Pregnancy of Uncertain Viability or of Unknown Location; Case Report and Overview of the Evolving Trend and Recommendations in the Literature

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Abstract

There can be situations as this unique case, where experienced staff, even with biochemical and sonographic assistance, would not be able to make early diagnosis of neither pregnancy of unknown location (PUL) nor pregnancy of uncertain viability (PUV). This is because the clinical picture remained unclear or may still be in evolution and thus constitute what some scholars may describe as “indeterminate pregnancy”, while the clinical puzzle lasts. In these cases, the early indeterminate clinical picture becomes more clear or apparent later if the patient adhered to the follow-up management plan as in this case. Thus, at the early stages; both clinical, biochemical and sonographic follow-up would most of the time make the clinical picture clearer; provides grounds for escalation of the care plan or provide reassurance to staff and patients that the lesion or complication was resolving or has resolved.

Even before the publication of the Early Pregnancy Loss, Management, RCOG Green-top Guideline 25 of October 2006, there had been characterisation of pregnancy of unknown location (PUL) and pregnancy of uncertain viability (PUV) by clinicians as separate early pregnancy clinical entities and essentially clinically distinct from ectopic pregnancy. At early stages of evolution of these early pregnancy lesions, complications or clinical entities, there can be overlap of symptoms or presentations. However, that publication among other things, sought to streamline the use of terminologies and definitions to avoid confusions which have consequent medico-legal significance.

Keywords: Early Pregnancy; Complications of Early Pregnancy; Clinical Puzzles in Early Pregnancy

Abbreviations

BHCG: Beta Human Chorionic Gonadotrophin; ET: Endometrial Thickness; USS: Ultrasound Scan; TVS: Transvaginal Scan; TAS: Trans Abdominal Scan; PUL: Pregnancy of Unknown Location; PUV: Pregnancy of Uncertain Viability; CRL: Crown Rump Length; MSD: Mean Sac Diameter; RCOG: Royal College of Obstetrician and Gynaecologists; VEGF: Vascular Endothelial Growth Factor.

Introduction

PUL and PUV are early pregnancy complications. There may or may not be bleeding and there may or not be pain in both complications, and the cervix is usually closed in both complications [1]. However, the sonographic findings and management differ slightly. In PUV, the USS findings usually show a gestation sac less than 25 mm. This may be represented in our case as the unclear and uncertain “a small fluid sac in the uterus” or an uncertain and unclear “area of bleed in the uterus is 18mm” on the second scan. In PUV, there is no fetal pole or yolk sac, there may be fetal echo with CRL of less than 7mm. PUV is essentially a clinical situation where there are not enough sonographic criteria to state with certainty and confidence that an intrauterine pregnancy is either a viable or a failed pregnancy.

In PUL, though the pregnancy test is positive and serum BHCG is more than 5 IU/L, there is no evidence of intrauterine pregnancy, ectopic pregnancy or retained products of conception on scan. For PUL, the plan is usually to perform serial BHCG assay of 48 hours apart but recently, initial serum progesterone assay was included to exclude ectopic pregnancy/failing PUL.

In both PUL and PUV, anti-D is usually given if bleeding is heavy or if there is pain in all non-sensitised rhesus negative women. Due to the clinical course of PUL and PUV, especially in early stages, many clinicians tend to adopt similar management strategy for both till the situation is clearer or the pregnancy is resolving or has resolved. So, it is not unusual to see management overlap as patients are followed-up and as the clinical picture evolves.

Case History

A 44 year old woman presented to our unit with a history of mild episodic left iliac fossa pain and intermittent bleeding per vaginam (PV). Her last menstrual period was 6 weeks before presentation. She was referred from ultrasound scan (USS) department. There were no other symptoms. She was gravida 2, para 0; that is, she had a history of miscarriage at 12 weeks gestation. There were nothing else significant in her medical, obstetric and gynaecological history. Serum BHCG was 4910 IU/L and USS showed endometrial thickness (ET) of 24mm, and a small fluid filled sac in the uterus. The diameter of this sac was not stated on scan. There were two 4mm fibroid on the uterus noted on scan.

