Hemorrhagic heterotopic pregnancy in a setting of prior tubal ligation and re-anastomosis

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Radiology Case. 2015 Jul; 9(7):38-46 :: DOI: 10.3941/jrcr.v9i7.2386

ABSTRACT

Heterotopic pregnancy is the occurrence of simultaneous intrauterine and extrauterine pregnancies. Heterotopic pregnancy most commonly occurs during the first trimester of pregnancy in women who have significant risk factors including assisted reproductive therapy, prior ectopic pregnancy, and prior pelvic surgery or pelvic inflammatory disease. Although rare, heterotopic pregnancy must be recognized using ultrasound so as to provide appropriate treatment to the extrauterine pregnancy with the goal of preserving the intrauterine pregnancy. The case presented describes a patient with a pathologically proven (figure 8A and 8B), surgically treated 1st trimester heterotopic pregnancy.

CASE REPORT

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A 35 year old Gravida7Para3123 woman with a 10 pack year smoking history presented with acute abdominal pain and cramping to our Emergency Department. The patient's last menstrual period (LMP) was six weeks prior to her presentation. Her significant past medical history included a tubal ligation 14 years ago followed by re-anastomosis 8 years later. Three years before her presentation, the patient had a tubal ectopic pregnancy that was successfully treated with Methotrexate. She has no anatomic uterine anomalies or history of pelvic surgery other than tubal ligation followed by tubal re-anastomosis. At the time of her current presentation, the patient's white blood cell count (WBC) was 12,800 (normal 4,500 - 10,000 per mcL) and her β-hCG was 35,871. Her basic metabolic panel, liver function tests, and urine analysis were unremarkable. She was afebrile, and her vital signs were stable. On physical exam, the patient was reported to have diffuse abdominal tenderness but no rebound or guarding.

The patient underwent transabdominal and transvaginal ultrasound, revealing a single live intrauterine pregnancy (IUP) with an estimated gestational age of 6 weeks, 4 days +/- 1 week (figure 1 and 2). Ultrasound also confirmed a thick walled cystic structure in the right adnexal region that was separate from the right ovary (figure 3A &3B) with a large amount of complex free fluid in the pelvis extending into Morisons and Douglas Pouches (figures 4 &5). One of two thick-walled cystic structures in the left ovary was thought to represent a corpus luteal cyst of pregnancy (figures 6 & 7).

Following evaluation by an Obstetrics and Gynecology physician, the patient was taken emergently to the operating room that day. Upon laparoscopy, an actively bleeding, ruptured right-sided tubal ectopic pregnancy was confirmed at the scarred site of tubal re-anastomosis and was subsequently removed. The patient had an unremarkable post-operative course and was discharged home the next day. The IUP was viable and the patient has continued to follow-up regularly at the Obstetrics Clinic.

DISCUSSION

Etiology & Demographics

Abdominal and pelvic pain in a pregnant patient can be caused by an extensive number of conditions including a normal early pregnancy, spontaneous abortion, ectopic pregnancy, molar pregnancy, and heterotopic pregnancy (1). An ectopic pregnancy is defined as an extrauterine pregnancy (EUP) without a viable IUP and is the leading cause of maternal death during the first trimester of pregnancy. EUP can occur in the fallopian tubes, uterine interstitium, corneal region of the uterus, ovaries, cervix, surgical scars (especially Caesarean), and intra-abdominally. However, approximately 95% of EUP are tubal, mostly occurring in the ampulla (70%).

A heterotopic pregnancy occurs when an IUP and EUP occur simultaneously (2). Heterotopic pregnancy is a potentially fatal condition, first reported in 1708 as an autopsy finding (3). The prevalence of heterotopic pregnancy is estimated to be 1%-3% in women who have undergone assisted reproduction, especially ovulation induction. In the general population, the incidence of heterotopic pregnancy is thought to be as low as 1 in 7,000 (4). Additional risk factors for heterotopic pregnancy are listed in Table 1 below, many involving damage to the fallopian tubes, which may inhibit the peristaltic movement of fertilized embryos into the uterine cavity (5). Therefore, suspicion and knowledge of heterotopic pregnancy risk factors is increasingly important as more women have these risk factors due to increased utility of reproductive assistance. Additionally, the diagnosis of heterotopic pregnancy should be considered when a patient with a history of an aborted IUP continues to experience adnexal pain with abnormal β-hCG levels (2). Even if the transvaginal US is negative, heterotopic pregnancy should remain in the differential diagnosis of any patient with significant risk factors for heterotopic pregnancy presenting with abdominal pain and/or clinical symptoms (5).

The majority of heterotopic pregnancy cases are discovered during gestational weeks 5-8 (70%), with remaining cases presenting during weeks 9-10 (20%) and after gestational week 11 (10%) (5). Symptoms can be acute or non-acute in nature and include a 5-9 week history of amenorrhea, mild pelvic pain and vaginal spotting (2).

