17 Ectopic Pregnancy and Pregnancy of Unknown Location (PUL)

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Introduction

Ectopic pregnancy (EP) represents 1–2% of pregnancies [1]. They have a risk of rupture, hemorrhage, and tubal damage, which can lead to decreased future fertility and even death. The most common presenting symptoms suggesting an EP are abdominal pain or vaginal bleeding. Advances in ultrasound technology allow the detection of ectopic pregnancies in their earliest state, allowing treatment alternatives, e.g., observation, medical therapy, or surgical treatment, with reduced morbidity and mortality. However, immediate diagnosis is not always accomplished. Thus, a systematic approach to patients with a possible EP is required to avoid interruption or mistreatment of an intrauterine pregnancy (IUP), timely diagnosis of an EP, and appropriate management with pregnancy failure. This chapter reviews such an approach emphasizing the value of various diagnostic tests.

Pregnancy of Unknown Location

Pregnancy of unknown location (PUL) describes a situation in patients with a positive pregnancy test when transvaginal ultrasound (TVS) fails to identify a pregnancy's location, either intrauterine or extrauterine. In patients with a positive urinary pregnancy test, the location of a pregnancy is usually confirmed in more than 90% of cases [2]. The remainder are categorized as a PUL [3]. In 2011, Barnhart et al. reviewed the consensus nomenclature associated with early pregnancy evaluation, categorizing such pregnancies into the following descriptive areas [4]:

- Definite ectopic pregnancy
- Probable ectopic pregnancy
- Pregnancy of unknown location
- Probable intrauterine pregnancy
- Definite intrauterine pregnancy

The earliest sign of pregnancy is the finding of a saclike structure, regardless of the location. The finding of such a structure in the uterus is considered a probable IUP. This same finding in the adnexa is consistent with a probable EP. The finding of a yolk sac within a gestational sac definitively diagnoses a pregnancy, regardless of the location. The finding of a gestational sac with a yolk sac in the uterus is consistent with a definite IUP, while this same finding outside of the uterus definitely diagnoses an EP. A PUL exists when there are no signs of either an IUP or an EP, representing ~10% of cases [5]. Expectant management with follow-up TVS and serial human chorionic gonadotropin (hCG) levels will lead to the diagnosis of a visualized IUP (34.3%), a visu-

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J. S. Abramowicz, R. E. Longman (eds.), *First-Trimester Ultrasound*,
https://doi.org/10.1007/978-3-031-24133-8_17

alized EP (8.7%), or a resolved PUL in 56.9% of these patients [5]. Thus, patients who are clinically stable with a PUL warrant expectant management [3]. A small number of patients will remain with a PUL, which can be treated medically, surgically, or with a diagnostic dilatation and curettage, or observed for spontaneous resolution [4].

A consensus regarding follow-up surveillance of patients with a PUL is still evolving. Individualized surveillance based on risk factors could lead to more accurate diagnosis and reduced cost. Barnhart et al. retrospectively assessed specific clinical factors to determine the frequency and immediacy of follow-up for patients with a PUL [6]. They created a scoring system to triage women into various risk groups. Those at age "extremes" were assigned increasing risk scores: age <18 received a +1 and age >38 assigned a +3. Prior EP increased a patient's risk, with those having one prior EP assigned +2, whereas those with two or more prior EP assigned +3. Patients with bleeding were assigned +4. Patients with a prior miscarriage or with an hCG >2000 mIU/mL were assigned −1. A patient's risk for a nonviable gestation was stratified into negligible risk (−2 to −1), intermediate risk (0 to +4), and high risk (equal to or greater than +5) based on the total score. Based on their risk stratification, patients received surveillance as follows:

- Low-acuity surveillance: "send home" with follow-up in 4–7 days
- Standard surveillance: "monitor" with repeat hCG in 2 days
- High-acuity surveillance: "intervention" including uterine evacuation, laparoscopy, or surveillance in 24 h, depending on the patient's clinical status

Overall, the proposed scoring system had a >90% specificity. Thus, clinical signs and symptoms of a woman with PUL may help optimize surveillance plans.

Condous et al. developed a logistic regression model using serial hCG and progesterone levels, drawn 48 h apart, to predict the outcome of PULs [5]. An hCG increase of >66% was predictive of an IUP with a positive predictive value (PPV) of 96.5%. A serum progesterone of <20 mmol/L predicted a failing PUL with a PPV of >95%. In summary, the change in hCG outperformed serum progesterone change in predicting the location and outcome of a PUL.

One can postulate that combining the results of these two studies would improve our surveillance of patients with PUL. Specifically, individualized risk assessment, correlated with serial hCG levels and complemented with ultrasound and, in select cases, serum progesterone, will help determine the ultimate outcome of PULs.

A more recent large, multicenter study evaluated a two-step strategy (2ST) to assess the outcome in a PUL [7]. The final pregnancy outcome was defined as a failed PUL (FPUL), an intrauterine pregnancy (IUP), or an EP (which also included persistent PUL [PPUL]). Step 1 included a serum progesterone and beta-hCG (BhCG) level on presentation. An initial progesterone level of ≤2 nmol/L identified PULs of low risk of EP, with a follow-up urine pregnancy test recommended in 2 weeks to confirm a negative result. In step 2, those patients with a progesterone >2 nmol/L had the initial BhCG compared to a second BhCG obtained 48 h later, and a BhCG ratio was calculated (BhCG at 48 h/BhCG at 0 h). A BhCG ratio between 0.87 and 1.66 was classified as having a high risk of an EP, defined as a risk ≥5% of an EP. If the ratio was <0.87, the PUL was classified as low risk of an EP, most likely a failed PUL (FPUL). If the BhCG ratio was >1.66, the PUL was classified as low risk for EP, most likely an IUP (Table 17.1). The two-step strategy classified 16% of PUL as "low risk" based on a progesterone <2 nmol/L, eliminating the need for a second visit in 1 in 6 cases of PUL. In step 1, 7 of 407 patients (1.7%) initially classified as "low risk" were ultimately diagnosed with an EP. In step 2, 8 of 1038 patients (0.8%) classified as "low risk" ultimately had an EP. None of the cases resulted in a ruptured EP or significant clinical harm. Of 901 women classified as "high risk" in step 2, 275 (30.5%) had an EP. Thus, 85.9% of EP were correctly classified as "high risk."

Table 17.1 Outcomes of a two-step strategy for pregnancy of unknown location [7]

		#		FPUL		IUP		EP	
Criteria		2625	%	#	%	#	%	#	%
Step 1	$P \leq 2$ nmol/L	407	15.5	386	94.8	14	3.4	7	1.7
Excluded from additional analysis	Outcome known <48 h	62	2.7						
	Protocol deviation	217	9.5						
Step 2	BhCG ratio	1989	87.7						
Low risk, FPUL	<0.87	727	37.5	685	94.2	40	5.5	2	0.3
Low risk, IUP	>1.66	311	16.0	0	0	305	98.1	6	1.9
High risk, EP	0.87–1.66	901	46.5	200	22.2	426	47.3	275	30.5

FPUL failed pregnancy of unknown location, *IUP* intrauterine pregnancy, EP ectopic pregnancy
BhCG ratio: <0.87: high risk for EP, 0.87–1.66: low risk, probable FPUL, >1.66: low risk, probable IUP

A recent multicenter study by the same group analyzed various protocols in cases of PUL [8]. The study compared the probability of a PUL being a failing PUL, an IUP, or an EP (including persistent PUL) based on different strategies: (1) simple BhCG cutoffs; (2) the initial BhCG and BhCG ratio (M4 protocol); (3) the initial BhCG, the BhCG ratio, with or without an initial serum progesterone (M6P or M6PN protocols); and (4) a two-step approach (2ST), only obtaining and calculating a BhCG ratio if the initial serum progesterone was >2 nmol/L. Patients with a progesterone ≤2 nmol/L were deemed low risk for EP, requiring only a follow-up urine hCG in 2 weeks to confirm a negative result. The authors concluded that the M6P approach is the best prediction model for PUL. However, the 2ST made PUL management more efficient with little loss of performance. The authors recommended using M6P and its incorporation into a two-step strategy (2ST) for PUL triage.

