



Is this pregnancy viable?

When bleeding or pain occur in early pregnancy and ultrasound is inconclusive, a single progesterone test can often answer that question.

PRACTICE CHANGER

Measure serum progesterone levels of women with bleeding or pain and inconclusive ultrasound in early pregnancy to rule out viability, potentially eliminating the need for serial β -hormone human chorionic gonadotropin (β -hCG) testing.¹

STRENGTH OF RECOMMENDATION

A: Based on a systematic review and meta-analysis of 26 diagnostic accuracy studies.

Verhaegen J, Gallos ID, van Mello NM, et al. Accuracy of a single progesterone test to predict early pregnancy outcome in women with pain or bleeding: meta-analysis of cohort studies. *BMJ*. 2012;345:e6077.

ILLUSTRATIVE CASE

A 20-year-old woman with an estimated gestational age of 7 weeks comes to your clinic because of vaginal bleeding, which started 4 hours ago. A transvaginal ultrasound is inconclusive for an intrauterine pregnancy. Should you obtain a serum progesterone measurement?

Between 21% and 27% of pregnant women experience vaginal bleeding in their first trimester.^{2,3} This leads to concern, both for patients and physicians, as it can be the first sign of a miscarriage or an ectopic pregnancy. A longitudinal population-based Swedish study of women who had ever been pregnant found that one in 4 had experienced an early pregnancy failure. Overall, about 12% of clinically recognized pregnancies ended in miscarriage.⁴

Our ability to predict early pregnancy loss is limited

Tools used by clinicians to evaluate vaginal

bleeding or pain in the first trimester include transvaginal ultrasound (TVUS) and serial serum β -hCG measurements.⁵ Even when combined with risk factors for pregnancy loss (serum levels of estradiol, inhibin A, and inhibin B; maternal age; smoking; past history of spontaneous miscarriage; and vaginal bleeding), TVUS is not accurate at predicting early pregnancy loss.^{6,7}

A suboptimal rise in β -hCG (<66%) after 48 hours has historically been used to indicate possible miscarriage or ectopic pregnancy,¹ but studies have found similarly low rates of increase in some viable pregnancies, as well.^{8,9} And β -hCG measurements need to be done on more than one occasion, making this an inconvenient means of predicting miscarriage.

Moreover, β -hCG levels vary based on gestational age, leaving family physicians with no solid diagnostic rule regarding the appropriate level of rise in a viable pregnancy.¹⁰ Thus, there is a need for a test that complements TVUS and β -hCG to increase diagnostic accuracy in predicting nonviable pregnancies.

Can serum progesterone testing fill the gap?

Serum progesterone measurement is a noninvasive predictive tool, with low values associated with miscarriage and ectopic pregnancy and higher levels with a viable pregnancy.¹⁰ Studies have found that serum progesterone combined with β -hCG measurements has the highest reliability in predicting nonviable pregnancy, with a diagnostic accuracy of 85.7% (sensitivity, 88.1%; specificity, 84.3%).

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INSTANT POLL

Which tests do you typically use when you suspect that a pregnancy is nonviable?

- Transvaginal ultrasound (TVUS) and serial β -hCG measurements
- TVUS and a single progesterone test
- Serial β -hCG and a single progesterone test
- TVUS, serial β -hCG, and a single progesterone test, as needed
- Other (Please specify) _____

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> In women with pain or bleeding when ultrasound is inconclusive, a low serum progesterone level is highly predictive of a nonviable pregnancy.

This compares with a diagnostic accuracy of 72.5% (sensitivity, 76.1%; specificity, 70.4%) for a single progesterone test alone, and 74.8% (sensitivity, 64.1%; specificity, 81.4%) for β -hCG alone.¹⁰⁻¹² The data are from older studies, including a meta-analysis, that did not include the use of TVUS.¹⁰⁻¹² But TVUS is now in widespread use and included in the systematic review and meta-analysis this PURL addresses.

STUDY SUMMARY

Progesterone test is predictive—when combined with ultrasound

Verhaegen et al performed a comprehensive literature search to identify studies in which a single serum progesterone measurement was used to predict the viability of pregnancy vs miscarriage or ectopic pregnancy. They included studies of women with spontaneous pregnancy of <14 weeks. Trials of women who had conceived after ovulation induction or in vitro fertilization or received progesterone supplementation were excluded.

Twenty-six cohort studies met the inclusion criteria. These included 7 mostly high-quality studies, with a total of 2379 women with pain or bleeding *and* inconclusive TVUS, and 19 intermediate-quality studies (n=7057) of women who had pain or bleeding but no ultrasound.

Five of the 7 studies in women with symptoms and inconclusive TVUS had a similar progesterone test cutoff value (3.2-6 ng/mL). In these 5 studies (n=1998), the progesterone test predicted a nonviable pregnancy with a pooled sensitivity of 74.6% (95% CI, 50.6%-89.4%) and specificity of 98.4% (95% CI, 90.9%-99.7%), a positive likelihood ratio of 45 (7.1- 289) and a negative likelihood ratio of 0.26 (0.12-0.57). When

progesterone was below the cutoff value, the probability of a nonviable pregnancy increased to 99.2%. In women with pain or bleeding but no ultrasound, a single progesterone test is less accurate in ruling out a viable pregnancy.

WHAT'S NEW

This test can end days of anxious waiting

This meta-analysis provides strong evidence that a single progesterone measurement is useful in predicting nonviable pregnancies in women with pain or bleeding when TVUS is inconclusive. In such patients, a low serum progesterone is highly predictive of a nonviable pregnancy.¹ This finding enables the physician to counsel the woman immediately on the likely pregnancy loss, without waiting days for serial β -hCG results.

CAVEATS

Progesterone is a poor predictor of ectopic pregnancy

An important caveat to our recommendation is that a single serum progesterone test has a poor predictive value for ectopic pregnancy and should not be used for this purpose. A combination of TVUS and serial β -hCG remains the optimal strategy for diagnosing ectopic pregnancy.¹³

It is important to note that there is no universally accepted definition of a low serum progesterone level: This meta-analysis included studies with a cutoff value of 3.2 to 6 ng/mL in women who had had a previous ultrasound. What's more, these studies did not evaluate the predictive value of a serum progesterone test combined with β -hCG measurements.

CONTINUED ON PAGE 316

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CONTINUED FROM PAGE 306

CHALLENGES TO IMPLEMENTATION

There are none

We do not see any challenges to the implementation of this recommendation. **JFP**

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