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GYNAECOLOGY
Case Report

Ultrasound Imaging: Usual and Atypical Findings of the Extrauterine Pregnancy

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Abstract

The most important way to reduce maternal mortality and preserve fertility related to EP is the diagnosis and early treatment. Transvaginal pelvic US is the first diagnostic tool in hemodinamically stable patients with suspected EP. Recently studies have shown that in 73, 9% of the cases it is possible to make a diagnosis by transvaginal US and in 94% of the cases EP is diagnosed even before the surgery. The ß-hcg values are another important mark to help the ultrasonographic evaluation. In particular EP is characterized by lower levels of ß-hcg, that increase less than the IUP; in presence of a ß-hcg around 500-1000 mUI/ml, the gestational sac is visible in the uterus, in the 80% of cases. Every time there is a clinical suspicion of ectopic pregnancy or when the ß-hcg levels lay down for a pathological pregnancy, the ultrasound evaluation is recommended. In these cases ultrasounds may be essential to determine the location of intra- or extra-uterine gestation. A series of ultrasound criteria, those relate to endometrium, tubal pattern, ovaries, aspect of uterine cornua and cervix and the pouch of Douglas, are the most relevant factors to establish a diagnosis. Furthermore in case of PUL, a term used to classify a pregnancy before the final clinical outcome is known, the US exam is fundamental to an exclusion diagnosis.

Keywords: *Ultrasound imaging; Ectopic pregnancy; Fertility; Pelvic; Gynecologic surgery; Hemoperitoneum*

Abbreviations: EP: Ectopic pregnancy; PUL: Pregnancy of unknown location; IUP: intrauterine pregnancy

Introduction

Ectopic pregnancy (EP) occurs when the blastocyst implants outside the uterine cavity. In developed countries, the incidence of this disease ranges from 11 to 20% for every 1000 live births [1, 2,3] and it remains the leading cause of maternal death during the first trimester of pregnancy, with a mortality rate equal to 9-14% [4,5]. It is evident that the diagnosis and early treatment of ectopic pregnancy are essential to reduce maternal mortality and preserve fertility.

Most of the ectopic pregnancies is localized at the level of the Fallopian tubes. Almost all ectopic pregnancies are not progressive and often are absorbed before the manifestation of any kind of symptoms. The trophoblast is able to erode the tubal wall causing intra-tubal (hematosalpinx) and extra-tubal (hemoperitoneum) bleeding. Sometimes it's possible to see an embryo with cardiac activity in the ectopic gestational sac. EP is often suspected when vaginal bleeding occurs along with abdominal or pelvic pain associated with sore and tender adnexal mass in patients at 5-9 weeks' gestation [6,7]. The greatest risk for the patient is the rupture of the Fallopian tube. The risk is not always easily related to the severity of pain, in fact the pain may even decrease or disappear following tubal rupture [7]. Any clinical suspicion as hypovolemic shock and shoulder pain, as indirect sign of diaphragmatic injury, should raise the suspicion of an ectopic pregnancy complicated by rupture of the tube and the management must include surgery in emergency conditions. Fortunately, these situations are not very common and the trans-vaginal pelvic ultrasound looks to be the first diagnostic tool in hemodynamically stable patients with suspected ectopic pregnancy [8]. In recent years studies show that in about 73.9% of the cases it is possible to make a diagnosis by trans-vaginal ultrasound [9] and that 94% are diagnosed even before the surgery [10].

Risk Factors

The risk factors for ectopic pregnancy are all conditions with a tubal damage secondary to surgery or infections, particularly Chlamydia related infections [11,12,13,14] and cigarette smoke. However, there are still cases of ectopic pregnancy with no apparent risk factors [15].

