ORIGINAL ARTICLE

# Pregnancy of unknown location: Outcome in a tertiary care hospital

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## Abstract

**Objective:** To find out the outcome of a cohort of women with pregnancy of unknown location presenting to a tertiary care hospital.

**Methods:** The prospective study was conducted from January to December, 2011, at Early Pregnancy Assessment Unit, King Faisal Military Hospital, Khamis Mushait, Saudi Arabia. Data was collected for women with early pregnancy or with history of amenorrhoea, bleeding or pain. These women were investigated with serum beta-human chorionic gonadotrophin levels twice weekly and transvaginal ultrasonography weekly. Expectant management was done for failing pregnancy of unknown location while medical or surgical management was considered for persistent pregnancy of unknown location and ectopic pregnancy.

**Results:** During study period, 7215 patients were admitted, and, of them, 2212(30.6%) were patients with early pregnancy. Meeting the inclusion criteria were 183(2.53%) patients who formed the study sample. There were 131(71.6%) patients presenting with amenorrhoea, 90(49.2%) had bleeding and 93(50.8%) presented with pain. Outcome of 100(54.6%) patients was failing pregnancy of unknown location, 58(31.7%) had intrauterine pregnancy, 14(7.7%) converted to ectopic pregnancy, while 11(6%) had persistent pregnancy of unknown location. All patients with persistent pregnancy of unknown location and 5(36%) patients with ectopic pregnancy were medically treated. Five (36%) patients having ectopic pregnancy were managed surgically.

**Conclusions:** Management of choice for asymptomatic patients having pregnancy of unknown location is expectant management. Most of the patients suspected to have Most of the patients with persistent pregnancy of unknown location and ectopic pregnancy can be managed medically.

**Keywords:** Pregnancy of unknown location, PUL, Ectopic pregnancy, Methotrexate, Saudi Arabia, Assir region. (JPMA 65: 1097; 2015)

## Introduction

Pregnancy of unknown location (PUL) is a descriptive term used for a woman who has positive pregnancy test, but no pregnancy can be visualised on transvaginal ultrasonography (TVS).[1] Incidence of PUL is 8-10% but some studies have reported incidence of 8-31%.[2] PUL has four possible outcomes; a) Intrauterine pregnancy (IUP), b) Failing PUL (F-PUL), c) Ectopic pregnancy (EP), and d) Persistent PUL (P-PUL).[3] Most common outcome is an F-PUL (44-69%) and 7-20% will subsequently be diagnosed with EP. A balance between late diagnosis of EP and over-treatment of possible IUP has to be made. Late diagnosis of EP can lead to increased morbidity, mortality and can have effect on future fertility of the woman.

PUL outcome can be predicted by measuring serum beta-human chorionic gonadotrophin (β-hCG) hormone and ultrasonography (USG).[4] Single value of serum hCG to predict outcome in a PUL is of limited value.[5] The concept of combined USG with serum β-hCG using discriminatory zone has been widely evaluated. It refers to defined levels of β-hCG above which gestational sac should be visible on USG with sensitivity approaching 100%.[3] With introduction of high resolution TVS, the discriminatory levels of serum β-hCG 1000-2400 iu/L has been used.[2] It is assumed that if serum β-hCG is above a certain discriminatory level and no IUP visualised on scan, the woman must have EP. TVS must be performed meticulously as pitfalls in image interpretation can lead to false results.[2] Serum progesterone along with serum β-hCG can be used to predict the outcome of PUL.[1] Meta-analysis showed that serum progesterone level <25 nmol/L is associated with non-viable pregnancy. However, viable pregnancy (0.3%) has been reported with initial level of <15.9 nmol/L. In the presence of PUL, serum progesterone level <20 nmol/L predicts spontaneous pregnancy resolution with sensitivity of 93% and specificity of 94%. Level >25 nmol/L are likely to indicate IUP and levels >60 nmol/L are strongly associated with IUP.[2] β-hCG level is also useful in following outcome of PUL. More