A recently published trial evaluated active versus expectant management in 255 hemodynamically stable patients with persisting PUL [9]. A persisting PUL was described as a pattern of serial hCG levels that suggests neither an ongoing pregnancy nor one undergoing spontaneous resolution. Empiric management consisted of close surveillance with serial hCG levels every 4–7 days. Active management included uterine evacuation with methotrexate as needed, or empiric methotrexate. Patients undergoing uterine evacuation had an hCG the day after the procedure. Those whose hCG did not decline at least 15% were treated with methotrexate, following a two-dose protocol of two intramuscular doses of 50 mg/m^2 given 3 days apart [10]. The two-dose protocol was also used for the empiric methotrexate treatment group. This trial found that a higher percentage of women had successful resolution of pregnancy with active management than expectant management (51.5% vs. 36.0%). There was no significant difference in resolution between the two active management groups (empiric methotrexate vs. uterine evacuation [54.9% vs. 48.3%]), although the median time to resolution was 6 days shorter for patients treated with uterine evacuation. Further, patients undergoing active management were less likely to undergo unscheduled surgery (12.7% vs. 26.7%). Five women in the study were diagnosed with a ruptured ectopic pregnancy, two undergoing expectant management and three undergoing active management. All were treated successfully with laparoscopy. Of note, one participant in the expectant management group ultimately had a normal intrauterine pregnancy, despite abnormally rising serial hCG levels initially: 7% in 2 days (86 mIU/mL and 92 mIU/mL) and 24% over 4 days (92 mIU/mL and 107 mIU/mL). Subsequently, her hCG levels rose normally. The etiology of this slow rise in very early pregnancy was not clear.

Human Chorionic Gonadotropin (hCG) Dynamics

Human chorionic gonadotropin (hCG) can be qualitatively assessed resulting in a positive or negative result. However, measuring the quantitative hCG level in the blood is quite useful if the

initial pregnancy evaluation is inconclusive. One can follow serial hCG levels, using the rationale that abnormally rising levels are more consistent with either an EP or a failed IUP. Older studies determined that the 2-day rise of hCG in a normal pregnancy is at least 66% [11]. A 2004 study determined that the 2-day rise in hCG (normal pregnancy) ranged between 1.53 and 3.28 times, with a median of 2.24 times [12]. The premise is that an ectopic pregnancy will have an inadequate rise in the hCG level over 2 days, as only 21% of EPs will have a rise of 53% or more [13]. In 2016, Barnhart et al. found differences in the rate of hCG rise based on the initial hCG levels. The predicted hCG minimal rise was 49% when the hCG was less than 1500 mIU/mL, 40% with a level of 1500–3000 mIU/mL, and 33% when the initial level was greater than 3000 mIU/mL [14]. Further, they determined that hCG levels rise faster in African American women.

An often overlooked finding of one early study was that 15% of normal pregnancies had abnormal hCG increases [11]. Thus, abnormally rising hCG levels are not necessarily diagnostic of an ectopic pregnancy, only highly suggestive. Thus, one should exercise caution when evaluating the rise in hCG. Abnormal increases in hCG values should raise one's index of suspicion for an ectopic pregnancy or an abnormal intrauterine pregnancy. TVS is valuable, regardless of hCG increase, to determine the location and status of the pregnancy.

Threshold and Discriminatory Levels of hCG

Threshold Level

The threshold level is the lowest level of hCG at which a normal intrauterine pregnancy can be detected, typically visualizing an early gestational sac. Older studies proposed a threshold value of 1000 mIU/mL [15]. However, advances in ultrasound technology have improved our imaging capabilities. Thus, more recent studies indicate that the threshold level may be as low as 390 mIU/mL [16].

Discriminatory Level

The discriminatory level is that level of hCG above which all normal (singleton) intrauterine pregnancies should be seen. This level typically ranged between 1000 and 1500 mIU/mL in most laboratories. The discriminatory level or value, however, has undergone revision, based on two key studies. Doubilet and Benson reviewed a decade of experience in patients with TVS and hCG done on the same day [17]. They identified those patients whose initial TVS did not visualize an intrauterine fluid collection, with embryonic or fetal cardiac activity found on subsequent ultrasound studies. They demonstrated that slightly more than 10% of patients with an IUP that was ultimately diagnosed had an initial hCG ≥1500 mIU/mL (5.9% with levels of 1500–1999 mIU/mL; 4.5% >2000 mIU/mL) (Table 17.2). Connolly et al. performed a similar study including patients who had a TVS and hCG within 6 h of each other. They tabulated the levels associated with 99% of IUPs. In this study, the discriminatory level was 3510 mIU/mL (Table 17.3). The current recommendation with an inconclusive ultrasound, assuming that the patient is hemodynamically stable, is to follow the patient until the hCG level is at least 3000–3500 mIU/mL before declaring that an IUP is not visualized. This would defer medical intervention, such as methotrexate, until the diagnosis is

Table 17.2 Evidence against the hCG discriminatory level [17]

hCG (mIU/mL) 3rd–4th International Standard	# (202)	%
<1000	162	80.2
1000–1499	19	9.4
1500–1999	12	5.9
≥2000	9	4.5

Table 17.3 Reevaluation of the threshold and discriminatory levels [16]

hCG (mIU/mL)	Gestational sac	Yolk sac	Embryo
Threshold level	390	1094	1394
Discriminatory level	3510	17,716	47,685

clarified. This recommendation will largely avoid the inadvertent treatment of an IUP with methotrexate, with resultant fetal anomalies or fetal loss [18]. These hCG levels and recommendations pertain only to singleton pregnancies (see Chap. 10). Multiple gestations often have much higher hCG levels before identifying the intrauterine gestations. Thus, caution is advised in patients who have undergone assisted reproduction.

Endometrial Findings in Ectopic Pregnancy

Endometrial Thickness

When a gestational sac or yolk sac is not visualized, endometrial thickness may be helpful in assessing the location of a pregnancy. Spandorfer and Barnhart reviewed the ultrasound-measured endometrial thickness in patients with an hCG below the discriminatory level. In general, an IUP had a mean endometrial thickness that was greater than an EP or a spontaneous miscarriage (13.42 mm vs. 5.95 mm vs. 9.28 mm, respectively) [19]. In their study, an endometrial thickness ≤8 mm was associated with an abnormal pregnancy in 97% of cases. A more recent study found no statistical difference in the endometrial thickness in patients with an IUP (12.24 ± 6.0 mm), a spontaneous miscarriage (10.19 ± 6.0 mm), or an ectopic pregnancy (9.56 ± 4.87 mm), noting the trend for an IUP having a thicker endometrium [20]. They further found that 99% of ectopic pregnancies had an endometrial thickness of less than 21 mm. Thus, they concluded that the lack of identifying a gestational sac with an endometrial thickness >21 mm is more commonly associated with an IUP. When evaluating early pregnancy, a thicker endometrium may be more commonly associated with an IUP, while a thinner endometrium is more common with an EP (Figs. 17.1 and 17.2).

