Can measuring the luteal phase progesterone level bridge the divide between the Atlantic?

A substantial amount of controversy still lingers regarding the best route of administration of progesterone in the luteal phase of frozen embryo transfers (FETs), an unsettled debate that becomes most obvious when one focuses on different practices observed in the United States and Europe. Specifically, many American centers prefer to use injectable progesterone, a stance that was recently validated by the findings of Devine et al. (1), who reported significantly higher live birth rates in FETs when intramuscular progesterone was administered. That said, while providing food for thought, these results may warrant validation in future studies especially because the researchers opted not to perform luteal phase progesterone measurements and use a dose of vaginal progesterone which is lower than what is generally advocated outside of the United States (200 mg twice daily). Conversely, in Europe, the vaginal administration of progesterone is predominant, not only based on the assumption that the superiority of the intramuscular route may still lack sufficient validation but also because it is frequently deemed more practical and patient-friendly. With that in mind, the recently published systematic review and meta-analysis by Melo et al. (2) presented a comprehensive understanding of the currently available data on the relationship between luteal phase serum progesterone levels and FET outcomes, a question that is of utmost importance for those who prescribe vaginal luteal phase support (LPS).

This study, which included an extensive electronic search on several databases from inception to March 2021 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, captures the state of the art on the subject and highlights the extreme relevance of serum progesterone threshold categorization on FET outcomes. The analysis of the results posited that for a progesterone threshold of 10 ng/mL, higher progesterone levels are correlated with better live birth and clinical pregnancy rates while also being associated with lower miscarriage rates. These findings suggest that a minimum concentration of progesterone is critical to ensure adequate embryo implantation and early pregnancy maintenance. This correlation, however, did not remain statistically significant when higher serum progesterone thresholds were considered, leading one to question whether such levels may impair implantation and decidualization (i.e., higher levels may not always be better). This issue is of great importance because the optimization of LPS is one of those instances in which treatment outcome may be improved without the need of any major technologic breakthroughs.

This review also emphasizes the importance of accounting for the route of progesterone administration while performing any clinical judgment, given that it is unlikely that a single circulating progesterone threshold may the best surrogate marker for endometrial progesterone concentrations in all settings. The clinical significance of these results for the readership of this journal is also strengthened by the large number of cycles evaluated deriving form treatment centers located all over the globe.

Although this study does encapsulate the current evidence on the topic very well, important limitations must also be acknowledged, the first of which is the quality of the studies included. Specifically, all studies included were noninterventional, and most not only were retrospective but also failed to present confounder-adjusted estimates. Moreover, there was a significant degree of variability in terms of what was deemed routine clinical practice among the studies included, not only with regard to the serum progesterone assays that were used but also in terms of the exogenous progesterone formulations, timing, and doses administered. Finally, although recognizing that the decision to subdivide the studies in regular intervals of circulating progesterone thresholds to define "low progesterone" was an elegant manner of performing the synthesis of this large number of studies using different thresholds, it came at the cost of arbitrarily considering "comparable" a rather loose interval of serum progesterone thresholds. All these limitations stress the need for future studies and should encourage clinics to reevaluate these findings in their own clinical setting to determine what would be the most appropriate threshold to define low serum luteal phase progesterone level for their patients.

It seems as if it is becoming more difficult to ignore the increasing amount of studies alluding to a potentially detrimental role of low circulating luteal phase progesterone levels on assisted reproductive technology outcomes. On one hand, for those who still opt to not to perform this measurement because of the lack of robust randomized controlled trials, although their concerns may be fair, the addition of more observational data available with a consistent finding may leave them more isolated in their decision and, ultimately, may even preclude researchers to ever accept the endeavor of conducting such a trial. For those already measuring the serum progesterone levels, this study may come as good news because it reinforces that the extra hassle may be worth it. There is also now a progressive shift of focus toward rescue strategies in those in whom the serum progesterone level is deemed low, including the use of combined therapy and/or alternative routes of administration, with an example also published recently in *Fertility and Sterility* (3). That said, although this search for the ideal rescue strategy may have the best of intentions, a hasty shift from "diagnosis" to "treatment" may leave out important information regarding the detailed mechanisms causing this apparent hindering of the luteal phase in some women, including the actual breath of the problem at hand and whether simple changes before FET could have avoided the issue altogether.

Findings such as these make one look back at so many previous randomized controlled trials that were once the backbone of our daily practice (i.e., comparing injectable

progesterone vs. micronized vaginal progesterone or natural FET cycles vs. artificial FET cycles) and ask "what would have the results been if the researchers had measured luteal serum progesterone"? Finally, only the future will tell whether such information may make the renowned differences across the Atlantic regarding LPS converge to what could ultimately one day become simultaneously the most effective and patient-friendly option available.

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https://doi.org/10.1016/j.fertnstert.2021.10.004

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