Evaluation & Imaging Approach

An initial evaluation begins with a urine pregnancy test and serum quantitative β-hCG level. β-hCG levels in heterotopic pregnancy begin to ascend in a curvilinear fashion before plateauing at approximately 9-11 weeks of pregnancy (2). The average β-hCG doubling time is approximately 48 hours for a single, normal IUP (2).

Ultrasound is considered the initial and ideal imaging modality of choice during pregnancy because of its wide availability, portability, and lack of ionizing radiation. Ultrasound is especially useful in pelvic evaluation because there are usually no overlying structures such as bowel to obscure imaging (4). Transabdominal and transvaginal US are performed with the goal of first identifying an IUP. Documenting a normal, early IUP is important as this will dramatically decrease the likelihood that an EUP is present (1). In fact, in many institutions and patient populations, heterotopic pregnancy is considered so rare that sonographic confirmation of an IUP is assumed to virtually exclude the presence of an extrauterine gestation (6).

As both intramuscular methotrexate and oral mifepristone have been used in the management of purely ectopic pregnancies, the presence or absence of an IUP is of paramount importance (2). Transvaginal ultrasound should be able to demonstrate an intrauterine gestational sac when β-hCG levels are greater than 2000 mIU/mL (2). In normal intrauterine pregnancies, transvaginal ultrasound can demonstrate an intradecidual sign approximately 4.5 weeks after the last menstrual period (2). The intradecidual sign is a small fluid collection surrounded by an echogenic ring that is eccentrically located within the endometrium, just beneath the endometrial stripe. By 5 weeks, the double decidual sac sign can be found, which is caused by the inner rim of chorionic villi surrounded by a thin crescent of fluid in the endometrial cavity, which is in turn is surrounded by the other echogenic rim of the decidua vera (1). After confirming the presence of an IUP, special attention is then given to the adnexal regions with the goal of first identifying the ovaries (5). Documentation of the adnexa is important as this is the most common location of EUPs in patients with risk factors for ectopic pregnancy.

An adnexal cyst or mass that is separate from the ovary is the most common finding in the setting of EUP (2). Another classic finding of an EUP is the "ring of fire", which is created by the low impedance high diastolic flow that can surround the tubal ring of an ectopic pregnancy. However, the "ring of fire" can also surround a corpus luteum, and is more likely to be seen around the corpus luteum than an EUP (1). Given that the "ring of fire" is not a differentiating characteristic between an EUP and a corpus luteum, one of the most reliable ways to differentiate between the two is with bimanual sonographic exam. A corpus luteum moves with the ovary on bimanual sonographic exam, while an EUP moves separately from the ovary. Ovarian ectopic pregnancies are extremely rare, and therefore if a lesion is seen in the ovary, statistically it most likely represents a corpus luteum.

EUP do not always occur in the adnexa, although this is their most common location. Interstitial pregnancies are located in the interstitial portion of the fallopian tube, with partial encompassment by myometrium. Interstitial pregnancies have a higher morbidity and mortality as the surrounding myometrium allows painless enlargement to occur. Cervical pregnancies are centered in the cervix. Scar pregnancies are increasingly being reported in Caesarian section scars, but can be found in any type of uterine scar. Abdominal EUPs typically develop in the ovarian ligaments, obtaining blood supply from the omentum and abdominal organs (1). Further, there are entities that can mimic an EUP in sonographic appearance, some of which include paratubal or mesenteric cyst, hydrosalpinx or tubo-ovarian abscesses, pedunculated fibroids, loops of bowel, and simple ovarian cysts (7).

Findings of an EUP can also include pelvic free fluid, hematosalpinx and hemoperitoneum (2). The presence of echogenic fluid within the right posterior subhepatic space (Morison's pouch) and within the cul-de-sac should heighten concern for a ruptured EUP (2). Transvaginal ultrasound is superior to transabdominal ultrasound for detecting small amounts of free fluid, in part because the distended urinary bladder required for transabdominal imaging displaces small quantities of free fluid out of the pelvis, rendering it invisible (8).

At times, transabdominal and transvaginal ultrasound may not yield any additional information to confirm an ectopic pregnancy (2). Pelvic fluid is a nonspecific finding that is seen in other conditions that can clinically mimic EUP such as ruptured ovarian cyst, pelvic inflammatory disease, and ovarian torsion (7). If the patient is clinically stable and has an adnexal mass of unclear origin or all the anatomy appears normal, it is possible to perform serial β-hCG levels and follow up ultrasound in 48 hours as the differential diagnosis still includes normal IUP, spontaneous abortion, and ectopic/heterotopic pregnancy (1). Subsequent exams may allow a confirmatory diagnosis as EUPs can grow and hemorrhage, making them more apparent (1). Serial β-hCG levels in heterotopic pregnancy can be misleading because subnormal hormone production by the EUP may be masked by the higher placental production from the IUP (3).

