

PREGNANCY OF UNKNOWN LOCATION - PUL

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1. INTRODUCTION

The term pregnancy of unknown location (PUL) is used to define a patient with a positive pregnancy test but no intrauterine or extrauterine signs of pregnancy. This diagnosis has increased as a consequence of the development of highly sensitive techniques to detect the beta subunit of chorionic gonadotropin hormone (β hCG), as well as the improvement in transvaginal ultrasound.

This situation may include early intrauterine pregnancies, intrauterine or extrauterine non-progressive pregnancies, as well as ectopic pregnancies. In most cases, there is a low risk of maternal complications. However, follow-up should be ensured until a final diagnosis is reached because of the risk of ectopic pregnancy (6-20% of PULs).

The rate of PUL in women who undergo early assessment of pregnancy varies between 7-30%, the incidence being higher in cases of poor ultrasound quality, the examiner's lack of experience, any ovarian or uterine pathology that complicates the visualization of the uterine cavity, and/or adnexa. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) suggests that the incidence of PUL should be less than 15%.

Pregnancies of unknown location represent a substantial consumption of healthcare resources, as well as a source of stress for patients who sometimes receive discrepant information, so it is essential to rationalise their management. Given that patients are presenting earlier and earlier to health services, and often with poor clinical presentation**, and bearing in mind that neither medical nor surgical treatment are risk-free, the indication for intervention in these patients should be made with caution. The aim of this protocol is to optimise the management of PUL in our setting.

2. DEFINITIONS AND DIFFERENTIAL DIAGNOSIS

The term PUL is used as a transient clinical situation** until a final diagnosis is made, which may be a viable intrauterine pregnancy, a non-viable pregnancy (intrauterine or extrauterine), an ectopic pregnancy or, more rarely, a persistent PUL.

The main differential diagnoses of PUL are made with:

- **Incipient intrauterine pregnancy:** If an intrauterine sac without embryonic structures is visualised, there is a possibility of incipient pregnancy. The viable intrauterine pregnancy is the most common outcome of PUL.
- **Gestational loss:** Difficulty in differential diagnosis because endometrial thickness measured by transvaginal ultrasound does not reliably predict the existence of chorionic villi. Similarly to the previous case, it is advisable to act with caution to avoid performing aspiration curettage in the presence of a possible viable intrauterine pregnancy.
- **Ectopic pregnancy:** Although the vast majority of PUL (80-96%) do not turn out to be ectopic pregnancies, the potential risk of maternal morbidity and mortality resulting from misdiagnosis should be considered.

In order to make the differential diagnosis we will base the diagnosis on the following:

2.1 Anamnesis and physical examination:

Risk factors for ectopic pregnancy are conditions that imply damage to the fallopian tubes: history of ectopic pregnancy or previous tubal surgery, pelvic inflammatory disease, IUD, bilateral tubal occlusion, infertility, assisted reproduction techniques, smoking.

Physical examination: assessment of metrorrhagia and cervical dilatation.

2.2. Ultrasound

The justification for early ultrasound screening in asymptomatic patients is not proven, even in high-risk patients (history of ectopic pregnancy, tubal or pelvic surgery or pelvic inflammatory disease, as well as IUD wearers), although an assessment should be made according to the prevalence of ectopic pregnancy in the setting in which it is applied. In countries where the prevalence is around 6%, the screening of asymptomatic high-risk patients reduces the number of patients with ruptured tubal pregnancy, but with a high false positive rate for ectopic pregnancy (64%).

Since the prevalence of ectopic pregnancy in our setting is low (2.3%), our recommendation is not to perform systematic early transvaginal ultrasound. In case of mild symptoms (abdominal pain VAS < 4, metrorrhagia less than menstruation) it is not recommended to perform it before 5 weeks of gestation in the case of regular cycles, and only** in the absence of risk factors for ectopic pregnancy.

2.3. Blood test

βhCG

The discriminatory level of βhCG for visualising a gestational sac has been decreasing over the years due to the increased sensitivity of biochemical and imaging techniques, currently standing at 1000-2000 mIU/ml.

Single βhCG measurements are not useful for predicting the prognosis of PUL. Furthermore, levels are not predictive of intrauterine vs. extrauterine pregnancy. In contrast, serial measurements of βhCG are good predictors of pregnancy viability and are better than a serum progesterone measurement for predicting localisation.

To facilitate clinical management, the ratio of βhCG (βhCG at 48-72h/βhCG at baseline) is useful.

- a) Viable pregnancy: there is an increase in βhCG ranging from 35-66%.
- b) Non-viable pregnancy: there is a decrease in βhCG of 21-35% (the greater the decrease, the higher the initial βhCG concentration). A decline > 13% in 48 hours or βhCG ratio <0.87 has a sensitivity of 92.7% and a specificity of 96.7% to predict a non-viable pregnancy.