Intrauterine Fluid

The characteristics and shape of the intrauterine fluid in early pregnancy help determine a pregnancy's location. Benson et al. determined that no intrauterine fluid was present in 83.4% of patients with an EP (191 of 229) [21]. Furthermore, 86.8% of those patients with an EP and intrauterine fluid (33 of 38) also had an adnexal mass. In most of these patients (31 of 38, or 81.6%), the fluid that was present tended to follow the contour of the endometrial cavity (Fig. 17.3). A smaller number (7 of 38, or 18.4%)

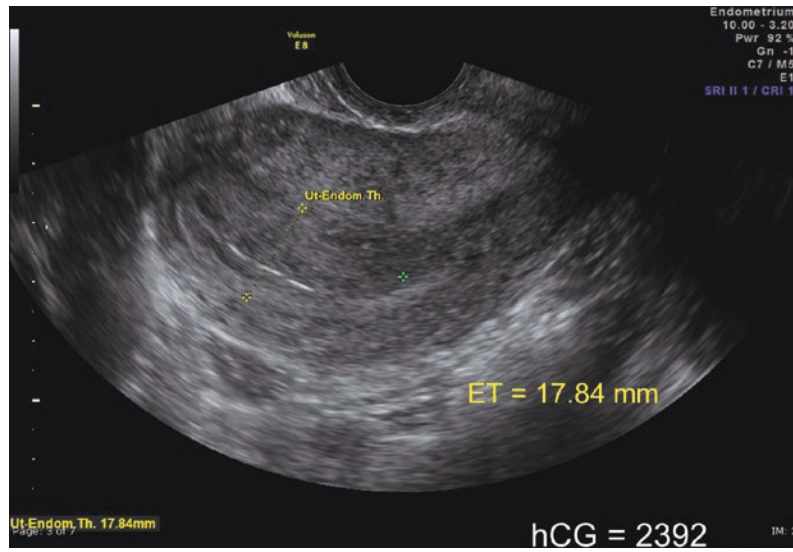

Fig. 17.1 Thicker endometrium (17.84 mm) in an early intrauterine pregnancy

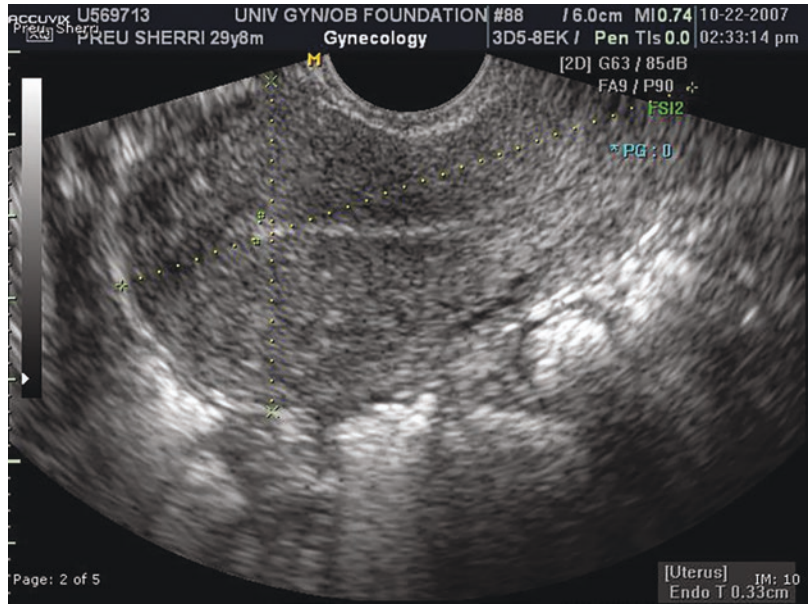

Fig. 17.2 Thin endometrium (3.3 mm) associated with an ectopic pregnancy

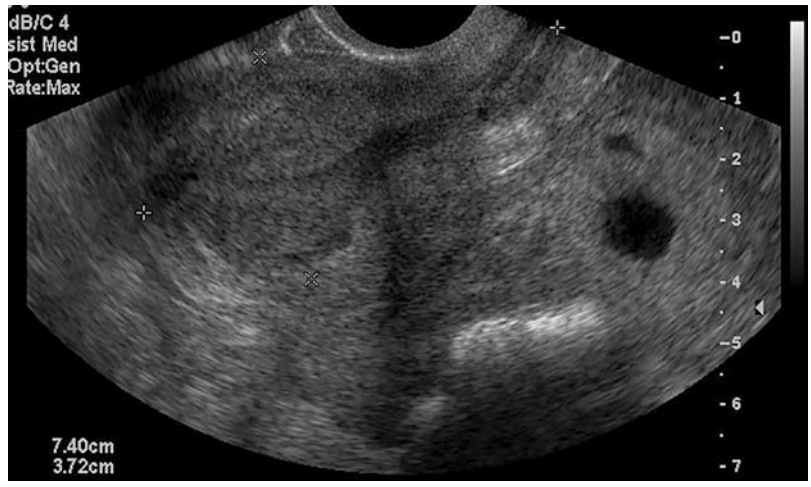

Fig. 17.3 Intrauterine fluid with low-level echoes following the endometrial contour in patient with an ectopic pregnancy

had a smooth-walled, cyst-like structure within the uterus. Such a cystic fluid collection can mimic an IUP. The differentiation is that the gestational sac of an IUP burrows into the decidua and is located slightly eccentrically (Fig. 17.4). One of the most important findings of this study was that a smooth-walled anechoic intrauterine cystic structure with no identified adnexal mass is associated with an IUP in 99.8% of patients (Fig. 17.5).

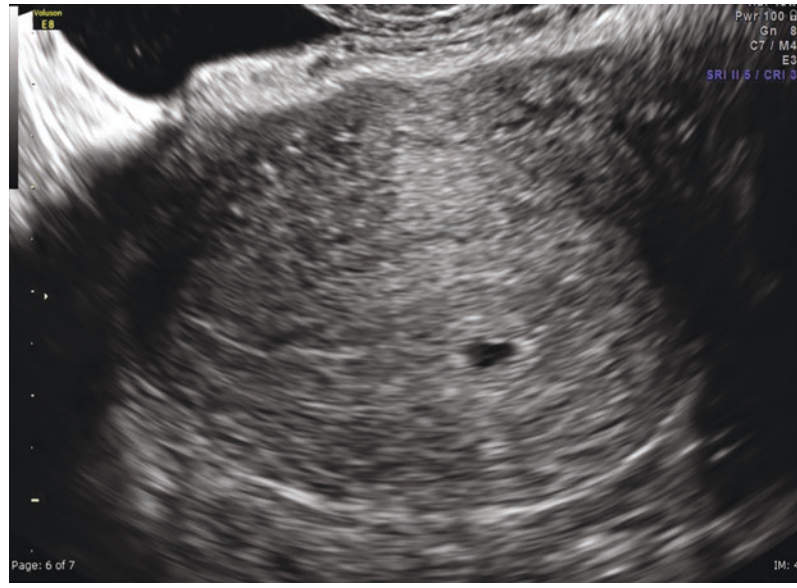

Fig. 17.4 Gestational sac located in the posterior endometrium in an early intrauterine pregnancy