Treatment & Prognosis

As fallopian tube status cannot be determined sonographically on the basis of adnexal mass appearance or presence or amount of free fluid, the risk of EUP rupture continues to increase with the passage of time (8). The size of an EUP does not necessarily correlate with pain, which may even decrease or disappear following rupture (2). Therefore, in an unstable patient, emergent surgical intervention is warranted (2), possibly prior to an imaging diagnosis given the emergent patient status.

Preserving the viable IUP component of the heterotopic pregnancy is a priority after the well being of the mother. The standard treatment for heterotopic pregnancy is salpingectomy or salpingotomy by laparoscopy or laparotomy to remove the EUP, with minimal uterine manipulation so that the IUP is preserved (2). A recent review of 139 cases of heterotopic pregnancy treated mainly by surgery confirmed a subsequent live IUP delivery rate of 66% (3). Alternatively, if an intact tubal EUP is present, a local injection of potassium chloride can be performed. While they are acceptable treatments for isolated ectopic pregnancies, methotrexate, prostaglandins, and RU-486 should not be used in heterotopic pregnancy due to their potential adverse effects on the IUP (3).

Differential Diagnosis

Abdominal pain and bleeding in the first trimester of pregnancy is a challenging differential diagnosis requiring a high index of suspicion. A wide variety of diseases including disorders of the obstetric, gynecologic, gastrointestinal, hepatobiliary, genitourinary, and vascular systems can be considered in patients with abdominal pain and bleeding.

Ectopic Pregnancy

An ectopic pregnancy is defined as an extrauterine pregnancy (EUP) without a viable IUP. EUP can occur in the fallopian tubes, uterine interstitium, corneal region of the uterus, ovaries, cervix, surgical scars (especially Caesarean), and intra-abdominally. On ultrasound, the classic adnexal finding includes an adnexal mass separate from the ovary (2). Intrauterine findings include a normal endometrium, pseudogestational sac, trilaminar endometrium, and thin-walled decidual cyst (1).

Uterine Anomalies

Uterine anomalies include duplication. Uterine duplication can result in twins with one gestational sac in each horn or a single sac with fluid in other horn. Notably, no adnexal mass or free fluid is identified during ultrasound survey (2).

Normal IUP

The normal IUP must always be included in the differential diagnosis of heterotopic pregnancy. The intradecidual sign will be present via ultrasound approximately 4.5 weeks after the LMP (2). Additionally, the double decidual sac sign is identifiable at 5 weeks. At 5.5 weeks, the yolk sac is visualized within the gestational sac (1).

Summary

The described case of heterotopic pregnancy occurred in a woman presenting 6 weeks after her last menstrual period with classic risk factors, including prior ectopic pregnancy and prior tubal surgery (tubal ligation and re-anastomosis). A thick walled cystic structure in the right adnexal region, separate from the right ovary, and a large amount of complex free fluid prompted laparoscopy which confirmed the diagnosis of a hemorrhagic heterotopic pregnancy. The IUP was successfully preserved and the patient was discharged from the hospital shortly thereafter. Being both in the first trimester and having a tubal location of the ectopic pregnancy coincided with the most commonly reported time and location in literature for reported heterotopic pregnancies. In conclusion, heterotopic pregnancy is a potentially life threatening condition of the first trimester pregnancy that is becoming increasingly more common but if managed appropriately can result in successful delivery of the IUP.

TEACHING POINT

Heterotopic pregnancy is an increasingly more prevalent diagnosis in the first trimester of pregnancy due to increased utilization of reproductive assistance, requiring a high index of suspicion. Sonographic evaluation of heterotopic pregnancy includes identifying a viable IUP and an adnexal mass separate from the ovary representing the extrauterine gestational sac. The extrauterine gestational sac may demonstrate peripheral blood flow and have a surrounding hyperechoic ring. Although a normal intrauterine pregnancy typically excludes the presence of an ectopic pregnancy, knowledge of the patient's risk factors for heterotopic pregnancy, clinical presentation, and presence of complex free fluid can increase the suspicion for heterotopic pregnancy.