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than 66% have increased β-hCG level in 48 hours in normal viable pregnancy, but in about 15% normal pregnancies there is abnormal doubling time of β-hCG. Similarly, 13-21% of ectopic pregnancies behave like IUP.[3,6,7] Other hormones like Creatinine Kinase (CK) and Cancer Antigen-125 (CA125) are non-specific. Ratio of CA125 (at 48 and 0 hours) can distinguish a failing pregnancy from IUP.[8] Inhibin A or Activin A are non-specific to predict the outcome of PUL.[1] Protocols using various diagnosis algorithms have been used to predict the pregnancy outcome (Figure). PUL can be managed conservatively and may need medical treatment in persistent PUL. Surgical treatment is required if patient becomes symptomatic or changes to EP. Medical management with methotrexate has been used successfully in asymptomatic P-PUL.[9,10]

## Subjects and Methods

The prospective study was conducted from January to December, 2011, at the Department of Obstetrics and Gynaecology, King Faisal Military Hospital, Armed Forces Hospitals, Southern Region, Khamis Mushait, Saudi Arabia, after approval was obtained from the institutional review committee. All patients presented with early pregnancy or with history of amenorrhoea, pain or bleeding were considered for inclusion. These patients were investigated by serum β-hCG and TVS. The discriminatory zone for the β-hCG was taken at 1500 iu/L. TVS helped to rule out IUP, free fluid in cul-de-sac and adnexal mass, including EP. Patients who were haemodynamically unstable were excluded. A proforma was filled in which relevant patient information was recorded keeping in view different risk factors for EP. All patients in the study were followed by clinical assessment, serial β-hCG and TVS to monitor the outcome. Patients were given information sheet about PUL, its outcome, treatment options and need of follow-up. The management was done according to clinical assessment, compliance and the wishes of the patients. Expectant management was done in PUL patients with decreasing β-hCG values. These patients were followed twice weekly for β-hCG and weekly for TVS. Medical treatment was given to the patients with three β-hCG values at plateau, haemodynamically stable and compliant to treatment. Medical treatment was done with injection methotrexate 1 mg/kg given intra-muscularly (IM) after excluding contraindications like haemodynamically unstable or non-compliant patient, hypersensitivity to methotrexate, active pulmonary disease, peptic ulcer disease, immunodeficiency, coexistent IUP and breastfeeding. Patients treated medically were admitted for 2-3 days, according to clinical assessment and their social needs. Medically treated patients were followed up with the symptoms, signs and β-hCG values at day 1, day 4 and day 7. A fall of 15% or more in β-hCG value at day 7 from day 1 was considered successful medical treatment, otherwise a second injection was discussed with patient. Surgical management was considered in patients who were haemodynamically unstable, not compliant or failed to resolve with medical treatment or refused injection methotrexate. These patients were admitted and they underwent laparoscopy or laparotomy, and salpingostomy or salpingectomy was done according to the clinical assessment. Data was collected on a proforma and various parameters were analysed using frequencies, percentages, mean and standard deviation as appropriate.

## Results

During the study period, 7215 patients were admitted, and, of them, 2212(30.6%) were patients with early pregnancy. Patients seen with or without symptoms and labelled as PUL were 199(2.76%). Out of these patients, 16(8%) were lost to follow-up or their files were missing at the time of data analysis. The final sample comprised 183(92%) valid patients. These patients were divided into four groups according to their outcome (Table-1).

Overall, 155(85%) were young patients (range: 17-35 years). Gestational age of 177(96%) patients was 4-6 weeks. Only 7 (3.8%) patients had gestational age of 7 weeks. a total of 131(71.6%) patients presented with amenorrhea, while bleeding was found in 90(49.2%) and pain in 93(50.8%) patients. Previous history of ectopic was found in 11(6%) patients. Out of these, 8(73%) patients belonged to sub-group having F-PUL. There were 14(7.7%) who were diagnosed to have EP with appearance of adnexal mass. Among these, β-hCG level of 4(28.5%) patients decreased and expectant management resolved EP. Five (36%) patients underwent medical treatment with methotrexate after ruling out contraindications. Out of these five patients, 4(80%) received single dose, while 1(20%) patient received 3 doses to resolve EP. Five (36%) patients with EP outcome underwent surgical management. These patients were