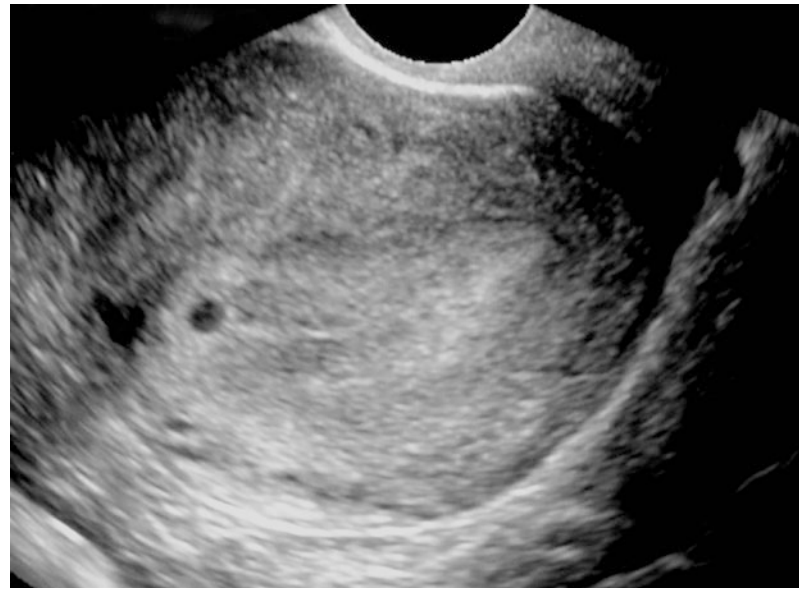

Fig. 17.5 Smooth-walled anechoic sac in a patient with an early IUP

Adnexal Findings in Ectopic Pregnancy

In 1994, Brown and Doubilet reviewed 10 studies with over 2000 patients with suspected EP to determine the adnexal findings associated with an ectopic pregnancy [22]. All ectopic pregnancies were surgically confirmed. They determined the following four categories of adnexal findings associated with ectopic pregnancies:

1. An adnexal embryo with a heartbeat (Fig. 17.6)
2. An adnexal mass with a yolk sac and no embryonic cardiac activity (Fig. 17.7)
3. An adnexal mass with a central anechoic area with a hyperechoic ring ("tubal ring" or the "bagel sign") (Fig. 17.8)
4. Any adnexal mass, other than a simple cyst or an intraovarian lesion (Fig. 17.9)

The first two findings are diagnostic of an EP. The likelihood of an ectopic pregnancy with a tubal ring is 95%. The likelihood of an ectopic pregnancy with any complex or solid adnexal mass that is not intraovarian is 92% (Table 17.4). Such adnexal findings are present in almost 95% of EP with each finding being visualized in 7.4%, 8.3%, 24.7%, and 54.1% (respectively) of EP [23].

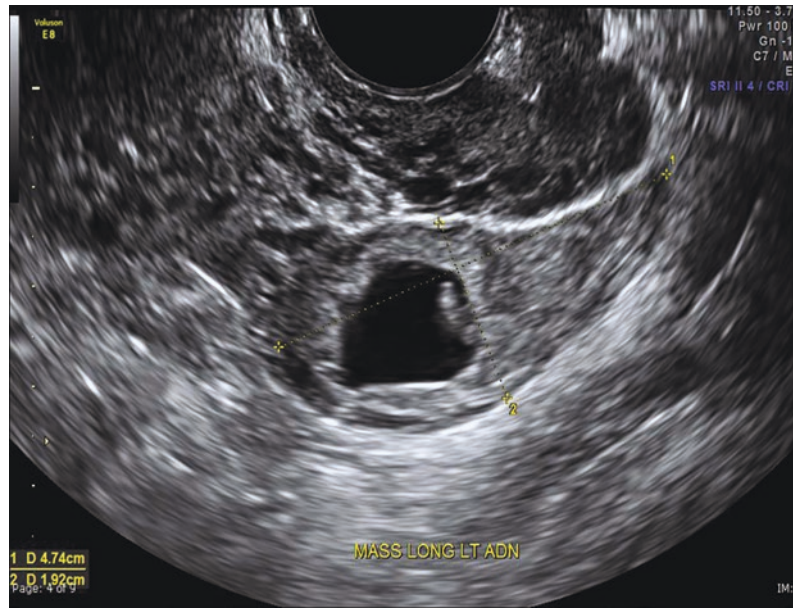

Fig. 17.6 Adnexal embryo with FHR = 172, which is diagnostic of an ectopic pregnancy

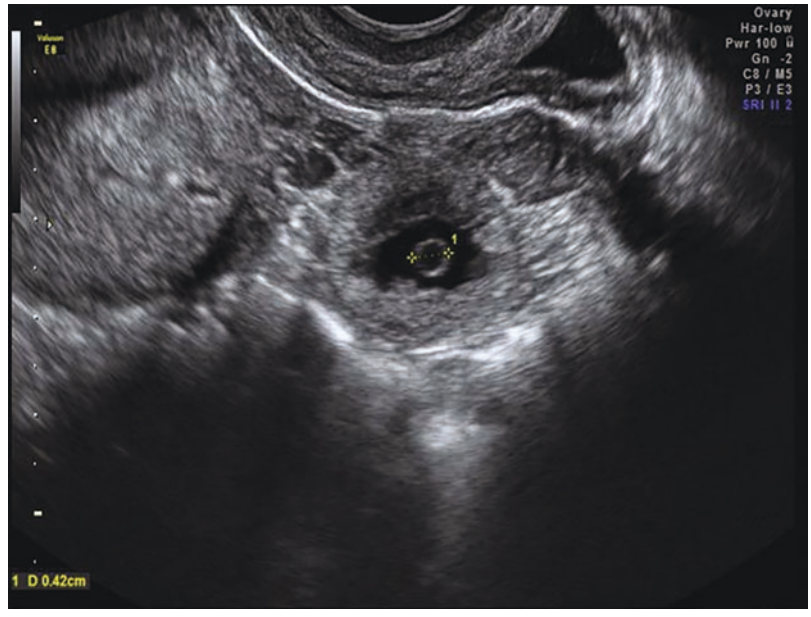

Fig. 17.7 Adnexal mass with a yolk sac, which is diagnostic of an ectopic pregnancy

