American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **First Trimester Bleeding**

Variant 1: **Positive urine or serum pregnancy test.**

Radiologic Procedure	Rating	Comments	RRL*
US pelvis transvaginal	9	Correlate finding with quantitative β-hCG and clinical scenario. M-mode for fetal heart rate.	O
US pelvis transabdominal	8	Correlate finding with quantitative β-hCG and clinical scenario. Should be used in conjunction with transvaginal US whenever possible.	O
US duplex Doppler pelvis	7	Pulsed Doppler of the embryo should be avoided.	O
MRI pelvis without IV contrast	3	For further evaluation of unusual ectopic pregnancy and gestational trophoblastic disease, pathology in the adnexa, or nondiagnostic US.	O
MRI pelvis without and with IV contrast	2	Contrast generally contraindicated. For unusual ectopic pregnancy and gestational trophoblastic disease.	O
CT pelvis without IV contrast	1		☢☢☢
CT pelvis with IV contrast	1		☢☢☢
CT pelvis without and with IV contrast	1		☢☢☢☢
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**			***Relative Radiation Level**

FIRST TRIMESTER BLEEDING

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Summary of Literature Review

Introduction/Background

Ultrasonography (US) is the primary imaging modality in the evaluation of patients presenting with bleeding in the first trimester of pregnancy. Magnetic resonance imaging (MRI) and computed tomography (CT) play a minor role in problem-solving the causes of bleeding but may be useful when US is severely limited, for unusual ectopic pregnancy, or for differentiating causes of severe pelvic pain and adnexal masses. US correlated with serum human chorionic gonadotrophin levels and clinical presentation, can differentiate causes of first-trimester bleeding. These include threatened abortion, ectopic pregnancy, failed intrauterine pregnancy, and gestational trophoblastic disease, which can all present with bleeding and pain. Bleeding in the first trimester occurs in around 27% of pregnancies, with an overall risk of miscarriage of approximately 12% [1]. US can differentiate an intrauterine from an ectopic pregnancy and a live from a failed pregnancy. The following is an overview of the US findings and correlative β-hCG findings that have been shown to be diagnostically useful.

Intrauterine Fluid Collection

The first visible US evidence of an intrauterine pregnancy is seen in the gestational sac (chorionic sac). Using current high-frequency transvaginal transducers, gestational sacs as small as 2-3 mm (mean sac diameter) may be visualized, corresponding to 4.5-5 weeks of gestation [2]. Before any structures are visualized within the gestational sac, the intradecidual and double decidual sign may be used to distinguish an intrauterine gestation from a fluid collection, known as a pseudogestational sac, within the endometrial cavity. The double decidual sign consists of two concentric echogenic rings. The inner fluid collection is the gestational sac surrounded by the echogenic decidua capsularis. This ring bulges into the endometrial cavity, which is lined by the second echogenic ring of the decidua vera (also known as parietalis). There is often a small amount of fluid in the space between the two sacs [3]. The double decidual sign is nearly 100% specific, but only 64% sensitive for an early intrauterine pregnancy [4]. As the double decidual sac sign may not be seen until after the yolk sac is detected, it is not required for the diagnosis of intrauterine pregnancy. The intradecidual sign consists of an intrauterine fluid collection with a discreet echogenic rim eccentrically positioned in the endometrium and separate from the distinct echogenic line that represents the collapsed endometrial cavity [5,6]. This sign, which can be visualized as early as 4.5 weeks, has a sensitivity and specificity of 60%-68% and 97%-100%, respectively [7]. It is important to recognize that the presence of the double decidual sac sign or the intradecidual sign indicates an intrauterine pregnancy; however, the converse is not true. The absence of these signs does not exclude an intrauterine pregnancy.