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FIGURES

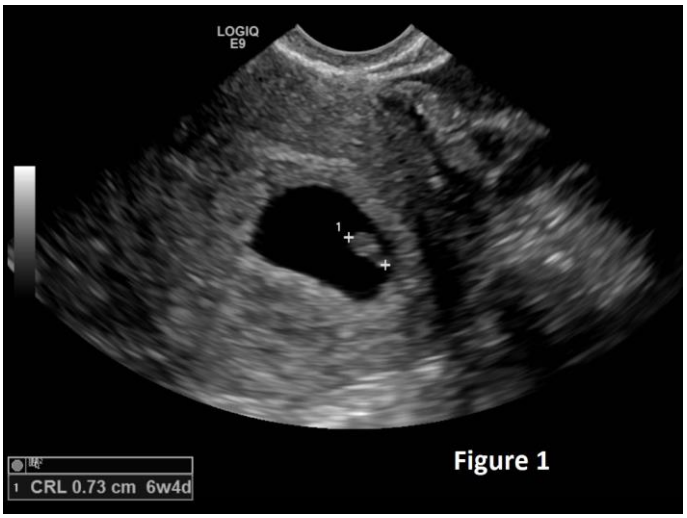
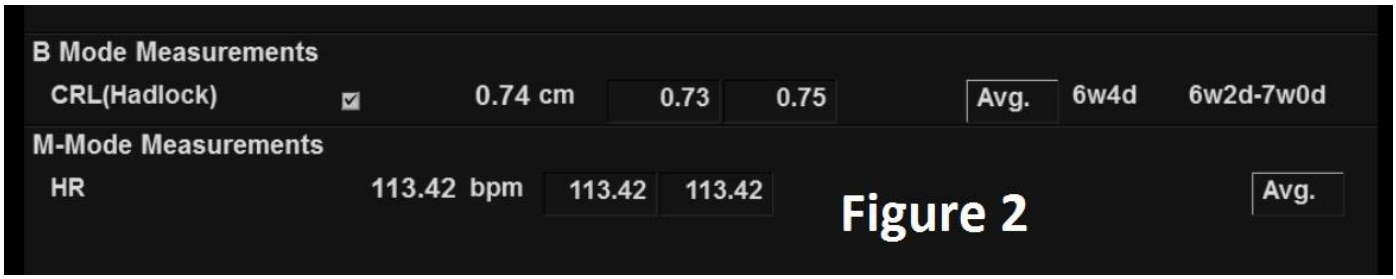


Figure 1: Hemorrhagic heterotopic pregnancy in 35 year old female with a history of prior tubal ligation and re-anastomosis.
Findings: Figure 1 demonstrates an ultrasound image of a single live, IUP with crown lump length of 0.73 cm, heart rate of 113 beats per minute, and an estimated gestational age of 6 weeks 4 days ± 1 week.
Technique: Transvaginal Ultrasound. Study performed with the General Electric Logiq E-9 ultrasound system with the IC-5 probe at 8 MHz.

Figure 2 (bottom): Hemorrhagic heterotopic pregnancy in 35 year old female with a history of prior tubal ligation and re-anastomosis.
Findings: Figure 2 demonstrates an ultrasound image of a single live, IUP with crown lump length of 0.73 cm, heart rate of 113 beats per minute, and an estimated gestational age of 6 weeks 4 days ± 1 week.
Technique: Transvaginal Ultrasound. Study performed with the General Electric Logiq E-9 ultrasound system with the IC-5 probe at 8 MHz.