Typically, ectopic pregnancies will have suboptimal βhCG increases relative to intrauterine pregnancies or decreases below non-viable PUL. However, up to 15-20% of patients who have double βhCG levels similar to intrauterine pregnancies, and up to 10% of patients in whom βhCG levels decrease similar to non-viable PULs, will ultimately be ectopic pregnancies.

Progesterone

Serum progesterone levels are good indicators of pregnancy viability, but not of its location (therefore, a single determination of progesterone alone does not have sufficient discriminative ability for the diagnosis of ectopic pregnancy). This is why the usefulness of progesterone potentially lies in classifying patients as low risk in case of non-progressive PUL and not requiring such an exhaustive control: values ≤2 nmol/l have a high positive predictive value for non-viable pregnancies (both intrauterine and extrauterine), while values >60 nmol/l correlate with progressive pregnancies.

If used, there is no evidence that serum progesterone levels correlate with the effectiveness of a medical treatment with methotrexate in case of ectopic pregnancy or PUL.

2.4. Mathematical prediction models

Several mathematical models based on logistic regression models and Bayes' method that combine various biochemical markers have been developed to predict the viability of PUL, dividing patients into a high-risk group (risk of ectopic pregnancy $\geq 5\%$) and low-risk group (risk of ectopic pregnancy $< 5\%$). Among them, the most relevant is the one that uses BHCG at diagnosis and the BHCG ratio (Model M4, Condous et al UOG 2007) and the model that uses progesterone, BHCG at diagnosis and the B-HCG ratio (Model M6, Van Calster et al UOG 2016).

The M4 model has a negative predictive value (NPV) and a sensitivity for diagnosis of ectopic pregnancy of 97.2% and 81.4%, respectively. The M6 model including progesterone has an NPV of 99.1% and a sensitivity of 94.9% for the diagnosis of ectopic pregnancy. The M6 model NOT including progesterone has an NPV of 98.6% and a sensitivity of 93% for the diagnosis of ectopic pregnancy.

In our context, clinical management will be performed according to the algorithm described at the end of the protocol, which is an adaptation of the M6 model.

3. CLINICAL MANAGEMENT

The majority of PUL does NOT present a risk of complications:

- 80-96% will be intrauterine gestations: approximately 47-70% are non-progressive pregnancies where the location is not determined, and between 17-41% of late menstrual periods (LMPs) are ultimately diagnosed as progressive intrauterine gestation.
- 8-16% of PUL end up with a diagnosis of ectopic pregnancy.

In haemodynamically stable patients with mild symptoms (visual analogue scale**VAS < 4 , light metrorrhagia, etc.), complementary tests will be indicated depending on the following conditions:

- Irregular cycles
- Amenorrhoea > 5 weeks
- Risk factors for ectopic pregnancy: history of ectopic pregnancy or previous tubal surgery, pelvic inflammatory disease, IUD, bilateral tubal occlusion, infertility, assisted reproduction techniques, smoking.

In patients with NO pre-existing conditions, expectant management has been shown to be safe. Intervention should be rationalised in these patients as neither medical nor surgical treatment are risk-free and both have an influence on the patient's future reproductive life.

In patients with any of the previous conditions, a transvaginal ultrasound is indicated, according to which we will find three possible scenarios: intrauterine gestation, ectopic pregnancy or PUL.

