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Ectopic pregnancy:
Forget the "classic presentation" if you want to catch it sooner

A new algorithm to improve detection

Practice recommendations

❚ Less than half of the patients with ectopic pregnancy present with the classic triad of a history of amenorrhea, abdominal pain, and irregular vaginal bleeding (**C**).

❚ Definite cervical motion tenderness and peritoneal signs are the most sensitive and specific examination findings for ectopic pregnancy—91% and 95%, respectively (**A**).

❚ Beta-human chorionic gonadotropin (β-hCG) levels can be used in combination with ultrasound findings to improve the accuracy of the diagnosis of ectopic pregnancy (**A**).

❚ Women with initial nondiagnostic transvaginal ultrasound should be followed with serial β-hCGs (**B**).

Despite advanced detection methods, ectopic pregnancy may be missed in 40% to 50% of patients on an initial visit.[1] Most women with ectopic pregnancy have no risk factors (**TABLE 1**),[2–5] and the classic triad of a history of amenorrhea, abdominal pain, and irregular vaginal bleeding is absent in more than half of cases.

Early diagnosis not only decreases maternal mortality and morbidity; it also helps preserve future reproductive capacity—only one third of women with ectopic pregnancy have subsequent live births.[2]

Management strategies for patients with ectopic pregnancy have evolved rapidly, with ambulatory medical therapy becoming an option for more patients.[6] Using a practical decision protocol, we discuss the physical findings that most reliably suggest ectopic pregnancy, describe sensible use of laboratory and imaging studies, and explain what to do when results are equivocal. In part 2 of this article (coming in the June 2006 JOURNAL OF FAMILY PRACTICE), we provide a decision protocol for managment of ectopic pregnancy.

❚ Evaluation
Clinical features of ectopic pregnancy highly variable

No single clinical feature accurately indicates ectopic pregnancy. Less than half of women with ectopic pregnancy exhibit the classic triad of a history of amenorrhea, abdominal pain, and irregular vaginal bleeding.[1] And, unfortunately, these features are seen commonly in patients with both viable (50%) and nonviable (25%) intrauterine pregnancies, as well as in threatened abortion, cervical irritation, infection, and trauma.[7]

Set a low threshold for suspicion. For any woman of childbearing age with abdominal pain and vaginal bleeding,

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TABLE 1

Risk factors for ectopic pregnancy

DEGREE OF RISK	FACTOR	ODDS RATIO (95% CONFIDENCE INTERVALS)		
		ANKUM ET AL[3]	MOL ET AL[4]	BOUYER ET AL[5]
High	Previous tubal surgery	21 (9.3–47)		4.0 (2.6–6.1)
	Tubal ligation		9.3 (4.9–18)	
	Previous ectopic pregnancy	8.3 (6.0–11.5)		
	In utero DES exposure	5.6 (2.4–13)		
	Current IUD use		4.2–45*	
	Tubal pathology/abnormality	3.5–25*		
Moderate	Infertility	2.5–21*		2.7 (1.8–4.2)
	History of PID	2.5 (2.1–3.0)		3.4 (2.4-5.0)
	Previous chlamydial or gonococcal infection	2.8–3.7*		
	Current smoking	2.3 (2.0–2.8)		3.9 (2.6–5.9)
	Spontaneous abortions ≥3			3.0 (1.3-6.9)
	Induced abortions (medical ± surgical)			2.8 (1.1–7.2)
	Lifetime sexual partners >1	2.1 (1.4–4.8)		
Low	Age first intercourse <18 years	1.6 (1.1–2.5)		
	Previous pelvic/abdominal surgery	0.93–3.8*		
	Vaginal douching	1.1–3.1*		

DES, diethylstilbestrol; PID, pelvic inflammatory disease; IUD, intrauterine device
* Range; summary odds ratio not calculated owing to significant heterogeneity between studies.

consider pregnancy and take steps to rule out ectopic pregnancy. Abdominal pain and vaginal bleeding are highly sensitive for ectopic pregnancy but are not specific for the disorder (**TABLE 2**).[8–17] Pain located in the hypogastrium or iliac fossa may be mild to severe. Vaginal bleeding, present in 50% to 80% of patients with ectopic pregnancy, can be mistaken for a normal menstrual period.[2,6] Pregnancy-associated symptoms of nausea and vomiting, breast tenderness, and fatigue may be present.