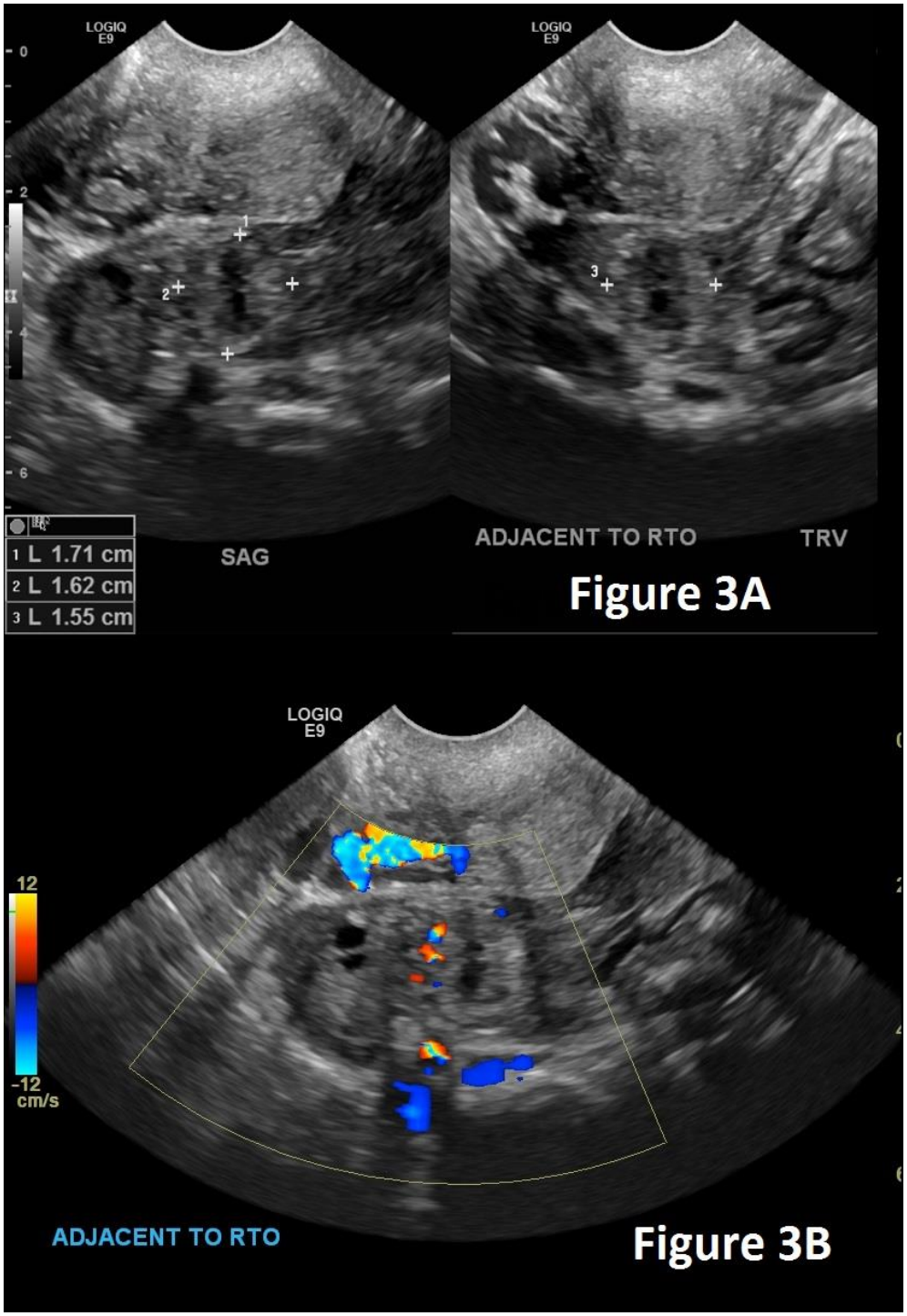


Figure 3: Hemorrhagic heterotopic pregnancy in 35 year old female with a history of prior tubal ligation and re-anastomosis.
Findings: Figure 3A demonstrates sagittal and transverse images of a thick-walled cystic structure in the right adnexal region measuring approximately 1.71 x 1.62 x 1.55 cm. This structure was shown to be separate from the right ovary. Figure 3B color ultrasound demonstrates vascularity of the structure.
Technique: Transvaginal Ultrasound. Study performed with the General Electric Logiq E-9 ultrasound system with the IC-5 probe at 8 MHz.

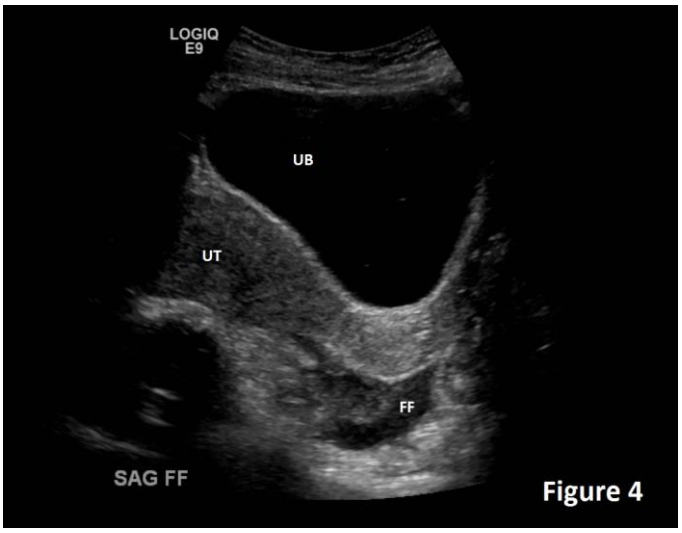


Figure 4: Hemorrhagic heterotopic pregnancy in 35 year old female with a history of prior tubal ligation and re-anastomosis.
Findings: Figure 4 is a sagittal ultrasound image demonstrating complex free fluid (FF) in the Pouch of Douglas. (UB - urinary bladder), (UT - uterus)
Technique: Transvaginal Ultrasound. Study performed with the General Electric Logiq E-9 ultrasound system with the IC-5 probe at 8 MHz.

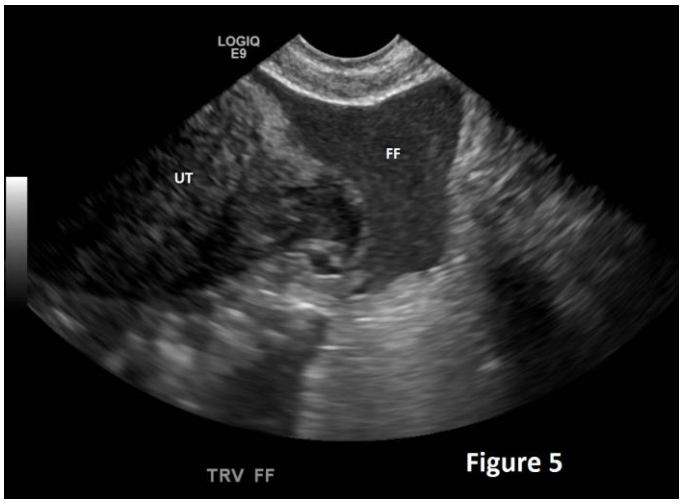


Figure 5: Hemorrhagic heterotopic pregnancy in 35 year old female with a history of prior tubal ligation and re-anastomosis.
Findings: Figure 5 (respectively) is a transverse ultrasound image demonstrating complex free fluid (FF) in the Pouch of Douglas extending into the right adnexa. (UT - uterus)
Technique: Transvaginal Ultrasound. Study performed with the General Electric Logiq E-9 ultrasound system with the IC-5 probe at 8 MHz.