The main risk factors for ectopic pregnancy are:

1. History of ectopic pregnancy
2. History of infertility
3. Intrauterine devices
4. *In vitro* fertilization
5. Congenital uterine anomalies
6. Endometriosis
7. Pelvic inflammatory disease
8. Gynecologic surgery
9. History of smoking
10. Exposure to diethylstilbestrol

Differential diagnosis

In case of clinical suspicion of ectopic pregnancy, the differential diagnosis has to be considered with other pathological conditions that can cause pelvic pain:

a. Normal early intrauterine pregnancy
b. Hemorrhagic corpus luteal cyst
c. Hemorrhagic ovarian cyst resulting in hemoperitoneum
d. Ovarian torsion
e. Tube-ovarian abscess.

In order to establish a diagnosis, the quantitative assay of plasmatic ß-hcg is essential. In the case with negative ß-hcg the diagnosis of ectopic pregnancy can be excluded. The ectopic pregnancy is characterized by lower levels of ß-hcg that increase less than the intrauterine pregnancy (IUP). In IUP the ß-hcg levels duplicate approximately every two days. The diagnosis of pregnancy by transvaginal ultrasonography is possible when the ß-hcg values reach of 500-1000 mIU/ml. With a ß-hcg value <500 mIU/ml, only in 20% of cases a gestational sac can be visible. With ß-hcg values ranging from 500-1000 mIU/ml, the 80% of the gestational sacs can be visible; the rate increases with ß-hcg >1000 mIU/ml. It is clear that in the presence of ß-hcg values higher than 1000-2000 mIU/ ml, without ultrasound image of gestational sac in the uterus, the ectopic pregnancy has to be suspected [16].

Ultrasound Evaluation

The ultrasound evaluation is indicated in all cases when there is a clinical suspicion of ectopic pregnancy or when the ß-hcg levels lay down for a pathological pregnancy. In these cases ultrasounds may be essential to determine the location of intra- or extra-uterine gestation. The use of ultrasounds for the diagnosis of EP was described for the first time about 40 years ago [17]. The trans-vaginal ultrasound, with high frequency probes is better than trans-abdominal ultrasound, because it is able to show a gestational sac when ß-hcg plasma levels are greater than 2000 mIU/mL, cut-off value to hypothesize a diagnosis of EP [18].

The trans-abdominal ultrasound can show an intrauterine pregnancy with ß-hcg values from 6500 mIU/mL [7]. In the first trimester, the purpose of the ultrasound is to show the presence of pregnancy in uterus, therefore the use of more accurate ultrasounds is essential to distinguish a normal pregnancy from an abnormal implant [19]. In normal pregnancy, trans-vaginal ultrasound can identify a *intradecidual sign* already after 4.5 weeks of gestation [18]. The intradecidual sign is a small collection of fluid that is eccentrically located within endometrium and is surrounded by hyperechoic ring. At 5 weeks the double decidual sac sign can be visualized. It consists

in two concentric hyperechonic rings that surround an anechoic gestational sac [19]. The *pseudo-sac* is an intrauterine fluid collection present in 20% of patients with EP and it is different from the gestational sac. The pseudo-sac is ovoid with a central localization and it has only a single decidual sign; instead early IUP has an eccentric position and double decidual sign [16]. The visualization of a yolk sac in gestational sac excludes the pseudo-sac. The yolk sac is always detectable before the embryo; it may be viewed from 4 weeks and 5 days and 5 weeks and 1 day, when the gestational sac has a mean diameter of 10 mm [20,21]. *Embryonic cardiac activity* is detected by trans-vaginal ultrasound about at 5-6 weeks, when the gestational sac measures more than 18 mm or when embryonic pole measures more than 5 mm [22]. When it is impossible to distinguish between intra- and extra-uterine pregnancy, it is necessary a close monitoring of the patient with serial ultrasound examinations and plasma assays of ß-hcg until a certain diagnosis [23]. In the absence of gestational sac, it is necessary to check for any ultrasound signs of ectopic pregnancy, but in 35% of cases there is no detectable sign of tubal abnormalities [18, 20].