Lower abdominal and adnexal tender-ness can be elicited in most women with ectopic pregnancy. Cervical motion tender-ness, peritoneal signs, and adnexal masses are most specific for ectopic pregnancy, but are not sensitive.[8] An adnexal mass is pal-pable in less than 10% of cases; when it is detected, one third of patients will have a *contralateral* ectopic pregnancy on ultra-sonography.[18] Symptoms of hemodynamic compromise (orthostasis, hypotension, shock) are becoming uncommon with earlier diagnosis of ectopic pregnancy, facil-itated by improved detection methods.

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Most women with ectopic pregnancy have adnexal and lower abdominal tenderness, with cervical motion tenderness and peritoneal signs the most specific

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TABLE 2

Significance of features associated with ectopic pregnancy

FEATURES	SN (%)	SP (%)	LR+	LR–
Clinical features[8]				
Any risk factors	23	83	1.4	0.9
Estimated gestational age <70 days	95	27	1.3	0.2
Vaginal bleeding	69	26	0.9	1.2
Abdominal pain	97	15	1.1	0.2
Abdominal tenderness	85	50	1.7	0.3
Peritoneal signs	23	95	4.6	0.8
Cervical motion tenderness	33	91	3.7	0.7
Adnexal tenderness	69	62	1.8	0.5
Adnexal mass	5	96	1.3	1.0
Transvaginal ultrasound				
No intrauterine gestational sac[9]	100	89	9.1	<0.1
Adnexal mass[10]				
Separate from ovary	93	99	93	0.1
Cardiac activity	20	100	∞	0.8
Yolk sac or embryo	37	100	∞	0.6
Tubal ring/yolk sac or embryo	65	99	65	0.4
Fluid in pouch of Douglas[11]				
Any	63	69	2.0	0.5
Echogenic	56	96	14.0	0.5
Color-flow Doppler[12]	95	98	47.5	0.1
β-hCG combined with transvaginal ultrasound				
Empty uterus				
≥1000 mIU/mL[10,13,14]	43–96	86–100	3.0–∞	0.04–0.66
≥1500 mIU/mL[13,15]	40–99	84–96	6.3–9.9	0.01–0.63
≥2000 mIU/mL[13,16]	38–48	80–98	2.3–25.3	0.63–0.68
Adnexal mass*				
≥1000 mIU/mL[13]	73	85	4.7	0.32
≥1500 mIU/mL[13,15]	46–64	92–96	5.9–16.5	0.38–0.58
≥2000 mIU/mL[13]	55	96	14.2	0.47
β-hCG *rise* in 48 hours (empty uterus)†				
>66%[17]	—	—	1.1	—
<66%[17]	—	—	7.4	—
>50%[13]	—	—	2.8	—
<50%[13]	—	—	3.3	—
β-hCG *fall* in 48 hours (empty uterus)†				
>50%[13,17]	—	—	0.8–1.4	—
<50%[13,17]	—	—	0–0.1	—

* Mass or fluid in cul de sac for β-hCG ≥1500 mIU/mL and ≥2000 mIU/mL.

† Strata-specific likelihood ratios reported, sensitivity and specificity not applicable.

Sn, sensitivity; Sp, specificity; LR, likelihood ratio; β-hCG, beta-human chorionic gonadotropin.