The generally accepted discriminatory level of β-hCG at which a gestational sac is expected on transvaginal US is 1,000-2,000 mIU/mL [8,9]. However, because of human variation and the possibility of multiple gestation, as well as technical limitations and operator dependency, this level should not be taken as an absolute. There are reports of normal pregnancies developing after the failure to detect an intrauterine gestational sac above the

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threshold of 2,000 mIU/mL [10]. Therefore, in a stable patient, a definitive diagnosis of failed or ectopic pregnancy should not be made in this scenario, and follow-up sonography and β-hCG assay are advised. Even in the presence of the intradecidual or double decidual signs, and particularly in a patient at high risk for ectopic pregnancy, US and β-hCG follow-up may be warranted to confirm normal progression of an intrauterine pregnancy. The interval for follow-up should be based on clinical factors such as date of last menstrual period, date of assisted reproduction, and patient symptoms, as well as established parameters of the normal growth rate of the gestational sac and corresponding rise in the quantitative levels of β-hCG (expected to double approximately every 2 days but which may vary).

Definitive Intrauterine Gestation

The yolk sac is the first definitive sign of an intrauterine pregnancy. It is usually visualized in any gestational sac >8 mm [11]; however, in some normal pregnancies the gestational sac will be larger before a yolk sac is seen [12]. The yolk sac is a discreet, round, thin-walled structure, which is usually eccentrically located within the gestational sac and grows slowly during the first trimester. The embryo will initially appear as a thickened, linear echogenic structure at the edge of the yolk sac. The embryo is usually seen by the time the gestational sac grows to a mean diameter of 16mm; however, in some normal pregnancies the gestational sac will be larger before an embryo is seen [13].

While the absence of a yolk sac in a gestational sac >8 mm mean sac diameter, or the absence of an embryo in a gestational sac >16 mm mean diameter are worrisome for an abnormal pregnancy, recent large observational cross-sectional studies have found these cut offs to be associated with a false-positive rate of up to 4.4% [12]. At a threshold of 21 mm, there were no false-positive diagnoses of failed pregnancy. However, because of measurement variability of up to 19%, authors have suggested that the mean gestational sac diameter at which the absence of an embryo is diagnostic of a failed pregnancy should be increased to 25 mm in technically adequate transvaginal US [12,14]. Given that growth rates of gestational sacs and embryos are variable, an empty gestational sac (ie, the absence of a yolk sac or embryo) on two scans performed 7-10 days apart is definitive evidence of a failed intrauterine pregnancy [15].

In general, cardiac activity should normally be seen in an embryo of any crown-rump length. Absence of cardiac activity in an embryo measuring 4-5 mm in crown-rump length has previously been considered definitive for embryonic demise. More recent data, particularly when considering measurement variability, have suggested that a failed intrauterine pregnancy should be diagnosed only when cardiac activity is absent in an embryo ≥7 mm, using transvaginal US [12]. Absence of cardiac activity in embryos <7 mm is still worrisome for failed intrauterine pregnancy, but the patient should generally be re-evaluated by a follow-up sonogram in 7-10 days. Continued absence of embryonic cardiac activity in 7-10 days is reliable evidence of a failed intrauterine pregnancy.

The normal range of heart rate from 6.2-7 weeks is 100-120 beats per minute, and after 7 weeks the mean heart rate is 137-144 [16,17]. Due to concerns about temperature elevation in tissues in the path of a pulsed Doppler beam, only M-mode US should be used to document cardiac activity and measure the rate [http://www.wfumb.org/about/statements.aspx]. Video clips can also be used to document cardiac activity.

Once an intrauterine gestation is definitely established by US, various US findings may be seen in patients with first-trimester bleeding that are associated with a poor outcome. These include: bradycardia [18,19], slow growth rate of the embryo, abnormally small [20] or abnormally large [21] gestational sac compared to embryo, enlarged amniotic cavity [22], empty amniotic cavity [23], absence of cardiac activity with visualization of the amnion [24], abnormal size or shape of the yolk sac [25], low position or irregular shape of the gestational sac, and decreased gestational sac volume after 7 weeks [26]. In these situations, follow-up can include a combination of clinical examination and US. Subchorionic hemorrhage, a common finding during the first trimester, is associated with a poor outcome when it is moderate to large in comparison to the size of the gestational sac [27]. Maternal age >35 years is also associated with an increased risk of poor outcome, with a reduction in live births and increase in miscarriages [28].