Ultrasound criteria for the diagnosis of ectopic pregnancy

Endometrium

The diagnosis of ectopic pregnancy is possible only after detecting the blastocyst in ectopic location (24). The *absence of intrauterine gestational sac* at transvaginal ultrasound examination, with high plasma ß-hcg values, is the first sign of suspected. In particular if ß-hcg value is more than 1000 ectopic pregnancy is very likely. If the value is less than 1000, it would be appropriate to check the patient with ultrasound examination and ß-hcg dosage every 2-3 days. The endometrium undergoes the decidual reaction, it appears echogenic and hypertrophic (with a thickness > 15 mm).

However in case of EP, endometrium resembles a three-layer hyperechoic structure. This image is also observed in the early luteal phase and for this reason it is not diriment. Sometimes in EP, the endometrium increases in size; It begins to bleed, leading to the framework called "*pseudo-sac*". The pseudo-sac is an intrauterine hypoechoic fluid collection, it is present in 20% of patients with EP and it is different from the gestational sac [25, 26]. To distinguish an intrauterine gestational sac from a pseudo-sac, it is useful to consider the position in the endometrial cavity. In EP, the pseudo-sac is ovoid with a central localization in the endometrial cavity, and it has only a single decidual sign; whereas in early IUP the gestational sac has an eccentric position and double decidual sign [27]. However a hypoechoic area in the endometrial cavity is most likely to be an early intrauterine pregnancy (28), so the diagnosis of ectopic pregnancy cannot be made only by this isolated sonographic sign.

Free pelvic fluid

An echogenic free fluid collection in the pouches of Douglas (Figure 1) or Morrison may be suggestive of hemoperitoneum secondary to rupture of an ectopic pregnancy or tubal abortion, but can also be secondary to the rupture of an ovarian hemorrhagic cyst. Free endopelvic fluid may be detected in case of EP [30], in fact the sign was reported in 28-56% of women with ectopic pregnancy [30,31] and it is often related with the hemoperitoneum [32]. However this ultrasound sign can also be present in IUP [30]. The erosion of tubal vessels by trophoblast causes bleeding; the blood is thus evacuated through the tubal orifice or through tubal breaking point leading to free pelvic fluid.

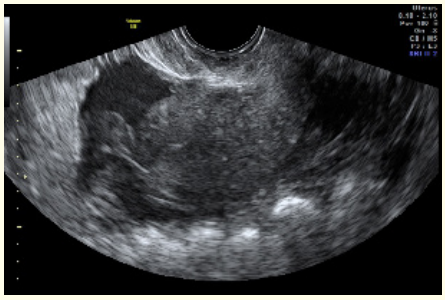

Figure 1: *Ultrasound scan of free pelvic fluid in tubal pregnacy at 7 weeks' gestation.*

The absence of free fluid collection in Douglas, however, cannot exclude the presence of ectopic pregnancy, and also a free pelvic fluid is not a specific sign for EP. In case of large amount of free fluid collection (massive hemoperitoneum) with echogenic appearance and in the presence of pain caused by pressure with the probe in the Douglas' pouch, the EP should be suspected.

Tubal pregnancy

The Fallopian tube is the most common location for an ectopic pregnancy. The 90% of EP are tubal; of these, 75% occurs in the ampulla, 13% is located in the isthmus, and 12% in the fimbria [33,34,35]. The etiology is still not completely understood, but the cause seems to be the impaired embryo-tubal carriage and the alterations of tubal homeostasis [14,36].

The main ultrasound sign of tubal pregnancy is an *adnexal mass* (Figure 2) separated from ovary in absence of image of IUP with positive values of ß-hcg; this image can be found in 89-100% of cases [37, 38]. More specific ultrasound sign for EP is the presence of an adnexal mass, movable with respect to ovary, inside which there is a yolk sac or embryo pole. This mass usually has a spherical shape, but in case of hematosalpinx it can have a tubular form [39]. In 20% of cases it is possible to see an empty extrauterine gestational sac [9, 10]. However, in 15-13% of patients with EP, it is not possible to see through transvaginal ultrasound the adnexal mass [18].