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▌ Laboratory tests

In an early normal pregnancy, the beta-human chorionic gonadotropin (β-hCG) level doubles every 1.8 to 3 days, rising to 1000 mIU/mL IRP (International Reference Preparation, measured by radioimmunoassay) by 5 weeks, to 2500 mIU/mL by 6 weeks, and to 13,000 mIU/mL (±3000) by 7 weeks. A single quantitative β-hCG level is not always

helpful, as it can range from less than 100 mIU/mL to greater than 50,000 mIU/mL with both ruptured and unruptured ectopic pregnancies.[19]

Rethinking the rate of rise in β-hCG. The oft-quoted maxim that ectopic pregnancy or impending miscarriage is associated with a rise in β-hCG of less than 66% in 48 hours arose from a 1981 study that included only 20 women and that was based on an 85% confidence interval (CI).[20] A recent study of 287 women suggests that the minimal expected rise in 2 days for a viable intrauterine pregnancy (based on a 99% CI) should be at least 53%.[21]

Combining β-hCG levels and ultrasound findings to improve diagnosis. Because the exact gestational age is often unknown in women presenting with features of ectopic pregnancy, the β-hCG level is used to determine whether a gestational sac can be identified on ultrasound. With a β-hCG level of 6500 mIU/mL, a gestational sac should be visible on abdominal ultrasound in the uterus of a woman with an intrauterine pregnancy; the sac should be absent in ectopic pregnancy. This β-hCG level is designated the discriminatory zone.[22]

With a high-resolution transvaginal ultrasound (TVUS), the gestational sac of a normal single intrauterine pregnancy should be visible at a β-hCG level above 1000–1500 mIU/mL, depending on equipment and technical expertise.[2,7] In multiple gestations the discriminatory zone is observed to be above 2300 mIU/mL.[2] Various ultrasonography findings have been combined with β-hCG levels to more accurately diagnose ectopic pregnancy (**TABLE 2** and **FIGURE**).

Serial β-hCG measurements. If TVUS findings are indeterminate, serial measurements of β-hCG levels at 48-hour intervals may be useful in managing suspected ectopic pregnancy. Dart et al[17] found that a rise in β-hCG level of 66% or more was usually associated with a viable intrauterine pregnancy, though 22% of women in that study had an ectopic pregnancy. Mol et al[13] found similar results using a cutoff of a β-hCG level rise of 50% or more;
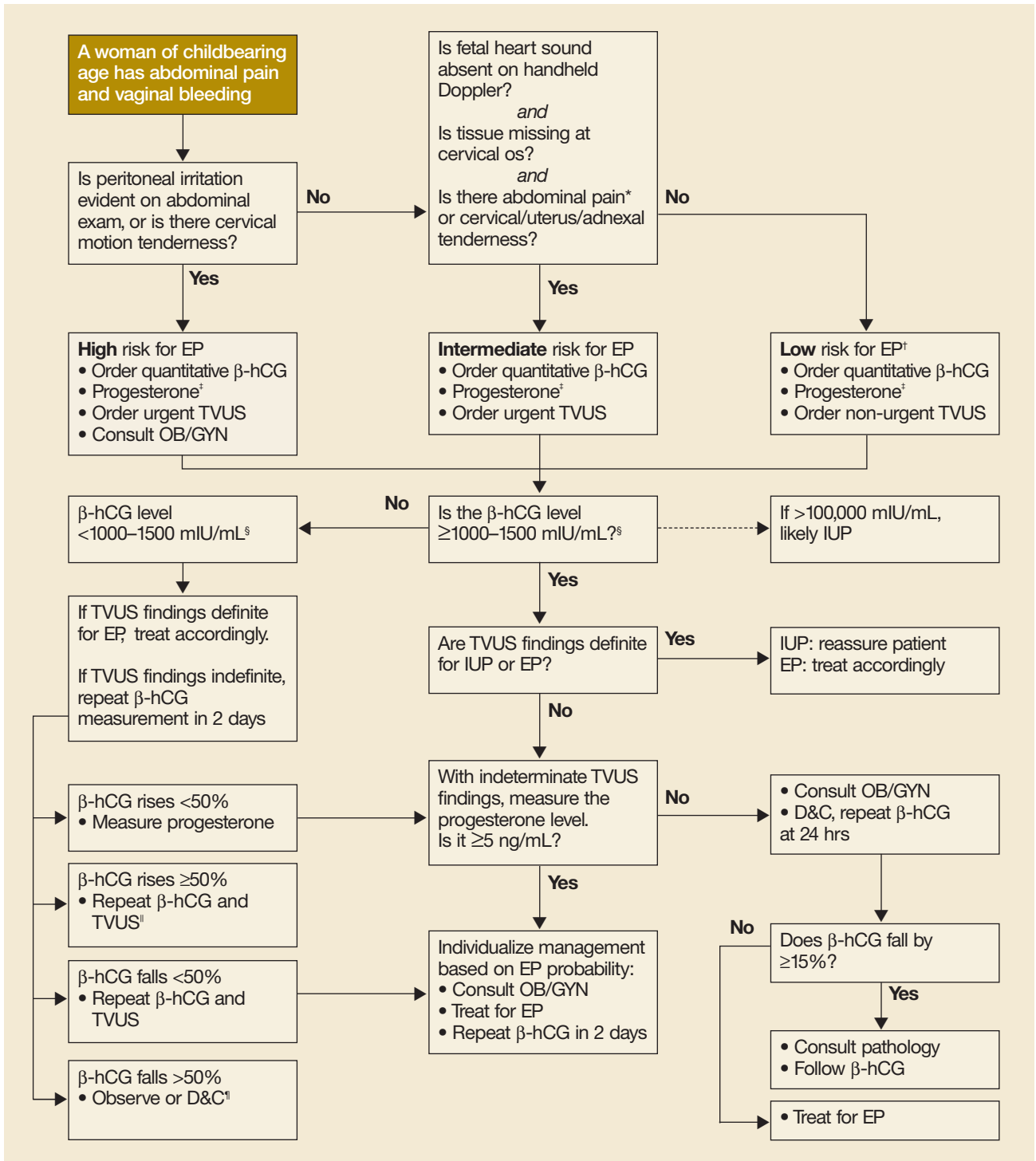
Scope of the problem