On clinical examination, there were no significant clinical findings and no tenderness in the left iliac fossa area. She was clinically stable.

Urinalysis showed leucocyte+ and +protein and the midstream specimen was sent for microscopy culture and sensitivity. She was reassured and sent home by the reviewing Specialist Registrar and was advised to return for repeat BHCG in 48 hours and to be review the day after. Her serum BHCG level went up to 6226 IU/L, an increase of 26.8% in 48 hours. She was reviewed the following day at the short stay unit. She was stable clinically and there were no signs and symptoms following assessment. Urine culture did not report anything significant.

The attending Specialist Registrar reassured her and made a plan for her to go home and be reviewed in 48 hours with a repeat BHCG and for a rescan in seven days. This plan took account of the fact that she lived locally; was stable clinically and not in distress or pain; had means of communication and transport and her partner lives with her. She was given an open access to the Unit and advised to contact our Unit if there were further concerns before she was due for review. However, on a second thought and due to the fact that the course of early pregnancy complications can give rise to
unexpected surprises, the cautious Specialist Registrar discussed with a consultant, who made a decision to take the patient for diagnostic laparoscopy and with intent on progressing directly to definitive surgical treatment of salpingectomy or salpingotomy if necessary, depending on findings at diagnostic laparoscopy. This decision was based on the serum BHCG level. She had diagnostic laparoscopy later that day under general anaesthetic.

**Operative Findings were as Follows**

Right fallopian tube, larger than the left but uniformly enlarged, right ovary, larger than the left ovary. No fluid in the Pouch of Douglas. No evidence of ectopic pregnancy noted.

**The Postoperative Follow-Up Plan**

Repeat serum BHCG and scan as planned by the Registrar before laparoscopy. Her postoperative period was uneventful. She was again reassured and advised that a follow-up was important. Her serum BHCG in 48 hours was 6876 IU/L an increase of 40% from the basal serum BHCG of 4910 IU/L in 96 hours but only an increase of 10% from the second serum BHCG of 6226 IU/L in 48 hours, compared with 26.8% increase in serum BHCG from 4910 IU/L to 6226 IU/L in 48 hours. Thus, in effect, the serum BHCG was not rising as much in the subsequent 48 hours compared to the earlier rise.

**USS Result in 7 Days Gave the Following Findings**

Anteverted uterus, area of bleed in the uterus is 18 mm. No gestation sac seen. She was sent home and advised to attend for repeat scan, BHCG and review. She wanted to know if she and husband are compatible in view of previous pregnancy loss, the present loss and the finding of small fibroids in her uterus. She was counselled and reassured. She was also informed that it was very unlikely the small fibroids on the uterus could be responsible for her condition.

She subsequently passed clots and on subsequent review, the clinical, biochemical and USS picture was that of a resolving, then subsequently resolved pregnancy of uncertain viability or pregnancy of unknown location.

**Discussion**

According to Collins S et al. [2], in PUV, there may or may not be bleeding, and there may or may not be pain, and cervix is usually closed. Scan findings show gestation sac less than 25 mm with no fetal pole or yolk sac, there may be fetal echo with CRL of less than 7 mm and the acceptable plan is to rescan the patient in one week, and to give her Anti-D prophylaxis if there is heavy bleeding or pain, in all non-sensitised rhesus negative women.

In PUL; just as in PUV, there may be bleeding or pain, and cervix is usually closed. Pregnancy test is usually positive on PUL but on sonographic findings, there is usually a departure as there is usually empty uterus and no sign of extrauterine pregnancy. Anti-D prophylaxis if there is heavy bleeding or pain, in all non-sensitised rhesus negative women. The plan is usually to perform serial BHCG assay 48 hours apart but recently, initial serum progesterone assay was included at first visit to exclude an ectopic pregnancy/failing PUL.

In our case, it could be seen that the first sonographic findings appeared to make it look like PUV rather than PUL but the serum BHCG parameters appear to make it PUL rather than PUV. The last scan also supported a working diagnosis of PUL. From the author’s experience, all the principles and criteria for expectant and medical management of ectopic pregnancy apply equally to PUL.

