Pregnancy of unknown location

Yeri bilinmeyen gebelik

Gökhan Boyraz, Gürkan Bozdağ

Department of Obstetrics and Gynecology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Abstract

Pregnancy of unknown location (PUL) is defined as the situation when the pregnancy test is positive but there are no signs of intrauterine pregnancy or an extrauterine pregnancy via transvaginal ultrasonography. It is not always possible to determine the location of the pregnancy in cases of PUL. The reported rate of PUL among women attending early pregnancy units varies between 5 and 42% in the literature and the frequency of PUL incidents has increased with the increase in the number of early pregnancy units. The management of PUL seems to be highly crucial in obstetrics clinics. Therefore, in the current review, issues identified from the literature related to pregnancy of unknown location, potential tools for prediction and algorithms will be discussed.

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Key words: Pregnancy of unknown location, ectopic pregnancy, spontaneous abortion

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Özet

Yeri bilinmeyen gebelik, gebelik testinin pozitif olduğu ancak transvajinal ultrasonografide intrauterin veya ekstrauterin gebelik bulgusunun olmadığı durumlar olarak tanımlanır. Yeri bilinmeyen gebelik vakalarında gebeliğin nihai yerini belirlemek her zaman mümkün olmamaktadır. Literatürde, erken gebelik ünitelerine başvuran kadınlarda yeri bilinmeyen gebelik hızı %5-42 arasında değişmektedir ve erken gebelik ünitelerinin sayısının artması ile yeri bilinmeyen gebelik vakalarının sıklığı da artmaktadır. Obstetri pratiğinde yeri bilinmeyen gebeliklerin yönetimi oldukça önemli görünmektedir. Bu nedenle bu derlemede, yeri bilinmeyen gebelik ile ilişkili literatür, sonuçların öngürülmesinde kullanılabilecek araçlar, ve yönetim algoritması tartışılmıştır.

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Anahtar kelimeler: Yeri bilinmeyen gebelik, ektopik gebelik, spontan abortus

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Introduction

Pregnancy of unknown location (PUL) is defined as the situation when the pregnancy test is positive but there are no signs of intrauterine pregnancy or an extrauterine pregnancy via transvaginal ultrasonography (TVUS). It should be noted that PUL does not mean an ectopic pregnancy (EP). It is not a final diagnosis and in a certain number of women the final diagnosis cannot be made. In general, sonographic evaluation in addition to interval serum human chorionic gonadotropin (hCG) measurements is essential for determination of the location of pregnancy. Surgical intervention such as uterine evacuation and laparoscopy are also used in daily practice to determine or confirm the location of pregnancy. However, it is not always possible to determine the location of the pregnancy in cases of PUL since both miscarriage and ectopic pregnancy may resolve spontaneously without any treatment (1-3).

The reported rate of PUL among women attending early pregnancy units varies between 5 and 42% in the literature depending on the presence of experienced physicians and/or equipment (4). The PUL rate will probably decrease and the location of pregnancies can be diagnosed more correctly with the availability of higher resolution ultrasonography equipment (5). In this context, it is suggested to keep the PUL rate under 15% by using high resolution ultrasonography equipment and employing experienced physicians in modern pregnancy units (6).

There are two main concerns related to the management of PUL. First of all, if the pregnancy is ectopic, being diagnosed late may cause serious effects. As might be accepted, ectopic pregnancy is the most feared outcome of the PUL among all possible outcomes. Late diagnosis might increase mortality and morbidity, the success of medical treatment will decrease and more frequently a surgical intervention will be required, which may further negatively affect fertility in the following years (7). On the other side, the second concern is the overtreatment of a PUL which might potentially turn into a viable intrauterine pregnancy in the following days. Therefore, management of PUL seems to be highly crucial in obstetrics clinics.

In the current review, issues identified from the literature related to PUL, potential tools for prediction and algorithms will be discussed.