Ectopic Pregnancy

Whenever an intrauterine pregnancy is not identified, extrauterine locations for the pregnancy must be carefully evaluated [29,30]. This involves identification of the ovaries and corpus luteum and a careful search for any nonovarian mass that is not a paraovarian cyst or pedunculated fibroid, since the vast majority of ectopic

pregnancies are in the fallopian tubes. In at least 80% of cases, the ectopic pregnancy is located ipsilateral to the corpus luteum and must be distinguished from it. The corpus luteum is characterized by a circumferential rim of low-resistance color Doppler flow, "the ring of fire," supplied by a prominent ovarian artery branch. The gray-scale appearance of the corpus luteum is variable, ranging from solid to complex and cystic. Pressure with the endovaginal transducer on the ovary can help to confirm the intraovarian location of the corpus luteum, distinguishing it from any extraovarian mass.

While visualization of an extrauterine gestational sac with a live embryo is 100% specific for an ectopic pregnancy, this situation is relatively uncommon. More likely, though slightly less specific, is an extrauterine tubal ring with central fluid or containing a yolk sac and/or a nonviable embryo. In most cases, the echogenicity of the tubal ring is greater than the echogenicity of the normal ovary and more echogenic than the corpus luteum [31,32]. Frequently, the ectopic pregnancy will appear as a complex, extraovarian, extrauterine mass. Color Doppler evaluation may show internal color flow, but the vascularity of ectopic pregnancies is variable, and color and pulsed Doppler imaging is not necessarily useful. In addition, some ectopics are avascular. Therefore gray-scale identification of an extraovarian sac or mass is the most important feature. Given the potential for inappropriate management with methotrexate or surgical intervention, the diagnosis of ectopic pregnancy should be based on positive findings and not solely on the absence of an intrauterine sac.

Assessment of the nature and amount of any free fluid is essential in the evaluation for an ectopic pregnancy. In this setting, echogenic material within the free fluid is assumed to be blood. The presence of free or clotted blood, even without identification of an extraovarian mass, is significant presumptive evidence of an ectopic pregnancy [33-35]. The infrequent mimic of this situation occurs when there is rupture of a hemorrhagic cyst with an early, nonvisualized intrauterine pregnancy. If blood is identified in the pelvis, transabdominal US should be extended into the flanks and dependent locations in the right upper (Morrison's pouch) and left upper quadrants. Larger amounts of blood correlate with ruptured ectopic pregnancy, but in one-third of cases with significant free fluid, the fallopian tubes are intact [36]. Clotted blood in the pelvis can be very mass-like and, when it surrounds an ectopic pregnancy, may simulate a uterus. The clotted blood can blur the margins of the uterus and ovaries, making their identification more difficult. In such instances, color Doppler may be helpful to show that all of this solid-appearing material is avascular.

In a small percentage of cases, probably less than 4%, the ectopic pregnancy may be in an unusual location. Intrauterine ectopic locations include interstitial, cervical, and within a Cesarean section scar, which account for the majority of unusual ectopic pregnancies [37-41]. Extrauterine ectopic locations, including the ovary and abdominal cavity, are extremely rare. Heterotopic pregnancies (coexisting intrauterine and extrauterine pregnancy) are also extremely rare, occurring in between one in 10,000 to one in 30,000 pregnancies. However, after assisted reproduction the incidence is much higher, as high as one in 100 [42]. Thus, in the routine population, identification of a normally positioned intrauterine pregnancy essentially rules out the possibility of a coexisting ectopic pregnancy.