**Table-1:** Outcome of pregnancy of unknown location (n=183).

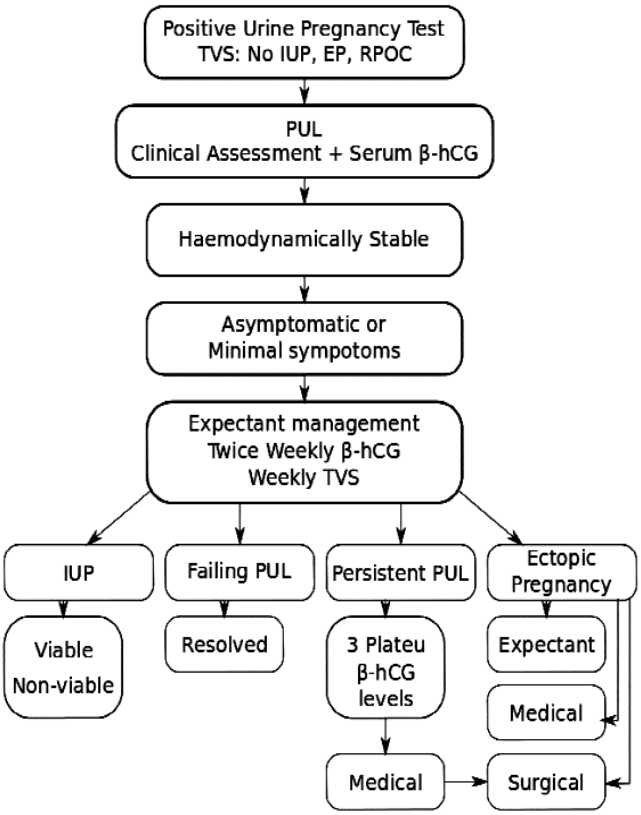
| Outcome | Number | Percent |
|---|---|---|
| Ectopic | 14 | 7.7% |
| Failing PUL | 100 | 54.6% |
| Intrauterine Pregnancy | 58 | 31.7% |
| Persistent PUL | 11 | 6.0% |

PUL: Pregnancy of Unknown Location.

**Table-2:** Characteristics among outcome of pregnancy of unknown location (n=183).

| Age Group | ECTOPIC | F_PUL | IUP | P_PUL | Total |
|---|---|---|---|---|---|
| 17-25 | 4.0 (2.2%) | 35.0 (19.1%) | 18.0 (9.8%) | 2.0 (1.1%) | 59.0 (32.2%) |
| 26-35 | 8.0 (4.4%) | 47.0 (25.7%) | 35.0 (19.1%) | 6.0 (3.3%) | 96.0 (52.5%) |
| 36-46 | 2.0 (1.1%) | 18.0 (9.8%) | 5.0 (2.7%) | 3.0 (1.6%) | 28.0 (15.3%) |
| **Gestational Age** | | | | | |
| 4 weeks | 1.0 (.5%) | 7.0 (3.8%) | 15.0 (8.2%) | 2.0 (1.1%) | 25.0 (13.7%) |
| 5 weeks | 2.0 (1.1%) | 43.0 (23.5%) | 24.0 (23.1%) | 1.0 (.5%) | 70.0 (38.3%) |
| 6 weeks | 10.0 (5.5%) | 45.0 (24.6%) | 19.0 (10.4%) | 7.0 (3.8%) | 81.0 (44.3%) |
| 7 weeks | 1.0 (.5%) | 5.0 (2.7%) | 0 (0%) | 1.0 (.5%) | 7.0 (3.8%) |
| Amenorrhoea | 12.0 (6.6%) | 83.0 (45.4%) | 30.0 (16.4%) | 6.0 (3.3%) | 131.0 (71.6%) |
| Bleeding | 10.0 (5.5%) | 62.0 (33.9%) | 11.0 (6.0%) | 7.0 (3.8%) | 90.0 (49.2%) |
| Pain | 5.0 (2.7%) | 46.0 (25.1%) | 36.0 (19.7%) | 6.0 (3.3%) | 93.0 (50.8%) |
| Previous Ectopic | 2.0 (1.1%) | 8.0 (4.4%) | 0 (.0%) | 1.0 (.5%) | 11.0 (6.0%) |
| **Methotrexate** | | | | | |
| 1 Injection | 4.0 (2.2%) | 0 (.0%) | 0 (.0%) | 11.0 (6.0%) | 15.0 (8.2%) |
| 3 Injections | 1.0 (.5%) | 0 (0%) | 0 (0%) | 0 (0%) | 1.0 (.5%) |

IUP: Intrauterine pregnancy
F-PUL: Failing pregnancy of unknown location
P-PUL: Persistent pregnancy of unknown location.