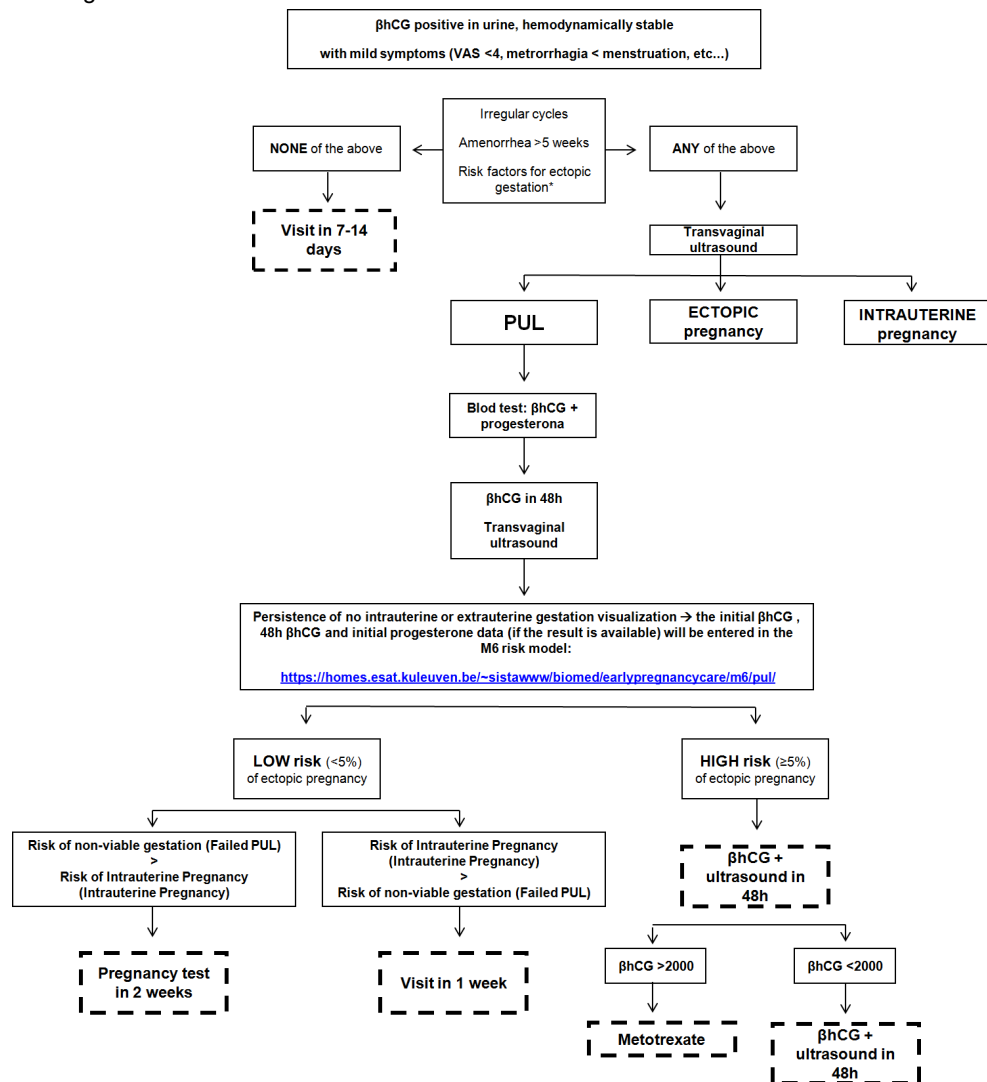
In the case of a patient with diagnosis of PUL, a blood test with β hCG and progesterone will be carried out and a new β hCG determination will be performed in 48h. At the second visit, another transvaginal ultrasound will be performed and, if the diagnosis of PUL persists, the risk of ectopic pregnancy will be calculated using the M6 model (<https://homes.esat.kuleuven.be/~sistawww/biomed/earlypregnancycare/m6/pul/>). In this model the progesterone result can be included or excluded depending on whether it is available.

In cases with a low risk of ectopic pregnancy according to the M6 model, the risks of non-progressive gestation vs. intrauterine gestation will be compared. If the risk of non-progressive gestation is higher,

a urine pregnancy test at home in two weeks will be indicated. If the risk of intrauterine gestation is higher, a new visit will be indicated in one week to confirm progression.

In cases with a high risk of ectopic pregnancy according to the M6 model, a new β hCG determination with ultrasound will be indicated after 48 hours. If β hCG >2000 and no visualization of an intrauterine gestational image, medical treatment with methotrexate will be proposed. If β hCG <2000 , a new control can be performed in 48h with β hCG.

The diagnostic algorithm is shown below:



* Risk factors for ectopic pregnancy: history of ectopic pregnancy or previous tubal surgery, pelvic inflammatory disease, IUD, bilateral tubal occlusion, infertility, assisted reproductive techniques, smoking.

4. PERSISTENT PUL

Persistent PUL for more than 10 days

When a diagnosis of PUL persisting for more than 10 days is made, the approach depends on the patient's symptoms, haemodynamic stability and β hCG levels. If progesterone levels are available, and they are <20 nmol/l, it would support expectant management as it is suggestive of non-progressive gestation (low risk of progressive gestation).

In general, if:

1. β hCG <2000 : expectant management has been shown to have the same efficacy as medical treatment (if the patient is haemodynamically stable). Weekly monitoring with β hCG and ultrasound will be offered until β hCG <20 .
2. β hCG >2000 : medical or surgical treatment can be chosen.

a) Medical treatment

In the absence of contraindications, the recommended medical treatment protocol is a single dose of methotrexate 1 mg/kg or 50 mg/m² (Grade of evidence A) for persistent PUL for more than 10 days in asymptomatic patients with β hCG >2000 IU/l.

In the case of an insufficient β hCG decrease (less than 15% in weekly control), a second dose can be administered (maximum 3 doses).

Prior to treatment, a blood test with a complete blood count, renal and hepatic function should be performed. Ovarian reserve and subsequent results in assisted reproduction cycles do not seem to be affected by methotrexate treatment.

b) Surgical treatment

Laparoscopy or laparotomy may be indicated if the medical treatment fails or as an alternative to medical treatment in cases of persistent PUL with β hCG > 3000 . Also, in cases of haemodynamic instability or ectopic pregnancy with contraindication for medical treatment.