombotic effects but also for its cytoprotective effect on trophoblast implantation and growth through the increase of HB-EGF secretion, the reduction of TNF-a-induced apoptosis of endometrial cells and the increase of matrix metalloproteinase-2 activity (MMP-2)
Further RCTs are needed in order to evaluate the efficacy and safety of antithrombotic agents in IVF, to identify patient groups that may benefit more from its administration as well as to establish guidelines for the timing, duration, and dose of LMWH.

KEY WORDS IVF, LMWH, thrombosis, pregnancy outcome

Since its first application in 1978 , in vitro fertilization (IVF) has been the most frequently used method of assisted reproduction, aiming to address the ever-increasing rates of infertility in the modern world. (1) The introduction of new techniques and new pharmacological approaches has led to an increase in the success rates of patients undergoing IVF (2); however, only one-third of IVF procedures result in pregnancy, and many women experience repeated failures over multiple IVF cycles, mainly due to implantation disorders. (3)

Thrombophilia, hereditary and acquired, is a known risk factor for secondary infertility, while its role is also being investigated in cases of repeated IVF failures. The successful use of antithrombotic agents, specifically low molecular

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weight heparin (LMWH) in pregnancies of patients with acquired thrombophilia, suggested its application also in the field of assisted reproduction, with encouraging results. The use of LMWH appears to increase success rates in repeated implantation failures after IVF, but also in pregnancy complications related to the placenta or delayed intrauterine growth, regardless of the presence of thrombophilic or autoimmune disorders, thus attributing to heparin potential cytoprotective actions duringthe processes following fertilization. (3,4,5)

Pregnancy as well as the postpartum period are characterized as hypercoagulable states, since during these periods there is a 4-5 times greater risk of thromboembolic events than the general population. (6) In the case of IVF, exogenous administration of gonadotrophins during the ovarian stimulation phase leads to a rapid increase in estradiol levels and changes in the concentrations of coagulation and anticoagulant factors, with the risk of venous thromboembolic disease being up to 3 times greater compared with a spontaneous pregnancy. (3,4)

The observed changes concern the increase in the concentration of coagulation factors (fibrinogen, factor V and VIII, vWF), d-dimers and markers of endothelial damage, such as thrombomodulin, and the decrease of natural inhibitors (protein C and S, antithrombin), while in global coagulation tests (thromboelastography) a significant reduction in clotting time is observed. (3,4) The coexistence of inherited or acquired thrombophilia, oocyte retrieval procedures, immobility, and repeated exposure to hormonal agents in cases of failure obviously further increase the thrombotic risk. (3)

Thrombotic complications during assisted reproduction are mainly venous and less often arterial, with deep vein thrombosis of the upper extremity being a frequent manifestation, due to the drainage of estrogen-rich intra-abdominal lymph into the major thoracic duct. (4)

A special clinicalentity is theovarian hyper-stimulation syndrome (OHSS), a serious systemic complication of controlled ovarian stimulation, characterized by swelling of the ovaries, very high concentrations of estradiol, increased vascular permeability and leakage of fluids into the third space. (7) The more pronounced changes in the concentrations of procoagulant and anticoagulant factors in the case of OHSS, combined with intravascular volume contraction and subsequent hemoconcentration, lead to a steep increase in thrombotic risk, with 1 in 128 women with OHSS developing a thromboembolic event. Therefore, women who develop OHSS are recommended to receive anticoagulation with LMWH for at least 3 months. (3,4,7)

The use of antithrombotic agents during IVF is widely considered today for the prevention of thrombotic complications, but also for their possible beneficial effects on achieving and maintaining a pregnancy. Aspirin, with its antiplatelet and anti-inflammatory effects, has been studied for its effect on successful implantation and pregnancy rates, but with conflicting results. (3) Its administration in combination with LMWH is well studied during pregnancy in women with antiphospholipid syndrome, however its routine use as prophylaxis during IVF procedures requires further investigation and questions regarding the benefit of anticoagulation administration, its duration and its dose have not been definitely answered. (3) LMWH is used for the treatment for thromboembolic complications during assisted reproduction and pregnancy, but also for prophylaxis in women with known thrombophilia and/or a history of thrombosis. However, its role seems to extend beyond the aforementioned, with the discovery and study of the interactions of heparin with growth factors, cytokines and adhesion molecules involved in the process of implantation and growth of the trophoblast. (4)

Pregnancies achieved by IVF are characterized by an increased risk of perinatal complications, such as prematurity, preeclampsia, perinatal mortality and intrauterine growth retardation, which are associated with implantation disturbances during the first trimester of pregnancy. (4) After implantation of the blastocyst in the endometrium, the trophoblast proliferates and differentiates into two forms, villous and extravillous trophoblast. The latter is responsible for the filtration of the placental and spiral arteries, establishing communication with the maternal blood and ensuring the survival of the fetus. Many molecules participate and regulate this process, with heparin binding epidermal growth factor (HB-EGF) playing a leading role. (8)

HB-EGF is produced by the endometrium and placenta of the first trimester of pregnancy and participates in the differentiation of the extrafollicular trophoblast, in the regulation of the motility of the endometrial stromal cells at the site of implantation, while it also exerts a cytoprotective effect, which is confirmed by the reduced expression of in trophoblast from placentas of patients with preeclampsia or antiphospholipid syndrome. (8,9)

LMWH appears to increase the expression of growth factors from the endometrium and exert its protective effect on trophoblast implantation and growth through the HB-EGF pathway. More specifically, in a study by D'Ippolito et al., the use of LMWH in extrafollicular trophoblast cells from women with six first-trimester miscarriages led to an increase in HB-EGF expression, improving trophoblast penetration and growth. (8) Similar results have also been observed in the study by Bolnick et al., where in addition to the increase in HB-EGF secretion in the presence of LMWH, inhibition of the growth factor abolishes the effects of heparin, thus emphasizing the interaction between these two molecules, with requires the integrity of the HB-EGF pathway. (9) In another study, LMWH appeared to exert a dose-dependent effect, promoting trophoblast proliferation, differentiation, and infiltration at low concentrations and inhibiting these at higher concentrations. (10) Additional data support the role of heparin in reducing TNF-a-induced apoptosis of endometrial cells, in increasing the activity of matrix metalloproteinase-2 (MMP-2) which participates in the infiltration of the extravillous trophoblast, but also in the possible its beneficial effect on endothelial function and angiogenesis during pregnancy. (8,9,11)

Evaluating the use of heparin in real-world settings, several studies are found in the literature with increased success rates with the administration of LMWH in patients with recurrent episodes of spontaneous abortion (12) or with two or more implantation failures after EG (5,13). However, the great heterogeneity in the inclusion characteristics of the patients in the studies and the timing and dosing of LMWH administration do not allow safe conclusions to be drawn. (3,14)

In summary, heparin emerges as a promising agent in assisted reproduction, on one hand, with its anticoagulant effect on the prothrombotic changes that take place during IVF processes and particularly in the presence of thrombophilia or OHSS predisposing factors, and on the other hand, with its action beyond its antithrombotic effect, i.e. its cytoprotective effect on trophoblast implantation and growth. Limited data exist regarding the role of antiplatelet therapy with aspirin in IVF. Further studies are needed in order to evaluate the efficacy of antithrombotic agents and their safety in pregnancy, as well as to establish specificr guidelines, for the timing, the duration, and the dose of anticoagulants , as well as for the selection of subgroups of patient that may benefit more from anticoagulation administration. ■

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