REI Pearls Pitfalls of Day 21 Progesterone

The Skinny

Verifying ovulation is a critical part of the fertility evaluation. History often gives strong clues regarding a patient’s ovulatory status. Regular predictable menses every 24-35 days is usually suggestive of ovulation, especially when accompanied by premenstrual symptoms such as breast tenderness, mood change, or acne. Actual signs of ovulation include Mittelschmerz and increased cervical mucus.

A physician can verify ovulation in several ways:
1) Having the patient use ovulation predictor kits
2) Having the patient perform basal body temperature charting
3) Measuring a serum progesterone level
4) Serial ultrasound evaluations
5) Endometrial biopsy – this is an outdated method for many reasons, see below.

The most popular method is measuring a serum progesterone level.

A commonly held belief is that a progesterone level of at least 10 ng/ml is an indication of quality ovulation and that values less than 10 ng/ml suggest that ovulatory dysfunction may be present.

Key Points

Serum Progesterone
- Serum progesterone > 3 ng/ml is consistent with ovulation.
- There is no uniform agreement supported by the literature as to what progesterone level is “normal” in the luteal phase.
- Testing progesterone on cycle day 21 is not appropriate for all women.
- The most appropriate time to measure serum progesterone is in the mid luteal phase (either 7 days after ovulation, or 7 days prior to expected menses). This is when you’re most likely to catch the peak. This day will vary according to the woman’s cycle length (ie for a 28 day cycle, a day 21 progesterone is appropriate; but for a 35 day cycle, progesterone would ideally be measured around day 28).
What’s Behind the Skinny

Prior to ovulation, progesterone levels do not exceed 3 ng/ml. The illustration below shows a typical 28 day cycle, with the peak progesterone coinciding with CD21.

The problem in measuring a solitary progesterone level is that progesterone is secreted in a pulsatile fashion under the influence of Luteinizing Hormone (LH). No matter when you measure it, you could be detecting it at a peak, or a trough. In 90 minutes progesterone can vary between 2 ng/ml and 40 ng/ml!

As you can see from the above illustration, even a normal ovulation can have a “low” (<10 ng/ml) progesterone if tested at the trough. Because of this, some reproductive endocrinologists have advocated for testing 3 serum progesterone levels over several days, arguing that a cumulative level greater than 30 ng/ml is adequate. We feel that multiple measurements are not practical and add little to the evaluation of the couple.
As said in the bullet points, measuring CD21 progesterone is not optimal in all patients. Women who have 30-35 day cycles generally ovulate later than women with 24-28 day cycles.

The above illustration shows that short or long cycles can have normal progesterone secretion, but misleading progesterone levels if drawn routinely on CD21. The best time to check progesterone is 7 days after ovulation, or 7 days prior to expected menses.

One way to maximize your chance of measuring progesterone at its peak is to measure a serum level 7-8 days after the LH surge, as determined by an ovulation predictor kit.

Of course there are other pitfalls to measuring and interpreting progesterone levels. Even progesterone levels that are very reassuring (>10 ng/ml) do not always indicate that the luteal phase is adequate.

In future clinical pearls, we will address how to determine if the luteal phase is adequate. As always, we welcome questions regarding the interpretation of labs.