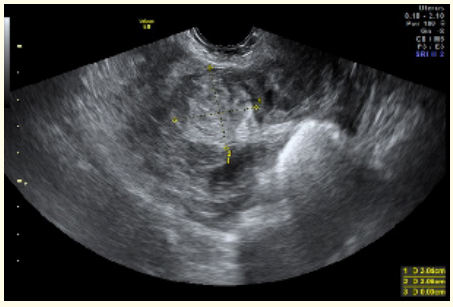

Figure 2: *Transvaginal ultrasound image of extraovarian adnexal mass in tubal pregnancy at 6 weeks' gestation.*

Another common sign of tubal pregnancy is the "*tubal ring*". This sign is a hyperechoic ring-like structure created by trophoblast surrounding an extrauterine gestational sac [40]. A related sign is the "ring of fire" (Figure 3; Clip1), it is recognized by peripheral hypervascularity of hyperechoic ring [40]. The term "ring of fire" describes an intense flow in tubal wall, with high speeds and very low resistances [41]. However the peripheral vascularization with high velocity and low impedance is not specific of ectopic pregnancy, but it may occur also in the presence of an ovarian follicle or corpus luteum [42]. In order to make a diagnosis and to distinguish an ectopic pregnancy from corpus luteum is important to assess whether the ring is visible inside or outside the ovary. It is extremely difficult and rare to see an embryonated extrauterine pregnancy within the Falloppian tubes (Clip 2).

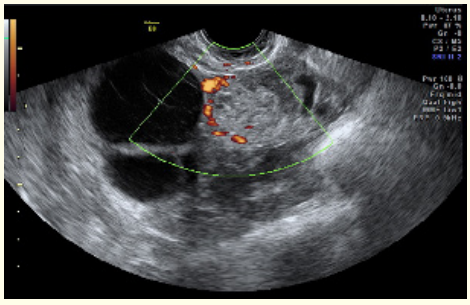

Figure 3: *Ring of fire sign. Transvaginal Color-Doppler ultrasound image of tubal pregnancy with peripheral hypervascularity.*

Clip 1: *Transvaginal ultrasound of extraovarian adnexal mass and ring of fire sign in tubal pregnancy at 6 weeks gestation*
http://youtu.be/NKhPlaz_HWo

Clip 2: *Embryonated extrauterine pregnancy*
http://youtu.be/JDTJZXTfQg8

Interstitial pregnancy

Interstitial pregnancy occurs when the gestational sac implants in the intramyometrial segment of the tube and represents the 2-5% of all ectopic pregnancies. It is associated with higher morbidity and mortality due to later presentation, usually in late first trimester or in the early second one [16]; moreover the rupture of this pregnancy can lead to an important hemorrhage due to its proximity to the uterine artery [43]. In the interstitial pregnancy the gestational sac is located in the fundus in an eccentrical position (Figure 4; Figure 5; Figure 6, Clip 3) separated from the most lateral edge of the uterine cavity (Clip 4); it is surrounded by a thin layer of myometrium that measures less than 5 mm [40]. Typical ultrasound sign of this ectopic pregnancy is the *Interstitial line sign* that is defined as a thin echogenic line extending into the upper region of the uterine horn and bordering the ectopic gestational sac [44]. The interstitial ectopic pregnancy has to be differentiated from septate or bicornuate uterus and from fibroids or myometrial contractions [16].

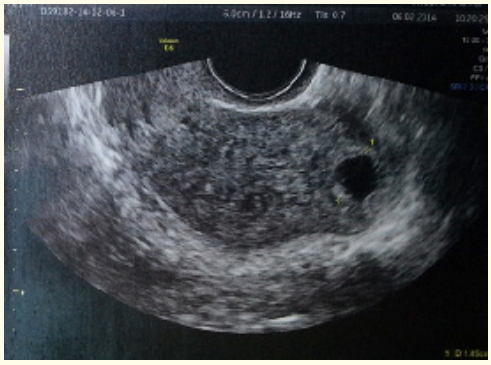

Figure 4: *Transvaginal ultrasound scan of interstitial pregnancy at 5 weeks' gestation.*