Signs of Intrauterine and Extrauterine Pregnancy in Ultrasonography

The clinicians must be aware of the indicators of not only an intrauterine pregnancy but also extrauterine pregnancy, to accurately diagnose PUL. For a normal viable intrauterine

Address for Correspondence: *Gökhan Boyraz, Department of Obstetrics and Gynecology, Faculty of Medicine, Hacettepe University, Ankara, Turkey*
Phone: +90 312 305 18 01 e.mail: gokhan.boyraz@gmail.com

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pregnancy, a gestational sac should be visualised under ultrasonography after a hCG level of 1500 mIU/L is noted. When the transabdominal approach is preferred, the threshold for hCG is up to 6500 mIU/L. The remarks related to intrauterine and EP should be seen in Table 1. Regarding the diagnostic importance of an EP, a non-homogeneous adnexal mass should be evaluated carefully.

The accuracy of EP might be as high as 90% (2). In some cases, there may be a collection of fluid within the endometrial cavity, which is often called a pseudosac; this has been reported in up to 20% of cases. It is not difficult to separate the pseudosac from early intrauterine gestational sac by using TVUS. A differentiating feature is the location of the fluid. An early intrauterine sac is intradecidual and is therefore seen as an eccentrically placed hyperechoic ring within the endometrial cavity, whereas a pseudosac develops within the uterine cavity and lacks a well-defined rim of surrounding echoes (8).

Conflicting results in the Literature

Although a huge number of studies have focused on the management of PUL, there is no clear algorithm for the management and predictor covering all kinds of potential results that will arise. The main reasons for inconclusive results can be summarised with the following factors: 1) The definitions of intrauterine pregnancy, miscarriage and ectopic pregnancy show wide variation among the studies. The final outcomes of women with a PUL in the literature originating from the United States have been categorised into three groups: Intrauterine pregnancy, ectopic pregnancy, and miscarriage/spontaneous abortion. The literature from the United Kingdom and European countries have been categorised by final outcomes into four groups: Intrauterine pregnancy, ectopic pregnancy, failed PUL and persisting PUL. 2) Different types of protocols are investigated for the management of PUL, and there is no comparative study. 3) The primary objective of the studies is different. Whereas ectopic pregnancy is considered the primary objective for prediction in some studies, the remaining considered abortion or intrauterine viable pregnancy as the outcome. In order to ensure homogeneity of studies, Banhart et al. (1) suggested categorising the patients into 5 groups based on their ultrasonographic findings:

- **Definite ectopic pregnancy:** extrauterine gestational sac with yolk sac and/or embryo with or without cardiac activity.
- **Probable ectopic pregnancy:** non-homogeneous adnexal mass.
- **PUL:** no finding for intrauterine pregnancy or ectopic pregnancy.
- **Probable intrauterine pregnancy:** intrauterine echogenic sac-like structure.
- **Definite intrauterine pregnancy:** intrauterine gestational sac with yolk sac and/or embryo with or without cardiac activity.

Initially, the patients might be stratified into one of those five groups based on their ultrasonography findings; however, they may be assigned to a different group during their follow-ups. The patient's symptoms and risk factors may also change the initial group of diagnosis (1-2).

Table 1. The remarks related with intrauterine and ectopic pregnancy

Ultrasound findings in intrauterine pregnancy	
Gestational sac	4.5-5 weeks
Yolk sac	5 weeks
Cardiac activity	5.5 to 6 weeks
Ultrasound findings in ectopic pregnancy	
Pseudosac	20%
Free pelvic fluid	56%
Non-homogeneous adnexal mass	60%
Gestational sac, embryo, foetal heart rate	20%

The most common final outcome among women diagnosed with PUL is the spontaneous resolution of pregnancy without the need for treatment (50-70%) (9). Those patients are considered to have either suffered a spontaneous abortion or a resorbed ectopic pregnancy. It is not always possible to determine the actual location of the pregnancy in patients with spontaneously failing PUL. Ectopic pregnancy, apparent either clinically or with TVUS, occurs only in 7-20% of the patients (5). In the remainder, clinical pregnancy becomes apparent, either viable or not (10). Only a minority of women (0.1%) will have a persisting PUL, defined as an inconclusive TVUS in combination with a slight rise or plateau in serial serum hCG levels (3).

