How far should we go to avoid PIO?

As fertility specialists, we tirelessly search for effective and patient-friendly treatment protocols to help individuals and families achieve their fertility goals with the highest satisfaction and least stress and discomfort. Frozen embryo transfer (FET) utilization is sharply increasing. Now, more than ever, FET protocols face appropriate scrutiny, with the goal of optimizing both patient experience and live birth rates.

In the current issue, Labarta et al. (1) present their retrospective cohort analysis of good-prognosis European blastocyst FETs (approximately 70% donor egg) after preparation with micronized vaginal progesterone (MVP) (400 mg twice daily). They showed that patients who received individualized luteal phase support (iLPS)—adding subcutaneous progesterone 25 mg daily from the day of transfer onward—were associated with good live birth rates among women noted to have low serum progesterone concentrations on the day of embryo transfer. A low progesterone concentration was defined as <9.2 ng/mL, a threshold established in their prior analysis (2). They compared the rates of live birth and secondary outcomes between a group with adequate progesterone concentrations (≥9.2 ng/mL) (continued with MVP alone), a study group with low progesterone concentrations on the day of FET (continued with iLPS), and a historical cohort of women with low progesterone concentrations who did not receive iLPS. Individualized luteal phase support for women with low serum progesterone concentrations was associated with equivalent live birth rates when compared with women with adequate progesterone concentrations (44.9% vs. 45%, respectively). However, when compared with a historical cohort of women with low progesterone concentrations on the day of transfer who did not receive iLPS, the live birth rates were statistically significantly higher (44.9% vs. 37.3%, respectively). While limited by its reliance on a historical rather than contemporaneous control group for its most relevant conclusions, the study provides clinically useful and reassuring information. The data indicate that the addition of subcutaneous progesterone may be able to “rescue” those FET cycles in which low serum progesterone concentration is encountered after vaginal-only progesterone preparation. The study is most relevant for European patients and practitioners, given that vaginal-only progesterone protocols are more commonly used for FET in Europe and that subcutaneous progesterone is not available in the United States.

The question of whether serum progesterone concentration should be measured and/or acted upon in the setting of programmed FET is undoubtedly a “hot topic.” A recent meta-analysis of 21 studies evaluated FET outcomes on the basis of serum progesterone concentrations. The investigators concluded that lower serum progesterone concentrations were associated with lower ongoing pregnancy rates and higher miscarriage rates and suggested a threshold of 10 ng/mL as clinically significant (3). As in the current study, the meta-analysis relied overwhelmingly on data from FETs in which vaginal progesterone only was used. The investigators concluded that there were insufficient data for appropriate meta-analysis of studies using other routes of progesterone. One can reasonably conclude on the basis of the available evidence that low serum progesterone concentration has a negative association with FET outcomes among patients receiving vaginal progesterone. Thankfully, the current study adds value by suggesting that these cycles have the potential to be rescued; however, it remains unknown whether low serum progesterone concentration has the same negative association in cycles where injectable progesterone is used from the outset.

We published data from a randomized controlled trial evaluating the route of progesterone in 1,060 programmed blastocyst FETs, showing that vaginal progesterone only (200 mg twice daily) resulted in significantly lower serum progesterone concentrations 2 weeks after FET as well as lower live birth and higher miscarriage rates, when compared with 50-mg intramuscular progesterone in oil (PIO) daily or every third day combined with vaginal progesterone (4). Unpublished data from the same study showed that the odds of having a serum progesterone concentration lower than 9 ng/mL were 3.0% (12/399 subjects) with daily PIO and 9.5% (37/388 subjects) with the combined protocol. This is in contrast with 29.7% (550/1,849 subjects) having low serum progesterone concentration requiring of iLPS in the current study, when measured on the day of blastocyst FET after 400 mg of vaginally twice daily. Furthermore, among those—thankfully, few—randomized controlled trial subjects who received PIO (alone or in combination) and had “low” serum progesterone concentrations, 43% (21/49) achieved live birth. This rate was not significantly different from that of the overall cohort of subjects receiving PIO nor from that of those who received PIO and had a serum progesterone concentration of ≥9 ng/mL. On the basis of these data, one could argue that when using a programmed FET regimen containing PIO, the measurement of serum progesterone concentration may not be needed. We must consider the difference in timing relative to the current study (at pregnancy test vs. at FET); however, published pharmacokinetic data suggest that the steady state should be achieved by 24–48 hours with either PIO or MVP twice daily (5).

Of course, patient preference must also be considered, and the main consideration driving predominance of vaginal progesterone (and avoidance of PIO) in Europe is undoubtedly a healthy concern for patient comfort and convenience. However, and somewhat surprisingly, US patients’ own expressed preferences do not indicate strong aversion to PIO, sufficient to recommend against its use. Published supplemental survey data demonstrated that fewer than 10% of patients were moderately or extremely dissatisfied with PIO, almost identical to the dissatisfaction for vaginal progesterone. In patients who used both PIO and vaginal progesterone, 56% preferred vaginal progesterone and 44% preferred PIO (4). When adding the consideration that if using vaginal
progesterone only, patients may need an extra blood draw to determine whether iLPS is needed, those preferences may equilibrate.

In the end, we all know that patients will prefer a route of supplementation that gives them the best chance of having a live birth—no matter what it takes. As such, we are challenged to do what is right for our vulnerable patients in the treatments we recommend, considering the best available evidence. On the basis of the current study, in settings where PIO cannot be used and subcutaneous progesterone is readily available, iLPS represents a good choice and one that likely improves outcomes relative to MVP alone. For those of us practicing in the United States, a well-designed comparison of iLPS to PIO is needed before we all change course.