Ectopic pregnancy is defined as the implantation of the fertilized egg that occurs outside the uterine cavity. It is practically synonymous with tubal pregnancy, as 97% occur in the Fallopian tube.[6,23] Ectopic pregnancy occurs in 2% of all pregnancies in the United States, affecting more than 100,000 patients each year. It is a leading cause of pregnancy-related death in the first trimester,[2] with a yearly monetary impact of greater than 1 billion dollars. The incidence has increased almost six-fold since 1970 due to delayed child-bearing, rising prevalence of sexually transmitted diseases, and sterilization procedures.[6]

5- to 7-week embryo

Oviduct

ILLUSTRATION BY RICH LaROCCO
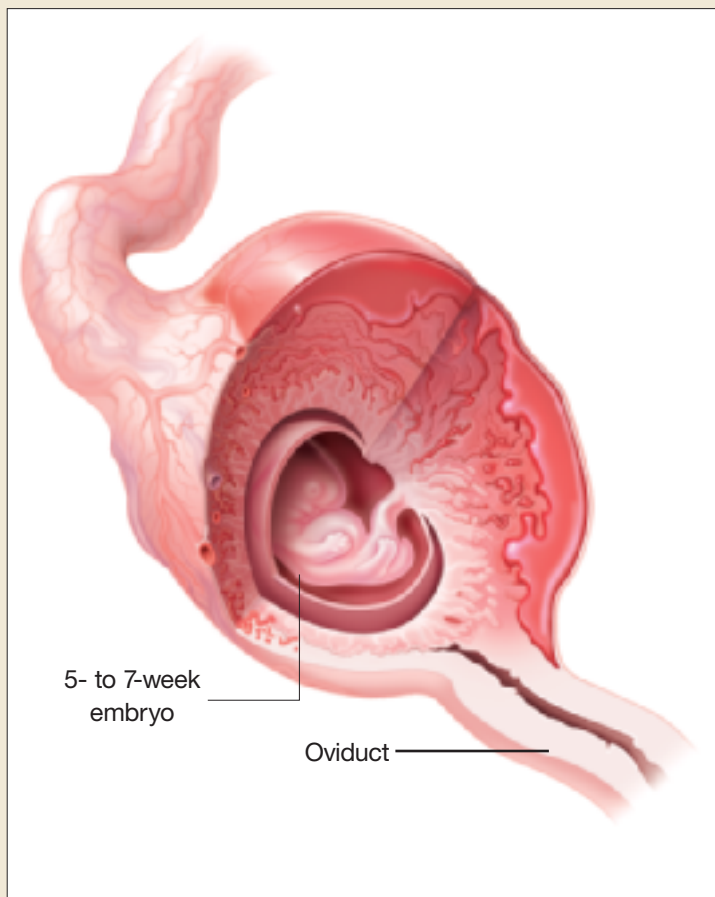
35% had an ectopic pregnancy. Increases in the β-hCG level less than these cutoffs almost always indicated an abnormal pregnancy, and about half of these women had an ectopic pregnancy.[13,17] Also a fall in the β-hCG level by less than 50% was almost always associated with an

FIGURE

Diagnostic protocol with high sensitivity and specificity for ectopic pregnancy

A woman of childbearing age has abdominal pain and vaginal bleeding

Is peritoneal irritation evident on abdominal exam, or is there cervical motion tenderness?

No →

Is fetal heart sound absent on handheld Doppler?
and
Is tissue missing at cervical os?
and
Is there abdominal pain* or cervical/uterus/adnexal tenderness?

No →

Yes ↓ (peritoneal box)

Yes ↓ (Doppler box)

High risk for EP
• Order quantitative β-hCG
• Progesterone‡
• Order urgent TVUS
• Consult OB/GYN

Intermediate risk for EP
• Order quantitative β-hCG
• Progesterone‡
• Order urgent TVUS

Low risk for EP†
• Order quantitative β-hCG
• Progesterone‡
• Order non-urgent TVUS

β-hCG level <1000–1500 mIU/mL§

← **No** — Is the β-hCG level ≥1000–1500 mIU/mL?§ - - - → If >100,000 mIU/mL, likely IUP

If TVUS findings definite for EP, treat accordingly.

If TVUS findings indefinite, repeat β-hCG measurement in 2 days

Yes ↓

Are TVUS findings definite for IUP or EP? **Yes** → IUP: reassure patient
EP: treat accordingly

No ↓

β-hCG rises <50%
• Measure progesterone

With indeterminate TVUS findings, measure the progesterone level. Is it ≥5 ng/mL? **No** → • Consult OB/GYN
• D&C, repeat β-hCG at 24 hrs

β-hCG rises ≥50%
• Repeat β-hCG and TVUS‖

β-hCG falls <50%
• Repeat β-hCG and TVUS

Yes ↓

Individualize management based on EP probability:
• Consult OB/GYN
• Treat for EP
• Repeat β-hCG in 2 days

No ← Does β-hCG fall by ≥15%?

Yes ↓

β-hCG falls >50%
• Observe or D&C¶

• Consult pathology
• Follow β-hCG

• Treat for EP

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* Other than midline suprapubic cramping.

† Risk may be higher in presence of these factors: previous EP, tubal surgery, tubal disease detected by hysterosalpingogram or laproscopy, diethylstilbestrol exposure, sterilization, intrauterine device.

‡ Progesterone is useful only when TVUS is indeterminate.

§ β-hCG level for criterion should be based on local values at which IUP visible on TVUS.

‖ TVUS should be repeated when β-hCG has risen above the discrimination zone.