In October 2006, the RCOG [3]; introduced changes in terminology: sensitivity, consistency in terminology and definition in relation to assessment, communication and management of early pregnancy complications. Indeterminate pregnancy was subclassified as follows:

1. Pregnancy of unknown location; positive pregnancy test, no signs of pregnancy (intra or extra uterine) or retained products of conception, general incidence stated to be 8-31% at first hospital but 8-10% in specialist units.
2. Pregnancy of uncertain viability; constitute 10% of cases at first visit to early pregnancy unit. Intrauterine sac less than 20 mm, no fetus or yolk sac; or fetal echo less than 6 mm CRL, no fetal heart activity on scan.

Other sonographic pictures includes; intrauterine location and eccentricity of empty sac, plus or minus double ring pattern. The plan is to rescan in one week.

**The Role of Progesterone for Pregnancy of Unknown Location was Stated as Follows**

- Levels less than 25 nmol/L means that the index pregnancy is non-viable pregnancy. However, no need for radical intervention because of these initial levels.
- Levels less than 15.9 nmol/L have been seen in viable pregnancy.
- Levels less than 20 nmol/L predicts spontaneous resolution with sensitivity of 93% and specificity of 94%.

The advantage of doing this test is that the need for surgical intervention in the form of evacuation of retained products of conception is reduced if expectant management is adopted.

- Levels more than 25 nmol/L and more than 60 nmol/L are likely to and strongly indicative of pregnancy respectively, that were subsequently found to be viable.

**Gestational Sac Diameters**

- 2 mm…..4 weeks
- 5 mm…..5 weeks
- 10 mm…..6 weeks
- 20 mm…..7 weeks
- 25 mm…..8 weeks

**Gestational Sac Volumes**

- 1 mL….6 weeks
- 31 mL….10 weeks
- 100 mL….13 weeks

For PUL, the statistics depends on which study you look at and how current. Kirk E and Bourne T [4], cited report of studies which stated that in women attending early pregnancy clinic and who have a positive urinary BHCG test, the location of the pregnancy can be up to 90-92% of cases on the basis of the initial TVS findings. According to these authors, many more would initially have inconclusive scans and be classified as PULs outside specialist centres. The author and many other clinicians in the UK have same experience.

Kirk E and Bourne T [4], cited studies which reporting that 8-31% of women referred for ultrasound assessment in early pregnancy may be initially classified as a PUL, majority of women (50-70%) will have spontaneously resolving pregnancies (failing PULs), while 7-20% will subsequently be diagnosed with an ectopic
pregnancy. On the significance of serum progesterone in PUL; Kirk E and Bourne T [4], stated the following:

“A serum progesterone level below 20 nmol/L has been shown to have a positive predictive value greater than 95% of predicting pregnancy failure.

*Levels above 25nmol/L are 'likely to indicate' and levels above 60 nmol/L are 'strongly associated' with pregnancies subsequently demonstrated to be viable. However, viable IUPs have been reported with initial levels below 16 nmol/L.”

The latter was comparable to the information cited in the RCOG Green-top Guideline 25 of 2006 [3]. On the use of serum BHCG, how the time have changed. You will recall that a single serum BHCG measurement was used by some as a discriminatory level to help with the detection of ectopic pregnancy. According Kirk E and Bourne T, this concept was initially developed with respect to TVS examinations, when it was reported that the absence of an intrauterine gestational sac at an BHCG concentration of greater than 6500 IU/L had a sensitivity of 100%, a specificity of 96%, a positive predictive value of 86% and a negative predictive value of 100% for the prediction of an ectopic pregnancy. This approach was 98% efficient, based on a 19.4% prevalence of ectopic pregnancies among the group the authors confirmed. However, the authors argued that a high negative predictive value for diagnosing a clinical outcome with a high prevalence does not demonstrate that the test has a high diagnostic performance.

The subsequent use of TVS, which has high resolution, led to the discriminatory BHCG level being decreased. Serum BHCG levels of 1000, 1500 and 200 IU/L have been used [5]. However, a study on the use of varying discriminatory levels has demonstrated that using a single value of serum BHCG in a PUL population is of limited value [5]. The authors demonstrated that varying the discriminatory zone does not significantly improve the detection of ectopic pregnancy. It is a common experience that many cases of ectopic pregnancies in a PUL population have a relatively low serum BHCG level, and so practitioners may be falsely reassured about the location of the pregnancy.