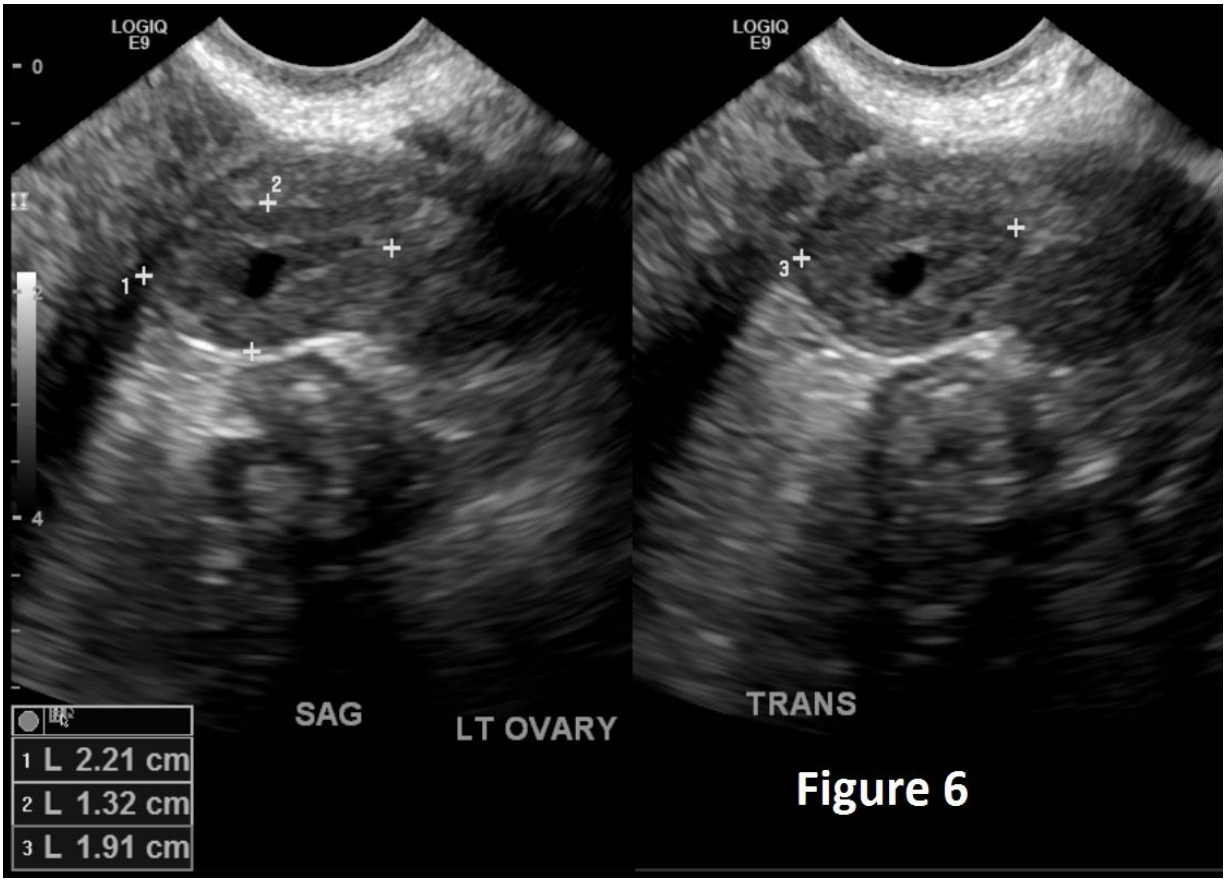


Figure 6: Hemorrhagic heterotopic pregnancy in 35 year old female with a history of prior tubal ligation and re-anastomosis.
Findings: Figure 6 demonstrates one of two, thick-walled cystic structures found in the left ovary. It measures approximately 2.21 x 1.32 x 1.91 cm. One of the structures likely represented the corpus luteum cyst of pregnancy.
Technique: Transvaginal Ultrasound. Study performed with the General Electric Logiq E-9 ultrasound system with the IC-5 probe at 8 MHz.