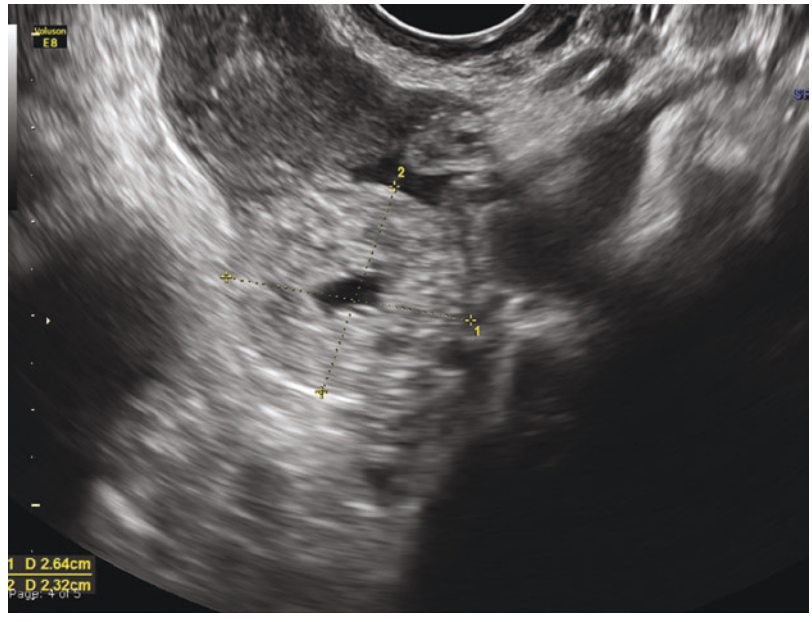

Fig. 17.8 "Tubal ring," or so-called bagel sign in an ectopic pregnancy

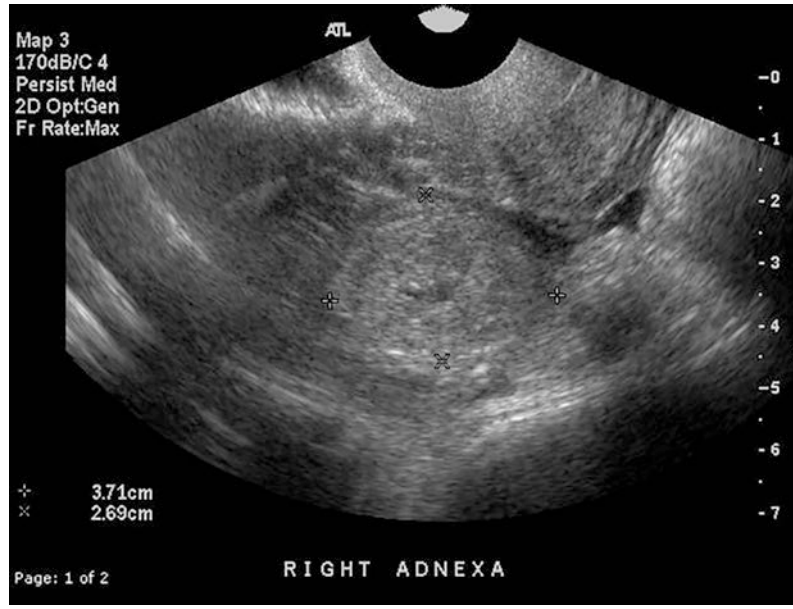

Fig. 17.9 Adnexal mass separate from the ovary in an ectopic pregnancy

Table 17.4 Adnexal criteria for ectopic pregnancy[22, 23]

Adnexal finding on TVS	Likelihood of ectopic (%) [22]	Frequency of findings (%) [23]
Extrauterine embryo with cardiac activity	100	7.4
Adnexal mass with yolk sac without embryonic cardiac activity	100	8.3
Adnexal mass with central anechoic area and hyperechoic rim ("tubal ring")	95	24.7
Any complex or solid adnexal mass other than a simple cyst or intraovarian lesion	92	54.1

Workup for Ectopic Pregnancy

This chapter reviews the hCG and ultrasound findings in ectopic pregnancy. The order in which one performs various tests, including serum progesterone, in patients with suspected EP was evaluated by Garcia and Barnhart in a 2001 paper [24]. The order of these tests included the following:

- Ultrasound followed by quantitative hCG if the ultrasound findings were inconclusive
- Quantitative hCG followed by ultrasound, when the hCG was > threshold value
- Progesterone followed by ultrasound and, if inconclusive, then quantitative hCG
- Progesterone followed by quantitative hCG and, when > threshold value, then ultrasound
- Ultrasound followed by repeat ultrasound
- Clinical examination only

They applied these algorithms to a theoretical cohort of 10,000 patients determining the number of ultrasounds, blood draws, dilatation and curettages, and laparoscopies performed. They then predicted the costs of the various strategies and their effectiveness in diagnosing EPs (Table 17.5). Ultimately, they recommended either of the first two strategies; as the progesterone methods missed more ectopic pregnancies, the ultrasound only strategy was too costly and the clinical exam-only

Table 17.5 Six strategies for diagnosing ectopic pregnancy [24]

Strategy	Days to Dx	Blood draws/10,000	Total charge per patient	Missed EP per 10,000	Interrupted IUP per 10,000
Ultrasound → hCG	1.46	5227	$1958	0	70
hCG → ultrasound	1.66	14,375	$1842	0	122
P → ultrasound → hCG	1.25	12,108	$1692	24	25
P → hCG → ultrasound	1.26	15,000	$1569	24	39
Ultrasound → ultrasound	1.21	0	$2486	0	121
Clinical exam only	1.0	0	$0	940	0

method too ineffective. Of note, although serum progesterone may be helpful in predicting the viability of a pregnancy [25], the Garcia study confirmed the findings of others that progesterone lacks adequate sensitivity in distinguishing ectopic and intrauterine pregnancies [26–28].

An Argument for Ultrasound First, Tubal Rupture Below the Threshold Level

The Connolly study previously discussed determined that the threshold level of hCG should be lowered to 390 mIU/mL [16]. Prior to this study, many practitioners deferred ultrasound until the hCG level was ≥1000 mIU/mL. However, an early study by Saxon et al. demonstrated that 50% of ruptured EPs had an hCG ≤999 mIU/mL [29]. This finding was confirmed by the 2014 report of Frates et al. also demonstrating that 41.2% of ruptured EPs had an hCG <1000 mIU/mL. Thus, in patients with suspected EP, performing ultrasound first has value in identifying a definite IUP, EP, or a significant hemoperitoneum (Fig. 17.10). Not visualizing a significant hemoperitoneum allows a more conservative evaluation of such patients while assuring patient safety.