**TVS: Transvaginal ultrasonography. IUP: Intrauterine pregnancy EP: Ectopic Pregnancy. RPOC: Retained product of conception PUL: Pregnancy of unknown location.**

**Figure:** Assessment and Management of pregnancy of unknown location (PUL).

not suitable for medical treatment due to high β-hCG levels or the patients were symptomatic. Four (80%) patients had laparoscopic salpingectomy and 1(20%) underwent laparoscopic salpingostomy. Eleven (6%) patients whose outcome was P-PUL were managed by medical treatment and all (100%) were resolved with single injection of methotrexate (Table-2).

## Discussion

It is important in evaluation of a woman with symptomatic first-trimester pregnancy to obtain history about her symptoms, and quantitative hCG value. TVS of uterus and adnexa is also needed if indicated. Some women who are diagnosed as having PUL at their first presentation can be observed as out-patients with serial β-hCG and TVS until definitive diagnosis can be made. Expectant management with follow-up of 48-72 hours can be done for women having PUL with minimal or no symptoms as they are at risk of having ectopic pregnancy. Improved clinical prediction of final outcome of PUL can potentially decrease the number of visits to outpatient as well as shorten the time for some patients to reach a definitive diagnosis. It is well known that patients at risk of having EP require timely and accurate diagnosis as delay in diagnosis of EP can lead to increased morbidity and mortality. However, early intervention may be unnecessary and could harm early IUP. A balance between frequent testing and risk of EP with its complications should be made as frequent testing can lead to more false positive results.[11] Depending upon the risk factors and clinical

determination, individual assessment of the patient may reduce morbidity and mortality. Our study observed the outcome of the patients who presented with pain, bleeding or amenorrhoea in first trimester and initially labelled as having PUL. Some of these patients were managed as out-patients according to their symptoms, previous history of EP, β-hCG level and compliance for follow-up. These patients were called twice weekly for β-hCG and weekly for TVS to observe the outcome of PUL. The patient, who needed admission because of their symptoms, prior history and β-hCG value, were managed accordingly. A woman with EP who presents with PUL is likely to have a lower risk of rupture than a woman in whom EP is visualised on TVS initially. The most common outcome of PUL (44-69%) is F-PUL.[12-17] In our study comparable results of 54.6% were observed for F-PUL. Early IUP may not be visible on TVS due to small size leading to diagnosis of PUL.[3,18] Various studies have found 30-37% patients having IUP after initial diagnosis of PUL.[3] In our study comparable result of 31.7% was observed for IUP after initial diagnosis of PUL. Various studies have found 8.1-42.8% of PUL patients having outcome as EP. Lower values (8-14%) have been observed in specialised screening units when diagnosis of EP was based on the visualisation of adnexal mass rather than the absence of intrauterine sac on TVS.[5,13,19-20] P-PUL accounts for approximately 2% of total PUL population.[21] In our study, this was found to be higher at about 6%. This can be due to our early medical intervention after three β-hCG plateau values. This protocol of early intervention has been adopted due to poor compliance and low rate of literacy of the patients in our population. If we had waited more, some of the patients labelled as P-PUL might have resolved as F-PUL or converted to EP. There is limited data available regarding medical treatment of PUL. According to a study, methotrexate 50 mg/m$^2$ has been used successfully in women with subsequent resolution of serum β-hCG level.[9,10] In medical treatment of EP, methotrexate has been found to be 90% effective.[3] In our study five patients having EP and 11 patients with P-PUL were treated with injection methotrexate and all of them resolved with one injection except one patient with EP who needed three injections. In our study patients with three plateau β-hCG values were treated medically as per hospital protocol. This can be revised as more wait may lead to one of the outcomes of PUL.

In this study we did not choose other methods of diagnosis, like serum progesterone, tumour markers and mathematical models. These methods have been shown to increase the diagnosis and predict the outcome of PUL. However, further studies are required to validate the mathematical model, use of hCG ratio and progesterone levels. Our study is easy to carry out in other centres with limited resources without burdening the healthcare system and patients.

## Conclusions

For determining the outcome of PUL, serial β-hCG levels and TVS are important markers, though cumbersome for the patient and physicians alike. Early determination of EP is important as this can be the cause of maternal morbidity and mortality. Management of choice for asymptomatic patients having PUL is expectant management. Most of the patients suspected to have PUL resolved either into F-PUL or IUP with expectant management. Most of the patients with P-PUL and EP can be managed medically. A few patients with EP would need surgical intervention.

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