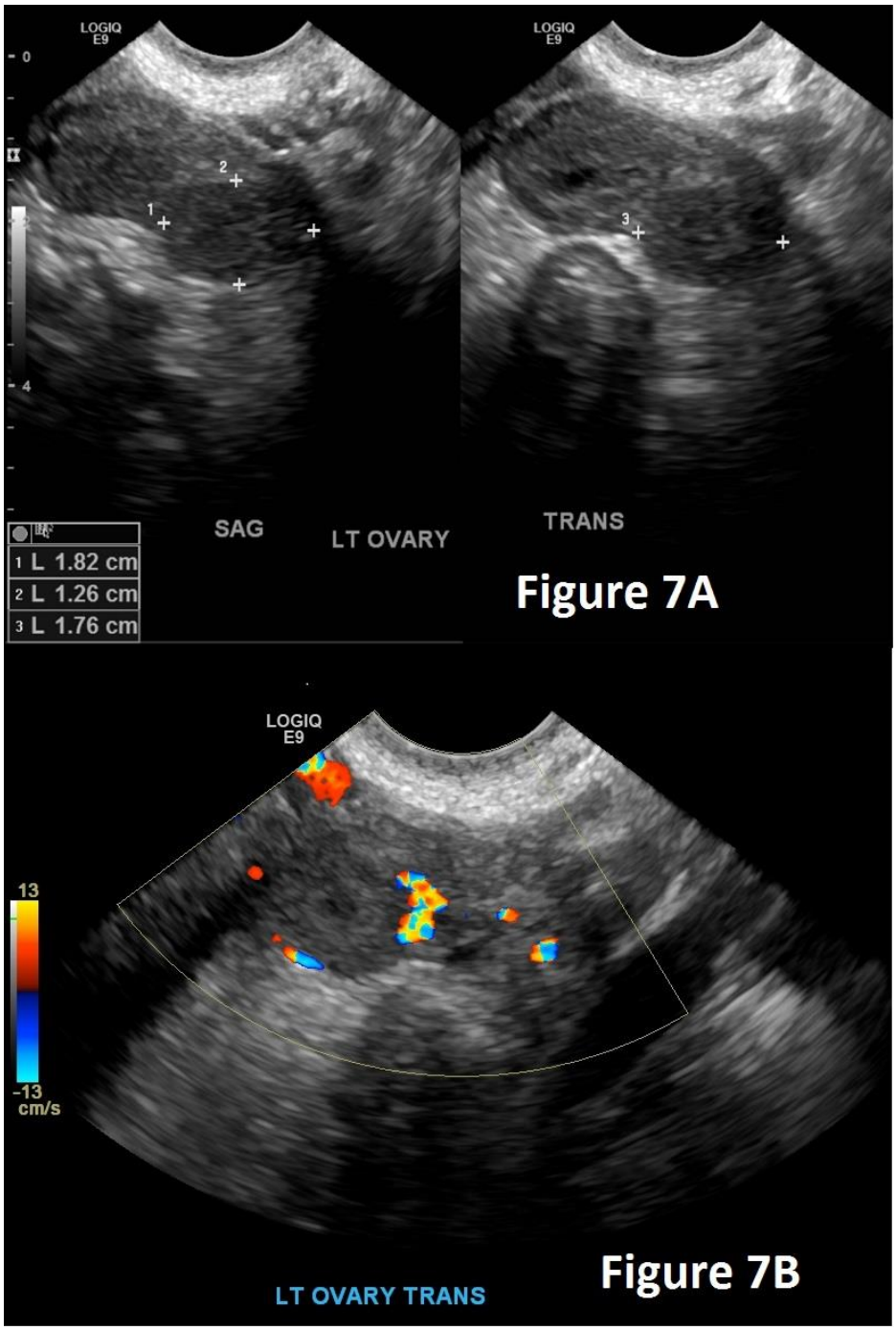
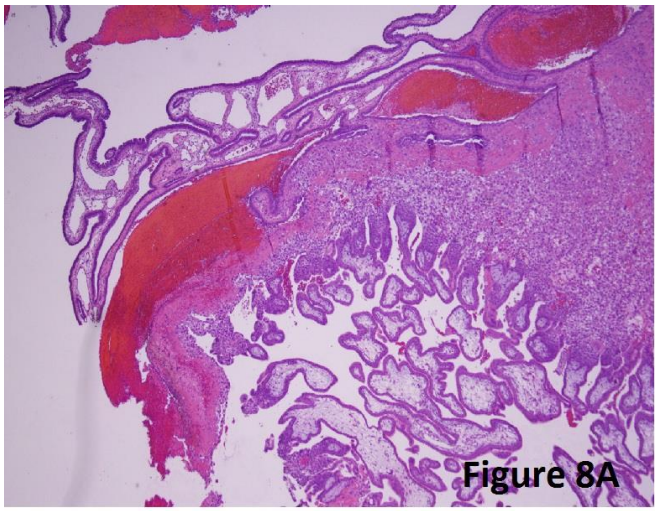


Figure 7: Hemorrhagic heterotopic pregnancy in 35 year old female with a history of prior tubal ligation and re-anastomosis.
Findings: Figures 7A and 7B demonstrate one of two, thick-walled cystic structures found in the left ovary. It measures approximately 1.82 x 1.26 x 1.76 cm. One of structures likely represented the corpus luteal cyst of pregnancy.
Technique: Transvaginal Ultrasound. Study performed with the General Electric Logiq E-9 ultrasound system with the IC-5 probe at 8 MHz.