According to Boyraz G and Bozdag G [6], it is not always possible to determine the location of the pregnancy in cases of PUL. The authors reported a wide range rate of 5–42% of PUL among women attending early pregnancy units and concluded that the frequency of PUL incidents has increased with the increase in the number of early pregnancy units.

In another current literature, PUL is stated to be the first diagnosis in 10% of patients in early pregnancy units [2]. The possible clinical outcomes are as follows; early intrauterine pregnancy; failing PUL; ectopic pregnancy, which can occur in 10% of PUL; persisting PUL; complete miscarriage and in very rare situations a BHCG secreting tumour may be the problem. Collins S et al. [2] warned that clinicians should in cases highly suggestive of complete miscarriage; classify the latter as PUL till there is evidence such was intrauterine pregnancy. This is because 5–10% of cases diagnosed as complete miscarriage on history alone with empty uterus on scan would end up as ectopic pregnancy. Some may argue that this 5–10% is only a small fraction of cases diagnosed as complete miscarriages based on history alone with empty uterus on scan. However, in the author’s opinion, experience has taught us that even 1% of the cases of missed ectopic pregnancy is clinically significant and can potentially involve loss of life.

Symptoms and clinical parameters of the patient are the most important things to consider just as when we diagnose ectopic pregnancy. Women with significant pain, abdominal tenderness or signs of haemoperitoneum need laparoscopy. In our case, it was the serum BHCG parameters and the fact that a patient’s clinical condition can deteriorate rapidly that led made us decide to perform laparoscopy. The later was no doubt reassuring to staff and the patient for the interim but was no guarantee that a tubal rupture event could not occur at a later stage, assuming it remained PUL and clinical and biochemical parameters became more exacerbated.

More recently, there appears to be “updated” guide or a narrative algorithm stated below [2] for interpreting serum BHCG and progesterone results in PUL which was not available at the time this patient was attended to. This “updated” guide included cut off level for serum progesterone and what action to be taken if serum BHCG is more than 1500 IU/L. It stated that if the serum BHCG was more than 1500 IU/L, it was likely to be ectopic pregnancy. In our case, there was no evidence of ectopic pregnancy at the time of laparoscopy.

**Serum BHCG and Progesterone Narrative Algorithm**

*If progesterone is less than 20 nmol/L*

- Failing pregnancy likely
- Repeat BHCG in 7days

*If BHCG rise by more than or equal to 66% in 48 hours*

- Likely intrauterine pregnancy
- Rescan in 10-14 days

*If serum BHCG rise less than 66% or plateauing (as in our case):*

- *Likely ectopic pregnancy*
- Close monitoring with serum BHCG and TVS till the diagnoses is made or BHCG falls less than 15 IU/L. If serum BHCG fluctuating or plateauing;
- Persistent PUL after 3 consecutive samples with no diagnosis
- Conservative management if asymptomatic or give methotrexate
- If initial serum BHCG is more than 1500IU/L as in our case;
- Probably ectopic pregnancy
- Consider all management options depending on clinical need

In our case, serum BHCG was more than 1500 IU/L; did rise but did not rise above or equal to 66% in 48 hours from basal level as one would expect from a viable intrauterine pregnancy and it was not found to be ectopic pregnancy on laparoscopy.

**Other Serum Markers for PUL**

There are other serum markers that have been tested to assess if they can predict pregnancy outcome in the PUL population. They are as follows: carcinoma antigen (CA) 125, creatine kinase, activin A and VEGF

CA-125 level in maternal serum peaks during the first 13 weeks of pregnancy and is believed to arise from the decidual cells affected by chorionic invasion or placental separation. According to an older study [7], CA-125 levels are significantly lower in ectopic pregnancies compared with IUPs. However, a more recent study reported that when CA-125 levels were incorporated into a logistic-regression model to predict the outcome of PULs, they were found to be able to distinguish failing PULs from IUPs, but were not able to detect those at the risk of ectopic pregnancy [5].
Creatine kinase is found in all smooth muscles, including the fallopian tube, and therefore is a nonspecific marker of smooth muscle damage. Though it has been suggested that damage to the fallopian tube, as occurs in a tubal ectopic pregnancy, can cause an increase in serum maternal creatine kinase levels, such increased levels cannot be used to predict the outcome of PULs [8].