¶ Only 2/170 patients in this category had EP; therefore, D&C is safe but may not be cost-effective.[11]

β-hCG, beta-human chorionic gonadotropin; EP, ectopic pregnancy; TVUS, transvaginal ultrasound; OB/GYN, obstetrician/gynecologist; IUP, intrauterine pregnancy; D&C, dilation and curettage.

TABLE 3

Detecting ectopic pregnancy with ultrasound and β-hCG levels

SUBCLASS	β-hCG <1000 mIU/mL, % (95% CI)	β-hCG >1000 mIU/mL, % (95% CI)
Empty uterus	17.9 (12.7–24.2)	6.0 (2.2–12.8)
Nonspecific intrauterine fluid*	12.2 (4.6–25.0)	1.2 (0.1–5.9)
Echogenic intrauterine material	10.5 (1.8–30.6)	2.7 (0.5–8.4)
Abnormal intrauterine sac†	0.0 (0.0–39.3)	0.0 (0.0–3.1)
Normal intrauterine sac	0.0 (0.0–34.8)	0.0 (0.0–8.4)

* Anechoic intrauterine fluid collection >10 mm diameter with no echogenic border.
† Anechoic intrauterine fluid collection >10 mm diameter with no yolk sac or fetal pole or grossly irregular border.
Source: Dart et al 2002.[32]

abnormal pregnancy, but only 19% of these women had an ectopic pregnancy.[13,17] Alternatively, decreases in β-hCG level of greater than 50% reduced the chance that patients had an ectopic pregnancy to less than 3%.[13,17]

Serum progesterone levels may have limited usefulness. Serum progesterone measurements are not considered accurate enough to diagnose ectopic pregnancy.[24] However, progesterone levels may be helpful if they are either very high or very low. Levels less than 22 ng/mL have a sensitivity of 100% for ectopic pregnancy.[25] Only 5 of 1615 patients (0.3%) in 13 studies with progesterone levels below 5 ng/mL had a viable intrauterine pregnancy.[24] By establishing the low likelihood of a viable intrauterine pregnancy, serum progesterone measurements may also be useful when β-hCG levels have reached 1000–1500 mIU/mL and the TVUS is equivocal.[25]

When D&C may help. Dilation and curettage (D&C) is an option for patients with an indeterminate ultrasound result and progesterone levels less than 5 ng/mL, as it can rule out an ectopic pregnancy with only a small chance of interrupting a viable intrauterine pregnancy. The presence of chorionic villi rules out an ectopic pregnancy. In the absence of villi, if β-hCG levels subsequently plateau or increase, it is pre-

sumptive of ectopic pregnancy. Chorionic villous sampling by pipelle curette has both insufficient sensitivity and predictive value in diagnosing ectopic pregnancy, and should not be considered a substitute for D&C.[26]

Other tests that have limited use. Patients with ectopic pregnancy may have elevated serum markers of smooth muscle destruction such as creatinine phosphokinase (CPK), myoglobin, and smooth muscle heavy-chain myosin (SMHC). However, these tests are of limited value in diagnosing ectopic pregnancy.[27] SMHC may be of use in evaluating pregnancies less than 5 weeks' gestation when the TVUS is not diagnostic. Serum vascular endothelial growth factor is another marker elevated in women with ectopic pregnancy; levels greater than 200 pg/mL distinguish ectopic pregnancy from intrauterine pregnancy (sensitivity=60%, specificity=90%).[28]

▪ Imaging

In normal pregnancies, a gestational sac is seen on TVUS between 4 and 5 weeks' gestation;[29] the yolk sac is visible at around 6 weeks; and an embryo can be detected between 6 and 7 weeks. A gestational sac greater than 10 mm in diameter without a yolk sac, or greater than 25 mm without an embryo, indicates an abnormal pregnancy.[9,29] Presence of an intrauterine