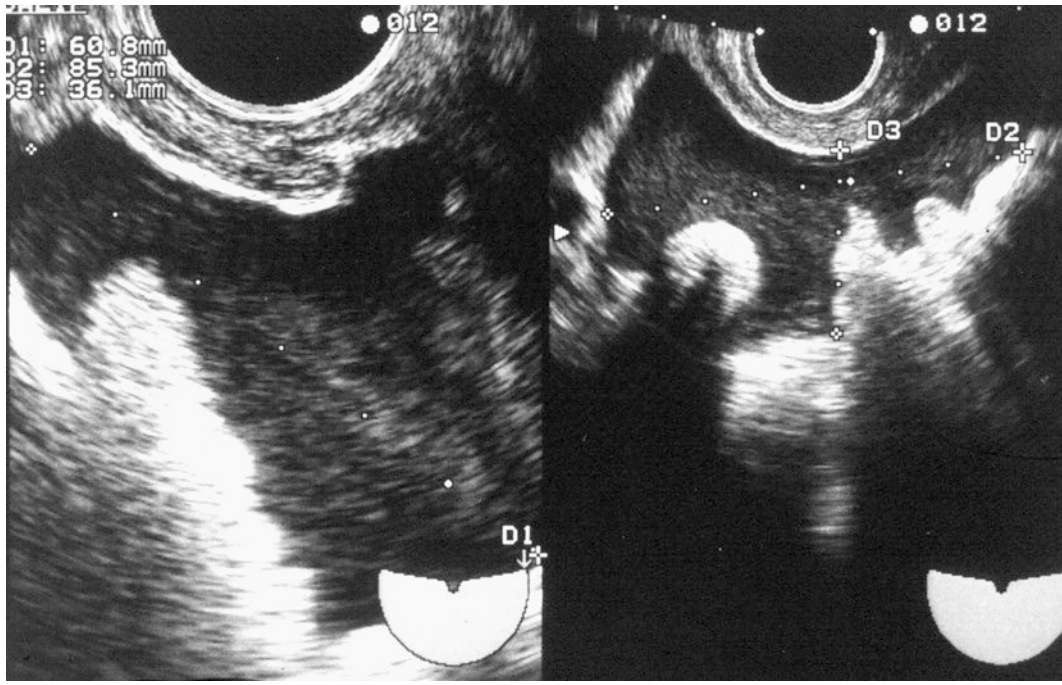

Fig. 17.10 Significant hemoperitoneum identified in a patient with an hCG = 465 mIU/mL

Spontaneous Resolution of Pregnancy

The use of ultrasound for initial patient evaluation can result in identifying adnexal masses that are highly suggestive of an EP, in association with hCG levels that are below the threshold level (Fig. 17.11). Clinicians often feel obligated to treat patients for fear of rupture of an EP. Frates et al. determined that, regardless of the four adnexal findings noted in the prior section, there was no significant difference in the rate of tubal rupture, which ranged from 17.6% to 28.4% [23]. They found that the most sensitive ultrasound finding of rupture was a moderate to large amount of free fluid. Thus, in a hemodynamically stable patient, there is no need for urgent intervention if there is either no or only a small amount of fluid in the cul-de-sac or abdomen. Korhonen et al. observed patients who had decreasing or stable hCG levels, an adnexal mass less than 4 cm in size, and no embryonic cardiac activity [30]. They found that the rate of spontaneous resolution of a suspected or definite EP was 88% when the initial hCG was less than 200 mIU/mL and 25% when the initial hCG was over 2000 mIU/mL. It must be emphasized that the hCG levels were stable or decreasing in these patients. However, this study demonstrated that observation is a reasonable option in well-selected patients meeting the criteria for spontaneous resolution of their EP.

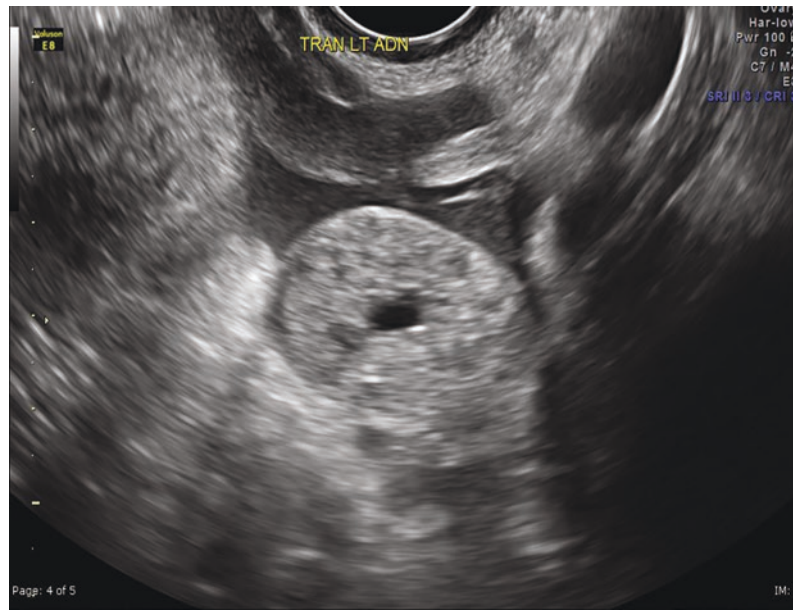

Fig. 17.11 "Tubal ring" consistent with an ectopic pregnancy in a patient with an hCG = 78 mIU/mL

Unusual Ectopic Pregnancies

Heterotopic Pregnancy

The presence of an EP in combination with an IUP is designated a heterotopic pregnancy (Fig. 17.12). The rate of such pregnancies with spontaneous conception may be as low as 1 in 30,000. However, the increased use of assisted reproductive technology has led to an increased incidence of heterotopic pregnancy, perhaps as high as 1 in 110 [31, 32]. One must establish a routine of performing a thorough evaluation of all patients to avoid missing a concomitant EP when a definite IUP is identified.

Interstitial Pregnancy

Interstitial pregnancies are those pregnancies located within the interstitial portion of the fallopian tube and lateral to the endometrial cavity, accounting for 2–4% of all ectopic pregnancies [33]. Three-dimensional (3D) multiplanar reconstruction of the coronal plane is incredibly valuable in localizing such pregnancies (Fig. 17.13). These pregnancies are defined by the ultrasound findings of an empty uterine cavity and a chorionic sac >1 cm from the lateral edge of the uterine cavity (the endometrium), with a thin (<5 mm) layer of myometrium surrounding the chorionic

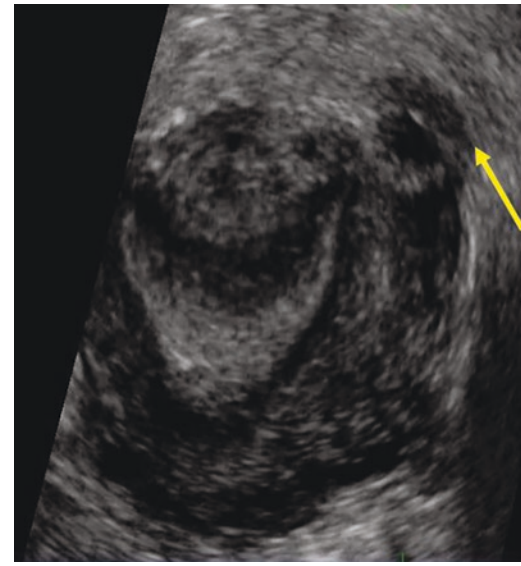

Fig. 17.13 Interstitial pregnancy identified on the 3D coronal view

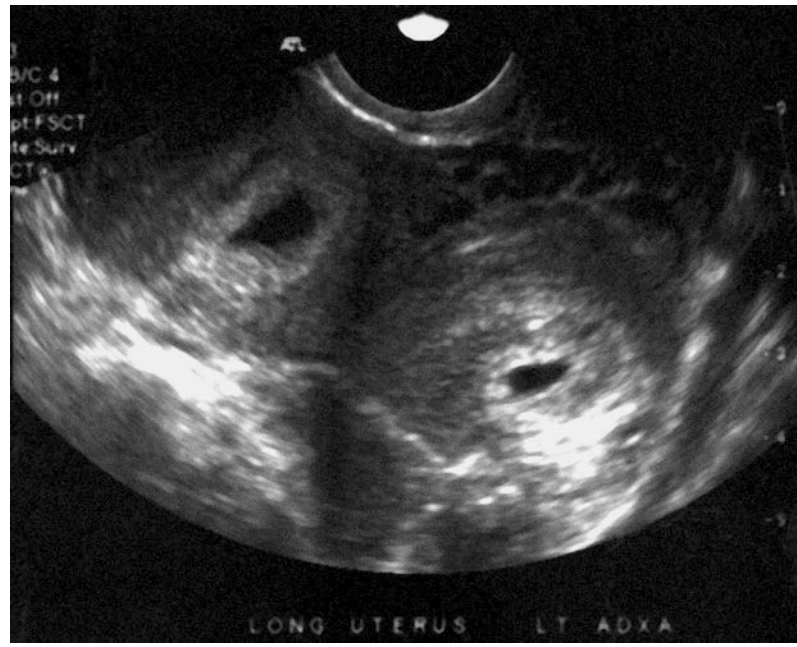

Fig. 17.12 Heterotopic pregnancy with both an intrauterine pregnancy and a tubal pregnancy

sac [34]. Unfortunately, interstitial pregnancies have also been erroneously referred to as cornual pregnancies.

