

Serum progesterone in the management of pregnancy of unknown location: A Singapore experience

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Dear Editor,

The management of pregnancy of unknown location (PUL) currently encompasses multiple blood tests to trend serum beta-human chorionic gonadotropin (hCG) levels every 48 hours and ultrasound scans (USS). This results in multiple hospital visits for patients, causing emotional and economic distress. Therefore, it is important to identify women with PUL at risk of an ectopic pregnancy (EP) requiring close monitoring, and to limit the follow-up for those who are likely to have a viable intrauterine pregnancy (IUP) or a failing pregnancy that may resolve spontaneously. Studies show that a single serum progesterone level can be used for triaging, with centres using cut-offs of 10 nmol/L to 30 nmol/L at which the pregnancy may spontaneously resolve.¹⁻⁵

To determine the feasibility of using a single serum progesterone level to differentiate non-viable pregnancies from viable IUP, and the low-risk PUL from the high-risk PUL requiring intervention, we conducted a prospective cohort study of women with a diagnosis of PUL who attended KK Women's and Children's Hospital, Singapore. The study included women aged 21 years and older who conceived spontaneously. Women who had conceived through assisted reproductive technologies or those on exogenous progesterone were excluded from the study.

All participants underwent serial serum beta-hCG tests and USS as per current practice. Serum progesterone level was obtained from the blood sample that was taken for the serum beta-hCG monitoring at their first or second visit, and compared with their eventual pregnancy outcome. We classified the outcomes into 4 categories: miscarriage, EP, persistent PUL and viable IUP.

Demographic and clinical data were collected concurrently in an electronic form. Data were reviewed and analysed by 2 separate team members using SPSS Statistics software version 29

(IBM Corp, Armonk, US) with comparison of means using the t-test ($P < 0.05$ to determine significance).

A total of 150 pregnant women presenting with PUL were recruited between December 2021 and July 2022. Data from 145 patients were analysed after excluding 5 patients that did not meet the criteria.

The median age of our study population was 31 years. More than half (54.5%, $n=79$) were nulliparous, 13.1% had at least 1 previous caesarean section, 24.1% had at least 1 previous EP, and 5.5% had 1 or more previous miscarriages.

The serum progesterone levels ranged from 1.6 to 125.7 nmol/L with a mean level of 27.1 nmol/L. The pregnancy outcomes of our study population are summarised in Table 1.

We found that the serum progesterone level was under 10 nmol/L in 44.8% ($n=65$). A miscarriage had occurred in 90.7% ($n=59$) of women, all of which resolved spontaneously. There were no women with a viable IUP or persistent PUL. An EP was diagnosed in 6 women (9.2%), of which 4 underwent surgical intervention while 2 were managed with systemic methotrexate (MTX).

Regarding women with serum progesterone between 11–20 nmol/L (12.4%, $n=18$), there were 11 miscarriages (61.1%), 5 EP (27.7%), 1 IUP (5.5%) and 1 persistent PUL (5.5%). The women with miscarriages did not require intervention. Of the women with EPs, 1 required surgery while 4 were managed with MTX. The woman with persistent PUL was managed with MTX.

When the serum progesterone levels were between 21–30 nmol/L (5.5%, $n=8$), there were 2 miscarriages (25%), 3 EPs (37.5%) and 3 IUPs (37.5%). Each woman who miscarried had a spontaneous resolution. Of the women with EPs, 2 underwent surgery and 1 received MTX.

In women who had serum progesterone levels above 30 nmol/L (37.2%, $n=54$), 63% ($n=34$) had

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Table 1. Summary of pregnancy outcomes.

Pregnancy outcome	Percentage % (no.)	Mean serum progesterone (range) (nmol/L)	Mean number of beta-hCG tests (range)	Mean number of USS (range)	Mean number of visits (range)	Average days to diagnosis (range)	Period of amenorrhoea (weeks)
Viable IUP	26.2 (38)	61.5 (19.5–125.7)	1.9 (1–3)	2.2 (1–4)	2.8 (2–5)	16.8 (2–30)	1.6–13.6
Miscarriage	59.3 (86)	13.0 (1.6–114.9)	2.2 (1–6)	1.7 (0–5)	2.5 (1–8)	7.0 (1–50)	1.4–26.3
EP	13.8 (20)	23.2 (1.6–79.5)	2.7 (1–6)	2.4 (1–5)	2.8 (1–6)	6.1 (1–30)	2.1–9.1
Persistent PUL	0.7 (1)	14.9	4	1	2	11	1.3

hCG: human chorionic gonadotropin; EP: ectopic pregnancy; IUP: intrauterine pregnancy; PUL: pregnancy of unknown location; USS: ultrasound scan

viable IUPs. A miscarriage occurred in 25.9% ($n=14$), of which 64.3% ($n=9$) were managed conservatively and 35.7% ($n=5$) needed intervention (2 surgical evacuations and 3 medical management). An EP was diagnosed in 11.1% ($n=6$) of patients, all of which required intervention (3 received MTX and the other 3 underwent laparoscopic salpingectomy).