Approaches to Predict the Outcome of PUL

There are a variety of ways to predict the outcome of PUL. Those approaches might be classified as single hCG determination, hCG ratio at 0/48 hours, single progesterone level, mathematical models with regression and lastly a combination of biochemical markers with other interventions. It is shown that the worldwide use of transvaginal ultrasonography and monitoring of hCG levels enable the follow-up of pregnancies with unknown location to be successful. Various algorithms including the combination of clinical examination, hCG follow-ups and recurring ultrasonography examinations generally succeed in determining the final location of the pregnancy in patients diagnosed with PUL. Besides these methods, measuring endometrial thickness, endometrial biopsy and cytology, inhibin A and inhibin pro-α C-RI insulin-like growth factor-binding protein 1 (IGFBP-1) are other methods that can be used to determine the location of the pregnancy. In the current literature, there is no optimal strategy to predict the possible outcome in patients diagnosed with PUL and there has been no study comparing any two of those methods for the prediction of any outcome. However, monitoring hCG levels and ultrasonographic examinations seem to be the most practical and valuable clinical tools (3).

1. Single determination of serum hCG measurement

HCG is the most commonly used hormone for the management of pregnancies with unknown location. Both single serum hCG measurements and series of serum hCG measurements can be used for predicting PUL outcomes. Single values of serum hCG to predict outcome in a PUL population is of limited value. The

reason for this is that many ectopic pregnancies in a PUL population have relatively low serum hCG levels (5). As a result of the performed meta-analysis, the sensitivity of a single hCG level for EP is found to be 11-90% and the specificity is 16-98% (3).

2. hCG ratio

The changes in serum hCG levels over 48 hour have been defined as the hCG ratio. A serum hCG increase over 48 hours of more than 66% (the hCG ratio >1.66) is a good predictor of an intrauterine pregnancy. A decrease in hCG of >13% or a hCG ratio of <0.87 has been found to have a sensitivity of 92.7% and a specificity of 96.7% for the prediction of a failing PUL; these patients have only a minimal need of subsequent follow-up (5). The sensitivity of hCG level for EP is found to be 85-100% and specificity is 28-97%. Since the study performed by Bignardi et al. (10) is the largest study of hCG levels to date, we would like to provide more detailed information from this study. Bignardi et al. (10) looked at hCG ratios with respect to the distribution of PUL results in their study. In total, 89.3% of the patients were diagnosed with ectopic pregnancy when the hCG ratio was ≤0.87, and 69.9% of the patients were diagnosed with ectopic pregnancy when the hCG ratio was between 0.87 and 1.66. When the hCG ratio was in the range of 1.66-2, the majority of patients were diagnosed with intrauterine pregnancy (56%); 39.7% of those women were diagnosed with non-viable intrauterine pregnancy and 16.3% were diagnosed with viable intrauterine pregnancy. Most of the patients (77.2%) were diagnosed with viable intrauterine pregnancy when the hCG ratio was ≥2. However, the risk of ectopic pregnancy still remains, even when the hCG ratio is ≥2, as shown by 8.2% of those patients being diagnosed with ectopic pregnancy. The hCG ratio was greater in viable intrauterine pregnancy compared with non-viable intrauterine pregnancy (3-10). According to this study, there may not be a need for further investigation and follow-up if the hCG ratio is ≥2 and if the patient does not have clinical symptoms like vaginal bleeding and groin pain. This potentially reduces the need for repeat ultrasound scans to determine viability. In women with PUL, diagnostic strategies using serum hCG ratios have the best diagnostic performance in the case of ectopic pregnancy (3).

Serum hCG levels in early viable intrauterine pregnancy

Barhart et al. (11) studied the hCG serum levels in patients diagnosed with PUL and the final outcome of viable intrauterine pregnancy. In their study, the median hCG level at the time of application was reported as 388 and the average increase in the hCG levels was reported as 50% for the first day and 124% for the second day.