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If findings on ultrasound are indeterminate, measure β-hCG every 48 hours— a low increase or a fall usually means abnormal pregnancy

pregnancy on ultrasound effectively rules out ectopic pregnancy because heterotopic pregnancy is rare (1 in 2600–30,000 pregnancies).[30] Hormonal changes associated with pregnancy result in a uterine endometrial fluid collection (pseudo-sac) in 8% of ectopic pregnancies.[31]

Specific diagnostic finding for ectopic pregnancy. A gestational sac visible on ultrasound with a yolk sac or fetal pole outside the endometrial cavity (**TABLE 2**) is diagnostic of ectopic pregnancy. The initial ultrasound is indeterminate in 15% to 20% of women with clinical features suggesting ectopic pregnancy.[14,15] Dart et al[32] developed a subclassification system of indeterminate ultrasound including 5 categories that stratify the risk of ectopic pregnancy (**TABLE 3**).

Endometrial stripe thickness of dubious value. For patients with an empty uterus on TVUS and a β-hCG level below the discriminatory zone, endometrial stripe thickness may identify an abnormal pregnancy. In a retrospective study of 117 patients with β-hCG levels less than 1500 mIU/mL, stripe thickness <6 mm had a sensitivity of 100% in identifying ectopic pregnancy or miscarriage; at >13 mm, it had a specificity of 100%.[33]

Two recent studies, however, have called into question the value of stripe thickness in identifying ectopic pregnancy. One suggested it was of little value with β-hCG levels <1500 mIU/mL,[34] and the other concluded its predictive value for ectopic pregnancy and the likelihood of obtaining chorionic villi on D&C is confined to β-hCG values at or below 1000 mIU/mL.[35]

Color-enhanced sonography. The addition of endovaginal color-flow imaging to sonography enables exclusion of ectopic pregnancy by establishing findings consistent with a nonviable intrauterine pregnancy: an intrauterine gestational sac, nonvisualization of an adnexal mass, and absent placental blood flow (sensitivity= 95%, specificity=98%).[12] Color-flow Doppler imaging shows enhanced blood flow to the affected tube. A cutoff value of 8% change in tubal blood flow has been

used to diagnose ectopic pregnancy (sensitivity=85%, specificity=96%).[36] In cases where the gestational sac is questionable or absent, color-flow Doppler may expedite diagnosis and possibly identify candidates for expectant or medical management.

When an MRI might help. Magnetic resonance imaging (MRI), in a small study of 37 patients, allowed recognition of tubal wall enhancements and fresh tubal hematoma, and was diagnostic in 21 patients.[37] An MRI may be useful when precise and early diagnosis of ectopic pregnancy is imperative, such as pre-existing damage to the contralateral tube where preservation of tubal patency is paramount and when prior TVUS is inconclusive.[37]

▌A practical evaluation algorithm

Prediction models based on clinical presentation, which classify patients into high-, intermediate-, and low-risk groups, are useful for estimating the risk of ectopic pregnancy in first-trimester patients (**FIGURE**). Diagnostic pathways incorporating physical findings, quantitative β-hCG levels, and ultrasound results have been developed to manage possible ectopic pregnancy.[38,39] A protocol created by Barnhart using β-hCG and TVUS was accurate and safe when applied to women presenting in emergency settings (sensitivity=100%, specificity= 99.9%).[30] If β-hCG levels were greater than 1500 mIU/mL, ultrasound was performed. Clinically stable patients with β-hCG levels below 1500 mIU/mL were followed with serial β-hCG levels.

A decision model comparing 6 possible diagnostic strategies that combined clinical examination, TVUS, β-hCG, serum progesterone, and D&C showed that TVUS followed by serial serum β-hCGs in those with initial nondiagnostic ultrasound scans was the most accurate and efficient model.[40] By using this strategy, all ectopic pregnancies would be detected, fewer than 1 in 100 normal pregnancies would be interrupted, and diagnostic lag would average only 1.46 days.

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FAST TRACK

A decision model comparing diagnostic strategies showed that TVUS followed by serial β-hCGs was the most accurate and efficient model