While US is usually sufficient for the diagnosis of unusually located ectopic pregnancies, there are increasing numbers of reports of using MRI to aid in these diagnoses. An interstitial pregnancy is characterized on US and MRI by the eccentric fundal location of the sac, which is only partially surrounded by myometrium. The sac is separated from the endometrial cavity by a junctional zone on MRI, an appearance described as the interstitial line sign on US [37[43]. A cervical ectopic pregnancy is embedded in the cervical stroma, this location and the presence of embryonic cardiac activity allow for differentiation from a passing abortion. The typical MRI appearance of a cervical ectopic pregnancy consists of a lobulated, solid mass with heterogeneous signal intensity containing enhancing papillary projections due to fetoplacental remnants [44]. MRI may also help in cases of unusual implantation sites in women with uterine anomalies.

Because CT (with its radiation exposure to the developing fetus during organogenesis) is generally contraindicated in the first trimester of pregnancy, it is also not a primary imaging modality for ectopic pregnancy. The few reported cases of CT being used with ectopic pregnancy were performed for other reasons or in patients not known to be pregnant. On contrast-enhanced CT, the ectopic pregnancy may demonstrate a brightly enhancing rim, similar to a corpus luteum. [45,46]. When a patient is clinically unstable, urgent or emergent care should not be delayed by additional imaging with CT and MR.

Pregnancy of Unknown Location

The terminology of "pregnancy of unknown location" is reserved for patients with no definite evidence of an ectopic pregnancy or an intrauterine pregnancy but with a positive β-hCG. Most of these patients will not have an ectopic pregnancy, potentially as few as 8% in experienced hands [47]. Most patients who present with bleeding and no identifiable intrauterine or extrauterine pregnancy in the first trimester will usually have had a spontaneous abortion. Clinical findings of cramping pain and passage of identifiable tissue will often support this diagnosis. If a prior pelvic US had demonstrated an intrauterine pregnancy, the empty uterus on a follow-up scan is definitive proof of a miscarriage. Following miscarriage, persistent elevation or rise of serum quantitative β-hCG may represent retained products of conception which can readily be diagnosed with gray scale and Doppler US. Focal endometrial thickening or material within the endometrial canal with low-resistance arterial flow in an endometrial or subendometrial location is highly suggestive of retained products of conception.

In the setting of a negative US, the differential diagnosis also includes an early intrauterine pregnancy <4.5 to 5 weeks or an early nonvisualized ectopic pregnancy. Patients with a pregnancy of unknown location (PUL) can pose a diagnostic challenge. Uterine curettage is no longer used to differentiate a failed intrauterine pregnancy from an ectopic pregnancy when the β-hCG is above the accepted discriminatory threshold, as this may rarely result in the loss of some early intrauterine pregnancies. Thus, if the patient is clinically stable, observation with serial β-hCG monitoring is preferred [10]. In a normal intrauterine pregnancy, the level should approximately double every 48 hours. If the initial level was low, when it reaches the discriminatory zone a repeat pelvic sonogram may be obtained to confirm an intrauterine pregnancy. If the level drops appropriately to undetectable levels, resolution of a nonvisualized PUL is assumed, and no intervention is required [48]. If the level fails to decline and plateaus, an ectopic pregnancy is more likely. In such situations, follow-up US may be obtained, and/or medical therapy may be initiated for a presumptive ectopic pregnancy. Confounding factors may include early multiple gestation, which may present with a higher than expected serum β-hCG but no sonographic evidence of pregnancy. Furthermore the β-hCG may remain elevated or plateau post miscarriage, or even rise due to retained products of conception. These situations may potentially lead to overdiagnosis of ectopic pregnancy and incorrect management.