Serum hCG levels in ectopic pregnancy

The rate of change in serial hCG values can be used to distinguish ectopic pregnancy from an intrauterine pregnancy or spontaneous abortion in only 73% of cases. There is no single pattern of hCG that is able to characterise ectopic pregnancy. In women with an ectopic pregnancy, 60% initially exhibited an increase in hCG values; however, this increase is lower when compared with the viable intrauterine pregnancy. In 39% of patients, the hCG values initially drop with a median slope of 15%, which is less than the mean 70%-75% decrease for complete spontaneous abortion. In 29% of patients, the hCG levels are inconsistent with increasing and decreasing hCG levels; the risk of late diagnosis and rupture is higher in these patients (12). Therefore, the increasing or decreasing hCG levels should not bias the physicians towards spontaneous abortion or intrauterine pregnancy. In women whose hCG levels are decreasing, serial hCG measurements should be performed until hCG is no longer detectable in the serum; sometimes this may take up to 6 weeks. In women whose hCG levels are increasing, ultrasonographic examination should be performed when the levels rise above the discriminatory value (2). The normal increase in serum hCG values does not exclude the possibility of a miscarriage or ectopic pregnancy (13). In fact, in 21% of women with ectopic pregnancy, the hCG levels imitate intrauterine pregnancy levels and in 8% can imitate the spontaneous abortion hCG levels. Similarly, in 1% of women with intrauterine pregnancy and in 10% of women with spontaneous abortion, the hCG levels are similar to ectopic pregnancy hCG levels (2).

Serum hCG levels in spontaneous abortion

Spontaneous abortion is the most common complication of early pregnancy and occurs in 15 to 20% of all pregnancies (2). Miscarriage defines women with spontaneously regressed serum hCG levels or women who underwent dilation and curettage with either histological features of chorionic villi, or no chorionic villi, on the condition that the postoperative serum hCG might be regressed (1). The rate of hCG clearance is dependent on the initial concentration of hCG. If the level of the first serum hCG level is high, it would decline more rapidly. The time required for hCG levels to clear following dilation and curettage is generally between 12 and 16 days (11). When a spontaneously resolving pregnancy has serum hCG levels declining to undetectable levels without surgical or medical intervention, this is defined as a failed PUL. Such a pregnancy can either be a failed intrauterine pregnancy or a resolved ectopic pregnancy; the location of the pregnancy remains undetermined (3).

3. Serum progesterone

In patients diagnosed with PUL, the serum progesterone measurement during the initial visit helps to evaluate the risk of early pregnancy complications. In this way, the number of follow-up visits can be reduced for patients diagnosed with PUL. It is not recommended to routinely follow-up patients if the serum progesterone level is ≤10 nmol/L (4). If the progesterone level is less than 20mmol/L, this is highly predictive of a failing pregnancy, whereas a progesterone level above 60 nmol/L is strongly associated with a viable pregnancy. Progesterone levels are good predictors for viability of pregnancies; however, they are not very reliable for determining the location of the pregnancy (5). High progesterone levels can be observed in both intrauterine and extrauterine pregnancies; it reflects the functionally normal corpus luteum and trophoblast. Serum progesterone is the best single marker and progesterone and hCG levels are the best way of predicting a spontaneously resolving PUL (14).

4. Mathematical models

Different mathematical models are proposed for predicting PUL outcomes. However, the accuracy of those models is not proven in different populations (3). Applying mathematical models may require complicated computations and should be verified by multiple centres.

5. Other Biochemical Markers

Inhibin A is the second most useful marker for identifying spontaneously resolving PUL after progesterone. Inhibin A levels for spontaneously resolving PUL are significantly lower when compared to the levels seen in intrauterine pregnancy or ectopic pregnancies. All pregnancies for which the inhibin A level is less than 11 pmol/L are considered spontaneously resolving PULs (14).

IGFBP-1 levels for spontaneously resolving PUL have a tendency to be higher when compared to other outcomes. The high level of IGFBP-1 reflects the defective implantation and is correlated with the increased risk of spontaneous expulsion of conception.

Inhibin pro-aC-RI levels have not found to be helpful in differentiating spontaneously resolving PULs (14).