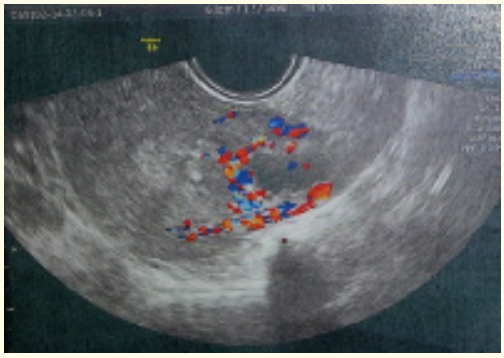

Figure 5: *Transvaginal Color Doppler ultrasound image of interstitial pregnancy at 5 weeks' gestation.*

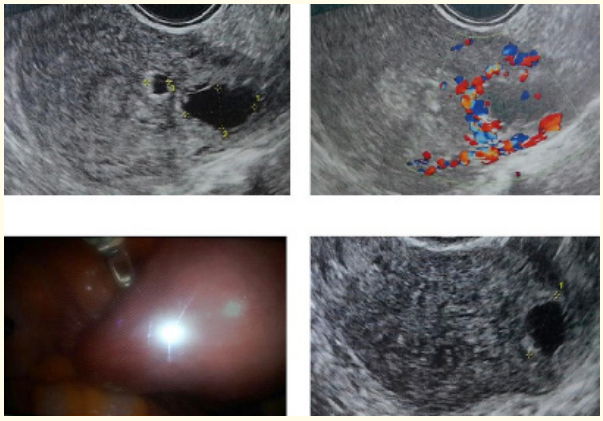

Figure 6: *Interstitial pregnancy. Bidimensional, Color Doppler and Laparoscopic view.*

Clip 3: *Ultrasound scan of interstitial pregnancy at 7 weeks' gestation.*
http://youtu.be/31klPSPcstQ

Clip 4: *US scan of an angular pregnancy at 6-7 weeks gestation.*
http://youtu.be/553CJJF4tg8

Cornual pregnancy

The cornual pregnancy is rare and represents less than 1% of all ectopic pregnancy. It occurs when the blastocyst implants in the cornua of a congenital bicornuate or septate uterus [37] (Figure 7). The ultrasound examination shows the bicornuate or septate uterus and the gestational sac in eccentric position surrounded by a thin layer of myometrium that measures less than 5 mm [45]. This thin layer of myometrium can lead to uterine rupture when the ectopic pregnancy expands.

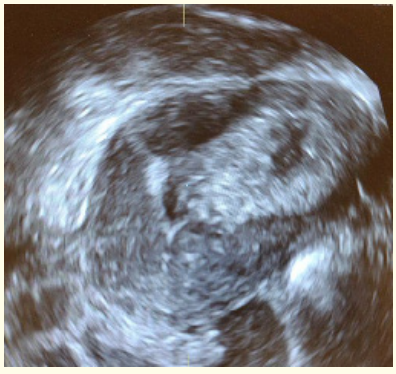

Figure 7: *US imaging of a corneal pregnancy at 6 weeks' gestation, with a small serous layer surrounding the placenta (Thanks to Prof. Palumbo).*

Cervical pregnancy

Cervical pregnancy occurs when the blastocyst implants in the endocervical canal. It is rare and accounts for less than 1% of all ectopic pregnancies [40]. Its specific risk factors are in vitro fertilization and history of curettage [46]. The ultrasound examination shows the gestational sac under the level of internal cervical orifice; the presence of embryo cardiac activity in the endocervical canal is highly suggestive for cervical pregnancy [47]. In cervical pregnancy, the uterus can show a barrel shape when the fetus grows [48]. Typical sign of cervical pregnancy is the absence of the sliding sign. It is used to differentiate the impending or incomplete abortion from cervical pregnancy. The sliding sign consists to apply a pressure with the probe in the cervix: in a miscarriage, the gestational sac slides against the cervix, whereas in the cervical pregnancy it remains adherent to the cervix [48]. Also in cervical pregnancy it is possible to identify with the Color Doppler a trophoblastic flow around the gestational sac in the endocervical canal (Figure 8, 9) [16].