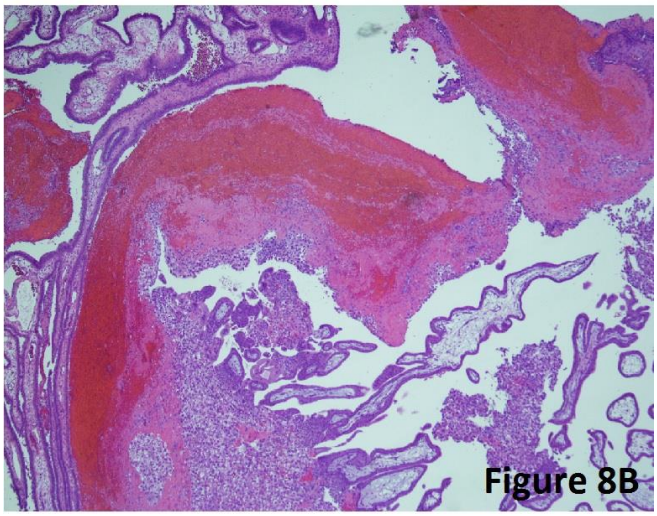


Figure 8 (left): Hemorrhagic heterotopic pregnancy in 35 year old female with a history of prior tubal ligation and re-anastomosis.
Findings: Figure 8A is a low power image of fallopian tubal epithelium (in the upper left) with hemorrhage and immature chorionic villi (right lower). Figure 8B is a low power image showing tubal epithelium on the left, with rupture site and hemorrhage and intraluminal immature chorionic villi in the center and right.
Technique: Hematoxylin and Eosin stain of gross surgical specimen.

Heterotopic Pregnancy Risk Factors (2)	
Prior ectopic pregnancy	**Congenital uterine anomalies**
History of pelvic inflammatory disease	**History of smoking**
History of gynecologic surgery	**Endometriosis**
Infertility	**Exposure to diethylstilbestrol**
Use of an intrauterine device	**History of placenta previa**
Use of vitro fertilization	

Table 1: Heterotopic pregnancy risk factors

Differential Diagnosis	Ultrasound
Heterotopic Pregnancy	• An intrauterine pregnancy must first be confirmed • Adnexal cyst or mass separate from the ovary • "Ring of fire" low impedance on Doppler Ultrasound • Echogenic pelvic free fluid
Ectopic Pregnancy	• Adnexal mass separate from the ovary • Tubal ring sign – hyperechoic ring surrounding an extrauterine gestational sac • "Ring-of-fire" flow in an adnexal mass • Intrauterine findings - "normal endometrium," pseudogestational sac, trilaminar endometrium, and thin-walled decidual cyst
Uterine Anomalies	• Uterine duplication – twins with 1 sac in each horn or single sac with fluid in other horn • No adnexal mass or free fluid
Normal Intrauterine Pregnancy	• Intradecidual sign approximately 4.5 weeks after the last menstrual period • The double decidual sac sign at 5 weeks • At 5.5 weeks, the yolk sac is visualized within the gestational sac

Table 2: Differential diagnosis of heterotopic pregnancy

Etiology	Concurrent intrauterine and extrauterine pregnancies
Incidence	• 1%-3% in women who have undergone assisted reproductive therapy • 1 in 7,000 pregnancies in the general population
Gender Ratio	1: 0, Female to Male
Age Predilection	Females of Reproductive Age
Risk Factors	• Prior ectopic pregnancy • Congenital uterine anomalies • History of pelvic inflammatory disease • History of smoking • History of gynecologic surgery • Endometriosis • Infertility • Exposure to diethylstilbestrol • Use of an intrauterine device • History of placenta previa • Use of vitro fertilization
Treatment	• All treatments have goal of preserving maternal health and the intrauterine pregnancy • Surgical – Salpingotomy or Salpingectomy • Localized injection of potassium chloride into extrauterine pregnancy sac
Prognosis	• Successful preservation of the intrauterine pregnancy estimated to be up to 66% • If not treated, significant morbidity and mortality to mother with loss of intrauterine pregnancy
Findings on Imaging - Ultrasound	• An intrauterine pregnancy must first be confirmed • Adnexal cyst or mass separate from the ovary • "Ring of fire" low impedance on Doppler Ultrasound • Echogenic pelvic free fluid

Table 3: Summary table for concurrent intrauterine and extrauterine pregnancies

ABBREVIATIONS

β-hCG - Beta Human Chorionic Gonadotropin
EUP - extrauterine pregnancy
IUD-intrauterine device
IUP - intrauterine pregnancy
LMP - last menstrual period
PID - pelvic inflammatory disease
US - ultrasound
WBC - white blood cell

KEYWORDS

Heterotopic pregnancy; Extrauterine pregnancy; High risk pregnancy; Ectopic pregnancy; Miscarriage; Spontaneous abortion