There were no viable pregnancies ($n=38$) at progesterone levels under 10 nmol/L. At serum progesterone levels under 20 nmol/L ($n=83$), there was only 1 viable IUP (1.2%), and at levels under 30 nmol/L ($n=91$), there were 4 viable IUPs (4.4%). When the serum progesterone levels were greater than 30 nmol/L, there were 34 viable IUPs (63%).

Progesterone levels rise in early pregnancy due to its production in the corpus luteum, with levels decreasing in a failing pregnancy.⁶ Progesterone levels may hence be used to predict the outcome of PULs.^{1–5,9–11} However, studies have also reported a transient decline in progesterone levels during the luteal-placental shift in normal pregnancies, with a nadir between weeks 6 and 8 of gestation.^{7,8} As most PULs present at this gestation, it may be difficult to distinguish if a low progesterone level is due to an early gestational age or a luteal production issue. Verhaegen et al. found that the cut-off progesterone range of 10–19 nmol/L predicts a non-viable pregnancy with a pooled sensitivity of 74.6%, specificity of 98.4%, positive likelihood ratio of 45 and negative likelihood ratio of 0.26.¹¹ Other studies have used cut-off progesterone levels ranging from 20.0 nmol/L¹⁰ to 30 nmol/L¹ to differentiate non-viable pregnancies from viable IUPs.

In our study, there were no women with a viable IUP or persistent PUL at progesterone levels under 10 nmol/L, and 90.7% resolved spontaneously without any complications. Cordina et al. reported that 93.4% of women with serum progesterone

levels under 10 nmol/L did not have any complications that required further visits to the hospital.² This is also comparable to other studies.¹² However, all women diagnosed with EPs (9.2%, $n=6$) in our study were managed either with surgery or MTX.

A serum progesterone level under 20 nmol/L has been linked to a higher risk of failing pregnancy.³ Ghaedi et al. reported that more than 90% of patients with progesterone under 20 nmol/L will be diagnosed with a non-viable pregnancy.¹⁰ In our study, 57.2% ($n=83$) had serum progesterone level of under 20 nmol/L. Of these, 98.8% had a non-viable pregnancy. Miscarriage occurred in 84.3% ($n=70$), an EP was diagnosed in 13.2% ($n=11$), and one woman with persistent PUL received systemic MTX. Only 1 woman (1.2%) had a viable IUP.

Hahlin et al. reported no viable pregnancies when serum progesterone level was under 30 nmol/L.¹ In our study, 62.8% of women ($n=91$) had a progesterone level of less than 30 nmol/L. Of these, 95.7% were non-viable. A miscarriage occurred in 79.1% ($n=72$) of women, an EP was diagnosed in 15.4% ($n=14$), and 1 had persistent PUL. All women with a miscarriage did not require any intervention for resolution. A viable IUP was found in 4.4% ($n=4$).

Ghaedi et al. reported that more than 90% with a progesterone level greater than 64–80 nmol/L will have a viable pregnancy.¹⁰ In our study, 80.7% ($n=21$) of PULs with serum progesterone more than 60 nmol/L ($n=26$) had a viable IUP. There were 2 EPs and 3 miscarriages. In conclusion, though a high single progesterone level has a higher chance of a viable IUP, it may not necessarily exclude a non-viable pregnancy.

Our study demonstrated that among women with PUL who had a final diagnosis of a miscarriage, those with progesterone level under 30 nmol/L had a spontaneous complete miscarriage, while

more than a third of women with levels greater than 30 nmol/L required intervention. Other studies similarly found cut-off serum progesterone levels of between 10 nmol/L^{2,12} and 20 nmol/L³ predicted pregnancies that were likely to resolve without intervention.

While our study did not establish a single serum progesterone cut-off to reliably distinguish high-risk from low-risk PULs, the findings offer valuable insights for managing patient expectations. A progesterone level below 10 nmol/L strongly indicates that a viable IUP is unlikely, with levels below 20 nmol/L offering only a 1% chance of a viable IUP. For levels below 30 nmol/L, the likelihood of a viable IUP increases to 4.4%, while levels above 30 nmol/L raise this likelihood to 63%.

It is crucial to emphasise that serum progesterone levels alone should not determine pregnancy viability, as viable pregnancies have been observed even at lower levels. For women diagnosed with miscarriage, a serum progesterone level below 30 nmol/L suggests the miscarriage will likely resolve without intervention.

Ethics statement

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements. The final study protocol, including the final version of the participant information and consent form, was approved in writing by the Centralised Institutional Review Board (CIRB reference: 2021/2088), prior to the enrolment of any patient into the study. Eligible patients were identified and approached by a member of the study team, and informed consent was taken.

Declaration

This study has secured funding from the 7th SingHealth Duke-NUS OBGYN Academic Clinical Programme Research Grant 2020. The authors have no affiliations or financial involvement with any commercial organisation with a direct

financial interest in the subject or materials discussed in the manuscript.

Keywords: *early pregnancy loss, ectopic pregnancy, miscarriage, pregnancy of unknown location, progesterone*

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