Cornual Pregnancy

A cornual pregnancy previously referred to the implantation of a pregnancy in one of the cornua of a bicornuate, septate, or subseptate uterus [35]. However, such pregnancies are in fact intrauterine. Baltarowich advocated for reserving the term "cornual pregnancy" when implantation occurs in a rudimentary horn attached to a unicornuate uterus, whether communicating or not [33] (Fig. 17.14). Again, 3D ultrasound can be helpful in diagnosing such pregnancies. Although there are few reports of progression into the third trimester, most cornual pregnancies ultimately rupture with fetal demise and potentially fatal maternal hemorrhage.

Angular Pregnancies

Angular pregnancies refer to the eccentric implantation of an IUP in the cornual area of a normally shaped uterus. Specific criteria for diagnosing an angular pregnancy were offered by Jansen and Elliott in 1981 [36]. These include the following:

- Painful asymmetric uterine enlargement
- Directly observed lateral distension of the uterus, with or without rupture, accompanied by displacement of the round ligament reflection laterally
- Retention of the placenta in the uterine angle

Angular pregnancies may carry to term, or at least viability, with more conservative management options available. TVS, particularly using 3D with its coronal views (Fig. 17.15), has remarkably clarified the diagnosis of these eccentrically located pregnancies, as it offers the ability to detect any uterine anomalies and define the specific implantation site of a pregnancy. Thus, diagnostic criteria are now based on ultrasound rather than surgical pathology. Correct designation is imperative for proper communication of the ultrasound findings.

Ovarian Pregnancy

Ovarian pregnancies are rare with 0.15–3% of EP occurring in the ovary [37, 38]. The diagnosis includes an empty uterine cavity with a gestational sac, yolk sac, fetal cardiac activity, or embryo visualized in the ovary [39] (Fig. 17.16). The ultrasound criteria for diagnosing an ovarian EP are (1) a wide echogenic ring with an internal

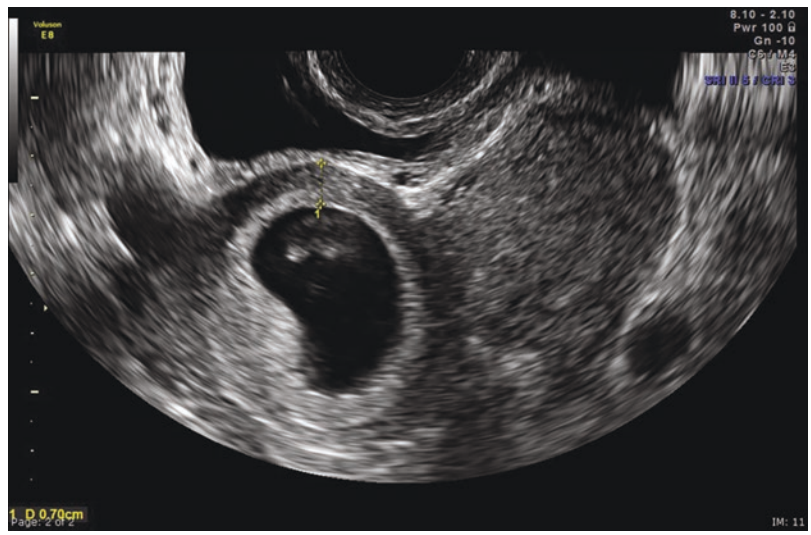

Fig. 17.14 Cornual pregnancy with pregnancy in a non-communicating uterine horn

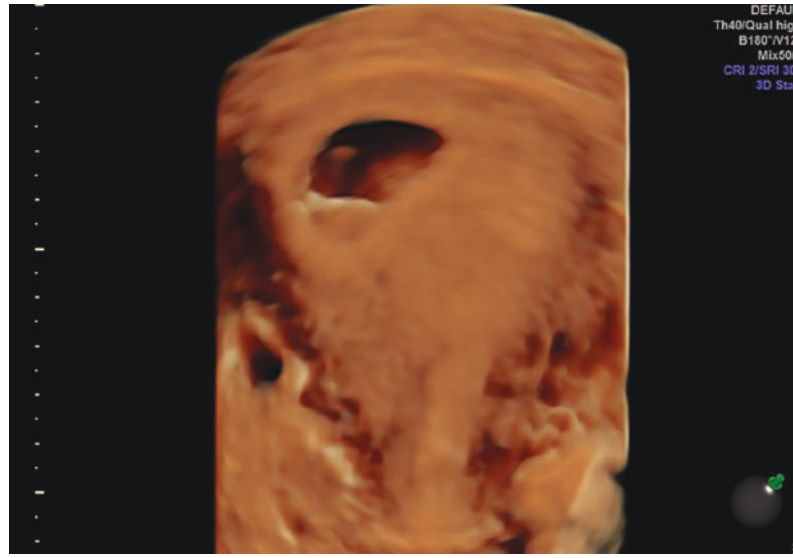

Fig. 17.15 Angular pregnancy that progressed to a full-term delivery

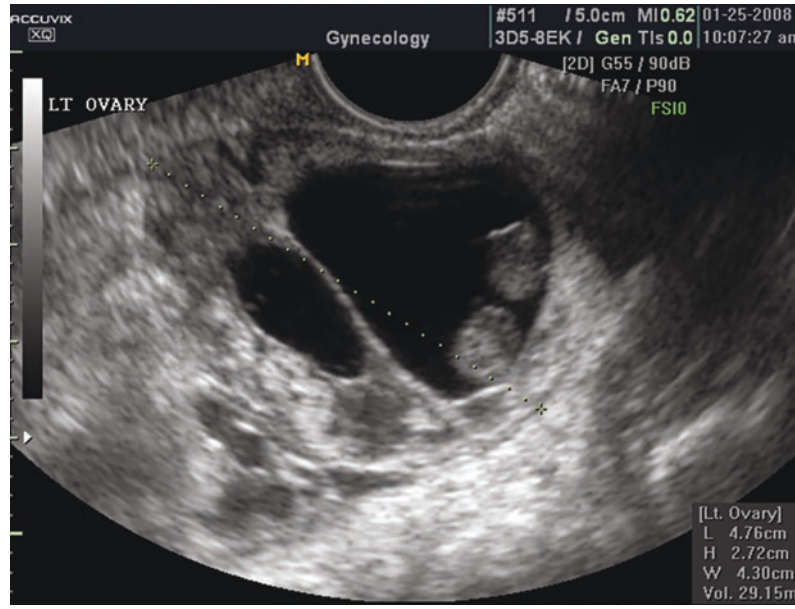

Fig. 17.16 Ovarian pregnancy with nonviable embryo identified in a gestational sac within the ovary

echolucent area and (2) a yolk sac or fetal heart motion in the ovary [39]. The diagnosis is confirmed histologically by the Spiegelberg criteria as follows [40]:

- The gestation occupies a normal position of the ovary.
- The gestational sac, and thus the ovary, must be attached to the uterus by the ovarian ligament.
- Ovarian tissue is histologically proven in the wall of the gestational sac.
- The fallopian tube on the affected side must be intact.