Creatine kinase (CK) is a non-specific marker used for identifying smooth muscle injuries. CK and CK-MB levels do not contribute to distinguishing the early intra- or extra-uterine pregnancies (15).

Increase in the endometrial thickness is used to predict the normal intrauterine pregnancy in patients who are diagnosed with PUL and have vaginal bleeding. The chances for normal intrauterine pregnancy are low when the endometrial thickness is below 8mm (16).

Cancer antigen 125 (CA 125) is released from decidual cells as a result of the chorionic invasion (5). Serum CA 125 levels cannot be used to predict the outcome of PUL (17).

These novel biochemical markers are not clinically useful in predicting PUL outcomes.

6. Histological and cytological techniques in PUL

When the pregnancy location cannot be determined, the diagnostic uterine curettage and pathological examination of specimens can be used. In PUL cases, the cytology can also be used for differentiating ectopic pregnancy and spontaneous abortion (18). Uterine curettage is not recommended as routine in PUL management; however, it can be used if the potential viable intrauterine pregnancy diagnosis is excluded (5).

Management of PUL

There is no definitive management algorithm for patients diagnosed with PUL. The objective is not to diagnose ectopic pregnancy late and not to end an early viable pregnancy mistakenly. The expectant approach based on hCG and progesterone levels is a reliable method and has high success rates:

1. If the serum progesterone is <20ng/mL and Serum β-hCG is >25 IU/L, then the possible diagnosis is resolving pregnancy and a urine pregnancy test should be performed in 7 days.
2. If the serum progesterone is between 20-60 ng/mL and Serum β-hCG is >25 IU/L (<1000 IU/L), then there is a high risk of ectopic pregnancy and serum hCG should be checked within 2 days.
3. If the serum progesterone is >60 ng/mL and Serum β-hCG is <1000 IU/L, then the possible diagnosis is normal pregnancy and the scan should be repeated when hCG levels go above 1000 IU/L.
4. If the serum progesterone is >20ng/mL and Serum β-hCG is >1000 IU/L, then the possible diagnosis is ectopic pregnancy and the scan should be repeated as soon as possible or laparoscopy should be performed (14).

The majority of PULs will resolve spontaneously regardless of their location. Therefore, it is important in PUL management to focus on identifying the high risk patients by reducing the number of follow-ups and interventions (4). There are two main strategies suggested for the management of PULs:

1. Serial hCG measurements within 48 hour intervals and triaging patients due to alterations in hCG levels.
2. Measurement of the serum progesterone level during the first visit. The advantage of the clinic management protocol based on the serum progesterone level measurement is that 40% of patients can be discharged from the routine follow-up after the initial visit. This protocol reduces follow-up visits and the number of required blood tests significantly (4).

The surgical interventions performed for the diagnosis of PUL outcomes are uterine curettage and diagnostic laparoscopy. However, these surgical methods should not be routine for the management of PUL (5).

Conclusion

In summary, the frequency of PUL incidents has increased with the increase in the number of early pregnancy units. However, the PUL frequency should be kept under 15% by employing experienced doctors on this topic and using high quality ultrasonography in early pregnancy units. Several hormones have been evaluated in the prediction of PUL outcome. Among those, serum hCG level is the most useful hormone; however, evaluating the changes in hCG serum levels within 48 hours is a more reliable method than a single measurement of the serum level. However, hormone levels are very similar in the case of intrauterine pregnancy, ectopic pregnancy and spontaneous abortion. Therefore, it is important to follow-up the patients diagnosed with PUL until the final diagnosis is concluded. Even though the hCG ratio is the best method for predicting ectopic pregnancy in patients with PUL, progesterone is the best indicator for viability. Mathematical models should be verified by multiple research centres before being used routinely in clinics. There are no published randomised controlled trials that compare different diagnostic strategies for ectopic pregnancies among women who were diagnosed with PUL. There is a clinical heterogeneity between the studied populations. Therefore, there is an increasing need for studies which use a common definition for intrauterine pregnancy. There are no conclusive management algorithms for women diagnosed with PUL. However, an expectant management is appropriate for patients who are haemodynamically stable.

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