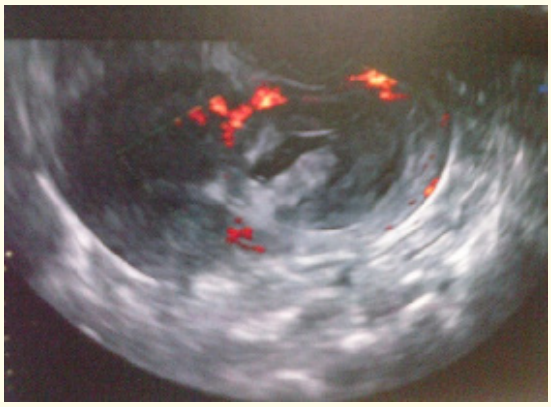

Figure 8: *Transvaginal Color Doppler ultrasound image of cervical pregnancy at 8 weeks' gestation.*

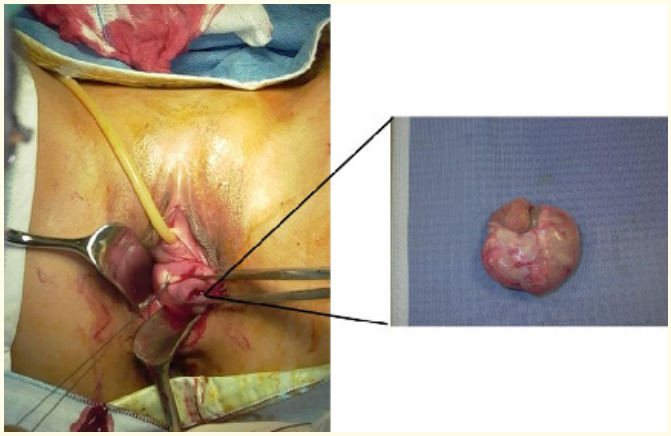

Figure 9: *Cervical pregnancy and surgical treatment.*

Ovarian pregnancy

Ovarian pregnancy occurs when a fertilized ovum implants in the ovary. It is responsible for 3% of all ectopic pregnancies [40] and its main risk factor is the use of intrauterine devices [49]. The ultrasound diagnosis is difficult because no specific ultrasound criteria are present and the visualization of yolk sac or fetal pole in the ovary is not usual [48]; sometimes the ovarian pregnancy is identified as a cyst with an echogenic outside ring that moves with the ovary, but the differentiated diagnosis with another ovarian pathology remains difficult [48]. However gestational sac, yolk sac, fetal pole and cyst with echogenic ring inside the ovary with a normal fallopian tube, suggests an ovarian ectopic pregnancy [50, 51].

Cesarean scar pregnancy

Cesarean scar pregnancy is rare and is responsible for less than 1% of all ectopic pregnancies [52]. It occurs when the implantation is within the scar of previous cesarean section; the blastocyst results surrounded by myometrium and fibrous tissue [53]. The ultrasound shows a mixed mass or an evident gestational sac with the anterior wall of the lower uterine segment at the site of the scar [54], with a thin myometrium layer that separates the gestational sac from maternal bladder wall [55]. This ectopic pregnancy is also characterized by the absence of sliding sign. The trophoblastic invasion into cesarean scar may lead to uterine rupture with severe hemorrhage [40].

Abdominal pregnancy

Abdominal pregnancy occurs when the implantation takes place in the intraperitoneal cavity. This localization can be primary or secondary to ectopic tubal pregnancy and subsequent tubal rupture with re-implantation of ectopic pregnancy in the abdominal cavity [16]. This finding is more frequent after *in vitro* fertilization procedure, and it is associated with a maternal mortality rate higher than the other ectopic pregnancy, because it can result in a serious hemorrhage related to a trophoblast invasion of abdominal structures. The ultrasound examination can show the absence of a normal intrauterine pregnancy, an implantation in intraperitoneal cavity and an eventually echogenic free fluid collection in case of hemorrhage [40].