Miscellaneous Diagnoses

When the US does not show an intrauterine gestational sac or pseudosac, but rather a moderate or even significant amount of mixed cystic and solid material within the uterus, one should consider the possibility of a first-trimester molar pregnancy, the most common form of gestational trophoblastic disease. Unlike the classic US findings in the second trimester of a distended endometrial cavity filled with innumerable small cystic spaces, in the first trimester the appearance is variable. The US appearance may include a small, echogenic endometrial mass without cystic spaces as well as mixed echogenic and cystic material [49]. The US findings overlap those of a failed intrauterine pregnancy with hydropic degeneration and retained products of conception. Thus, the differential diagnosis should include these possibilities. The β-hCG is often, but not always, inappropriately elevated, and definitive diagnosis is based on histopathological evaluation of uterine contents. Molar pregnancies may be associated with theca lutein cysts in the ovaries in 20%-50% of cases, but this is less common in the first trimester. With complete molar pregnancies, hydropic degeneration occurs within villi. As complete moles are relatively avascular, color Doppler imaging of the uterine contents does not typically aid in the diagnosis [50]. However in invasive moles and choriocarcinoma, low-impedance flow is typical at color and pulsed Doppler, a finding that is especially useful in evaluating residual or recurrent disease [50].

Usually the combination of US and clinical factors is sufficient for diagnosing gestational trophoblastic disease; however, some of the traditional clinical features associated with molar pregnancy are less common in the first trimester, such as hyperemesis and pregnancy-induced hypertension [51]. In confusing cases, pelvic MRI may be helpful to differentiate molar pregnancy from incomplete abortion or ectopic pregnancy. MRI may be helpful in the diagnosis of persistent gestational trophoblastic disease, which requires chemotherapy [52]. CT can also detect extrauterine spread of gestational trophoblastic disease.

US can also depict some unusual causes of first-trimester bleeding, and color Doppler imaging is crucial in their evaluation. These include vascular abnormalities such as pseudoaneurysm and arteriovenous malformation. The latter entity may overlap with the findings of retained products of conception [53]. In the setting of postmiscarriage bleeding, vascular shunting is typically secondary to nonregression of trophoblastic tissue. Usually either conservative management or evacuation of residual contents is recommended in stable patients.

Treatment of symptomatic arteriovenous fistulae typically includes transcatheter embolization of the uterine arteries [54]. However, some patients can be successfully managed conservatively [55].

Summary

- Although transabdominal or transvaginal US may be used for patients with first-trimester bleeding, transvaginal US is the study of choice for early pregnancies.
- Transabdominal imaging is particularly useful to assess the amount of free fluid and for abnormalities beyond the field of view of a high-frequency vaginal probe.
- The results of imaging should be correlated with the quantitative β-hCG level and with the clinical presentation. The lack of an intrauterine gestational sac above the discriminatory β-hCG level does not necessarily indicate ectopic pregnancy. If the patient is stable with no signs of ectopic pregnancy, conservative management is advised.
- A failed pregnancy may be diagnosed when a gestational sac >25 mm in mean diameter does not contain a yolk sac or embryo or when an embryo measuring ≥7 mm does not have cardiac activity.
- M-mode imaging should be used to document embryonic viability and measure heart rate.
- Doppler US should not be used to evaluate a normal early embryo.
- MRI of the pelvis may be used in clinically stable patients if US is insufficient for diagnosing unusual ectopic pregnancies, gestational trophoblastic disease, or vascular abnormalities, but should not delay urgent or emergent care in an unstable patient.
- CT may be useful in pregnant patients with trauma or acute non-gynecologic pain, for staging of malignancy, or if MRI is not possible.

Safety Considerations in Pregnant Patients

Imaging of the pregnant patient can be challenging, particularly with respect to minimizing radiation exposure and risk. For further information and guidance, see the following ACR documents:

- ACR Practice Guideline for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation
- ACR-ACOG-AIUM Practice Guideline for the Performance of Obstetrical Ultrasound
- ACR Manual on Contrast Media
- ACR Guidance Document for Safe MR Practices

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document.

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢ ☢	0.1-1 mSv	0.03-0.3 mSv
☢ ☢ ☢	1-10 mSv	0.3-3 mSv
☢ ☢ ☢ ☢	10-30 mSv	3-10 mSv
☢ ☢ ☢ ☢ ☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies".		

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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