Abdominal Pregnancy

Abdominal pregnancies are quite rare. However, there is significant maternal and perinatal mortal-

ity and morbidity encountered with such pregnancies. This is due to the implantation that occurs outside of the uterus, anywhere in the abdomen. Mortality is markedly higher when attachment occurs to the liver or spleen [41]. The diagnosis is often made later in pregnancy, as the pregnancy has the ability to expand in the abdomen. Studdiford's criteria for appropriate diagnosis include the following [42]:

- The fallopian tubes and ovaries are normal.
- There is no abnormal connection, e.g., fistula, between the uterus and the abdominal cavity.
- The pregnancy is related solely to the peritoneal surface without signs of prior tubal rupture.

Diagnosis requires demonstration of an empty uterus, often normal in appearance, with the fetus contained within a gestational sac, which is separate from the uterus and cervix [43] (Fig. 17.17).

Cervical Pregnancy

Cervical pregnancy has an incidence of 1:1000 to 1:16,000 [44]. Diagnosis requires the demonstration of a gestational sac with a yolk sac or embryo in the endocervix, with an "empty" uterine cavity (Fig. 17.18a, b). If the pregnancy implants higher, near the uterine cavity, it is called a cervico-isthmic pregnancy [45]. Previously, diagnosis of a cervical pregnancy was confirmed histologically with Rubin's criteria applied to the surgical specimen. These criteria include the following [46]:

- Cervical glands are opposite to the trophoblastic tissue.
- The trophoblastic attachment is below the entrance of the uterine vessels to the uterus or the anterior peritoneal reflection.
- Fetal elements are absent from the uterine corpus.

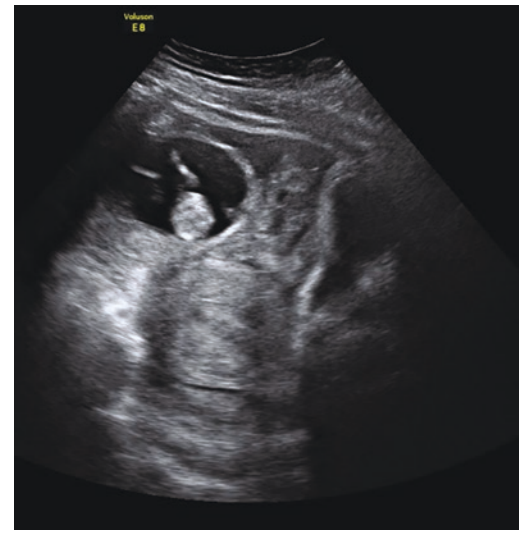

Fig. 17.17 Abdominal pregnancy on transabdominal ultrasound. Note the "empty" uterus

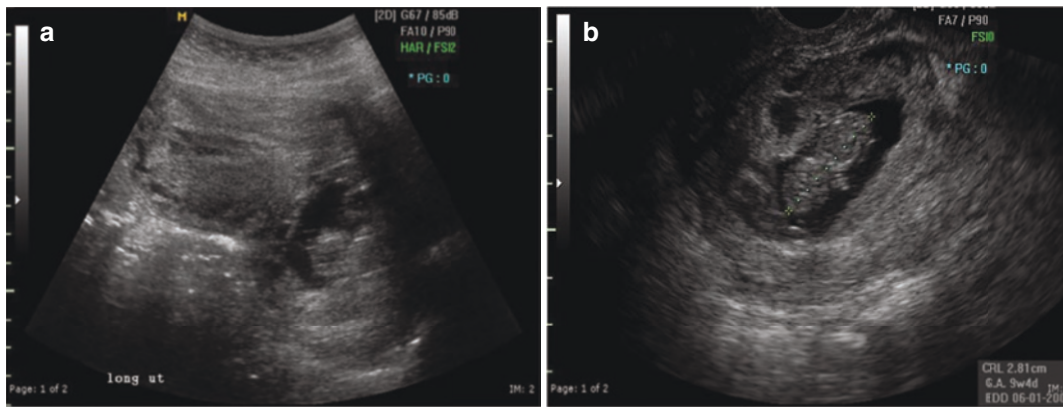

Fig. 17.18 (**a**) Cervical pregnancy with an embryo visualized in the endocervix-abdominal study. (**b**) Cervical pregnancy with an embryo visualized in the endocervix-vaginal study

Current treatment is more conservative often with direct injection of methotrexate or potassium chloride (KCl), uterine artery embolization, or more conservative surgical approaches [44]. Thus, Rubin's criteria cannot be applied to pregnancies treated without hysterectomy.

Cesarean Scar Pregnancies

These pregnancies are increasing in frequency. Timor-Tritsch, who has published extensively on the topic [47], will discuss cesarean scar pregnancies in a subsequent chapter (see Chap. 18).

Summary

Ectopic pregnancy continues to be a challenging and critical diagnosis, as conservative medical and surgical treatment options rely on early diagnosis. Ultrasound remains the mainstay in diagnosis in coordination with other laboratory tests, particularly quantitative hCG and, in select patients, serum progesterone. Clinical care algorithms are appropriate when ultrasound fails to determine the pregnancy location, the so-called pregnancy of unknown location. In hemodynamically stable patients, such algorithms allow appropriate follow-up until one determines the pregnancy location and its viability status. An established examination protocol is crucial in evaluating patients with suspected ectopic pregnancy, to assure proper diagnosis of pregnancies implanted in unusual locations. Strict adherence to such protocols and algorithms allows timely and accurate diagnosis, with appropriate and patient-specific treatment options.

Teaching Points

- Patients with pregnancies of unknown location who are hemodynamically stable can be managed expectantly as most are ultimately diagnosed as a viable or failed intrauterine pregnancy.
- In patients whose hCG is below the discriminatory level, a thin endometrium, ≤8 mm, is associated with an abnormal pregnancy in 97% of patients.
- In early pregnancy, a cystic structure within the endometrium, in the absence of an adnexal mass, is associated with an intrauterine pregnancy in >99% of patients.
- A yolk sac or embryo with or without a heartbeat in the adnexa is diagnostic of an ectopic pregnancy.
- Ultrasound is justified prior to obtaining a quantitative hCG, as almost 50% of ruptured ectopic pregnancies have hCG levels <1000 mIU/mL.
- Observation is appropriate in hemodynamically stable patients, as spontaneous resolution of ectopic pregnancy occurs in 25–88% of patients.
- There are specific criteria for the diagnosis of ectopic pregnancies in unusual locations.

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