Heterotopic pregnancy

Heterotopic pregnancy occurs when intrauterine and extrauterine pregnancies are present simultaneously [40]. This particular form occurs more frequently in patients who undergo reproductive techniques and its prevalence in this category of women is 1-3% [56]. Heterotopic pregnancy should be suspected in patients who undergo assisted reproduction with presence of pelvic pain [40]. Ultrasound examination can show the presence of intrauterine and extrauterine pregnancies with the identification of two gestational sacs localized in two different sites [40]. Please refer to the specific paper related to the heterotopic pregnancy.

PUL

Pregnancy of unknown location (PUL) is a descriptive pattern used whenever there is no sign of either intra- or extrauterine pregnancy or retained products of conception on transvaginal ultrasounds, despite a positive pregnancy test [57]. PUL is not a diagnosis but only a term used to classify a pregnancy until the final clinical outcome is known. Women classified as having a PUL, should be followed up until the final outcome will be determined. There are four final outcomes of PUL: failed PUL; intrauterine pregnancy; ectopic pregnancy; persisting PUL [58]. Most women with PUL are subsequently diagnosed with intrauterine pregnancies that were too early to be seen on the initial transvaginal ultrasounds, or with spontaneously resolving pregnancies. Only the 7-20% of PUL pregnancies have an ectopic pregnancy [59]. A small group of PUL have a "persisting PUL" that is defined when the ß-hcg levels do not decline and no intra- or extrauterine pregnancy is identified with subsequent ultrasound evaluations [60].

Expectant management is the best treatment for asymptomatic hemodynamically stable women with PUL. Single and serial measurements of ß-hcg are most commonly used in the management of PUL. The ß-hcg discriminatory zone (1000-2000 IU/L) is utilized for the prediction of ectopic pregnancy in women with PUL, but the importance of a single value of ß-hcg is limited (61). Serial serum ß-hcg levels can be used to predict failing PUL, IUP and ectopic pregnancy within the PUL population. Recently, a minimal rise in serum ß-hcg of 35% over 48 hours has been suggested as the minimal rise consistent in a viable IUP [62].

The serum progesterone level is a good indicator of early pregnancy viability and it is often used in association within ß-hcg to predict the outcome of PUL, but it is a poor indicator of pregnancy location. In particular levels of less than <20 nmol/L have been shown to have a high positive predictive value for failing pregnancies [63]. Levels above 25 nmol/L are likely to predict viable pregnancies and levels above 60 nmol/L are strongly associated with viable pregnancies [57]. The diagnostic laparoscopy and uterine curettage are recognized forms of surgical intervention in the diagnosis of PUL outcome [58].

The combination of the absence of an IUP using transvaginal ultrasound and a serum ß-hcg level above a discriminatory zone historically was considered an indication for diagnostic laparoscopy, but many failing PUL and some IUP may have initial ß-hcg levels above, and some clinically significant EP will have ß-hcg levels below, given any discriminatory zone. Actually, laparoscopy is rarely indicated and it is suitable for symptomatic or haemodynamically unstable women [58]. Uterine curettage is used to diagnose pregnancy location to discriminate between an EP and a non-viable IUP. The indications for curettage, that exclude a potentially viable IUP, include non visible IUP on transvaginal ultrasound with a serum ß-hcg > 2000 IU/ml; an abnormal rise in ß-hcg level, defined as <50% increase in 2 days and an abnormal fall in ß-hcg level, defined as <20% decline in 2 days [64]. Uterine curettage should therefore not have a routine role in women with PUL. It can have an important role to diagnose the location of failing PULs, once the potentially viable IUP has been excluded [58]. Mostly women with a PUL will be subsequently diagnosed with a failed pregnancy, resolving spontaneously without intervention [23]. Women with PUL should be divided into low-risk (IUP, failed PUL) and high-risk (EP, persistent PUL) groups that require different levels of intensity for follow-up [58]. The management of PUL should concentrate on women with the highest risk of significant pathology, whilst minimizing intervention and follow-up in women at low risk of complications [58].

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