Serum activin A levels have been used to predict ectopic pregnancy and serum levels were found to be significantly lower in women with ectopic pregnancies compared with those with IUPs or miscarriages. Using a cut off value of 0.37 ng/ml, gave a sensitivity and specificity of 100 and 99.6%, respectively, for the prediction of ectopic pregnancy, according to Florio P et al. [9].

Felemban A et al. [10] reported that serum levels of VEGF have also been shown to be higher in women with ectopic pregnancy. VEGF levels have also been found to be elevated in IVF patients who were subsequently diagnosed with ectopic pregnancies, according to Fasouliotis SJ et al. [11].

Future perspective

In the author’s opinion, while serum activin A and CA-125 appear to be the stronger contenders in that order, it remains to be seen if, and when these containing biomarkers would be in wider clinical use alone or as adjuvant tests or supplemental tests, to increase the sensitivities and predictive values of the established tests.

Also the International Society of Ultrasound in Obstetrics and Gynecology has created a consensus statement on PULs and advocates that PULs should initially be managed expectantly and both biochemistry and mathematical models can be used to predict PUL outcome, according to Condous G et al. [12].

In every clinical setting, the author’s view is that, attention should be concentrated on reducing the number and duration of follow-up required in women with a PUL and PUV. This is because women classified with PULs and PUVs can provide a significant workload as a large number of these patients merely reflects patients attending for ultrasound assessment at early stages of pregnancy. Therefore, reduction in workload reduces the number and durations of follow-up attendance required to the benefit of staff and patients.

PUL is so important that various trusts in the UK have Patient Advice Information to help patients [13–16], while some have clinical guidelines on PUL for instance [17].

On the other hand, generally, PUV appear to be comparatively less frightening to patients and appear easier to manage when compared to PUL or ectopic pregnancy. Various authors [18–20], agree that TVS will show the followings:

* Intrauterine gestational sac containing an embryo with CRL < 7 mm with no fetal cardiac activity

* Gestational sac with mean sac diameter (MSD) of less than 25 mm containing no embryo.

However, emphasized the important of confirming that the pregnancy has failed with absolute certainty, even in situations where the practitioner thought this was highly likely, but does not meet the established criteria. More recently, Preisler J et al. [21] outlined recommendation for follow-up management stated below:

* If MSD < 12 mm with no embryo- rescan in 14 days

* If MSD has not doubled and there is still no embryo-diagnosis of failed pregnancy can be made.

* If MSD 12-25 mm with no embryo- rescan in 7 days

* If no embryo with cardiac activity present - diagnosis of failed pregnancy can be made.

* If CRL < 7mm no heart beat- rescan in 7 days

* If still no heartbeat with any size CRL - diagnosis of failed pregnancy can be made.

It is almost certain, the author argues, that changes would be made to these recommendations in the future as these recommendations are still evolving as new sonographic evidence comes to light.

PUV is also important and some NHS Trusts in UK for instance, Belfast Health and Social Care Trust [22] has Patient Advice Information to assist patients.

Conclusions

In the management of cases of PUL and PUV, there have been evolutions of recommendations and recent inclusions of more information in the literature to help with diagnosis, definitions, characterization, separations and management of clinical entities in early pregnancy complications. However, there is still great clarity that the clinical parameters and the clinical status of the patient are the most important and influential factors that determines the course of action, and when that action(s) could be taken, despite the availability of other parameters.

Conflict of Interest

No conflict of interest.

References


17. Pregnancy of unknown location (PUL)- Clinical Guide. Royal Cornwall Hospital NHS Trust.


22. Pregnancy of uncertain viability; Belfast Health and Social Care Trust. [Cited 2017 March 30].

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