Systemic progesterone optimizes programmed frozen embryo transfer outcomes: the only Level I evidence still indicates intramuscular administration

Exogenous steroid hormones have induced endometrial receptivity since the early days of assisted reproductive technology (ART). Initially administered to women with complete ovarian failure, exogenous estrogen, and progesterone (historically administered intramuscularly) formed the foundation for successful donor oocyte programs. The stated purpose for replacing corpus luteum-derived progesterone was to replicate its direct uterine effects, rather than any broader systemic actions. Regardless, intramuscular (IM)-progesterone protocols achieved laudable success rates, particularly in donor egg ART, leading to their adoption for endometrial preparation and luteal support in frozen embryo transfer (FET) cycles.

Early adopters of IM progesterone recognized its ability to consistently maintain high serum progesterone levels. However, patients and clinicians sought alternatives to the discomfort of IM progesterone injections, prompting investigations into less invasive yet equally effective routes. Vaginal progesterone gained popularity for its patient-friendly administration, and more than a decade ago, an abundance of high-quality data demonstrated its equivalence to IM progesterone for luteal supplementation of endogenous corpora lutea in "fresh" embryo transfer, after ovarian stimulation and egg retrieval. The "First Uterine Pass Effect," a phenomenon by which vaginal progesterone administration yields high endometrial concentrations with lower serum levels, was postulated to "permit targeted drug delivery to the uterus, thereby maximizing the desired effects while minimizing the *potential* for *adverse* systemic effects" (emphasis added) (1).

Although vaginal progesterone supplementation is adequate with corpus luteum-derived, endogenous progesterone, multiple studies—bolstered by randomized controlled trials (RCTs)—have found it insufficient for optimal progesterone replacement in programmed FET and donor egg cycles. Retrospective studies have suggested suboptimal outcomes when serum progesterone concentrations <10 ng/mL were noted, in the setting of vaginal-only progesterone administration (2). Additionally, our large RCT (the Sustain RCT) demonstrated that vaginal progesterone alone was associated with significantly more miscarriages and fewer live births, compared with IM progesterone containing regimens (3). Together, these findings illuminate the indispensable role of systemic progesterone in achieving sustained implantation and ART success, highlighting the transformative power of high-quality RCTs in resolving longstanding clinical ambiguities.

Beyond this, Labarta et al. (4) showed that when low serum progesterone was noted after vaginal administration and subcutaneous (SubQ) progesterone was added, success rates were superior to that of a historical control group that underwent FET in the setting of low serum progesterone concentrations without the addition of SubQ progesterone. Although conclusions from this study ought be interpreted with caution, given the use of historical control group, the work by Labarta et al. (4), along with the other studies summarized in Melo et al. (3), entail an important logical inference: although vaginal progesterone provides high local uterine concentrations, the many-times replicated finding that low serum progesterone concentrations are associated with a reduction in sustained implantation indicates that systemic progesterone must have an important role in successful sustained implantation and ART success.

The corpus luteum naturally secretes progesterone (approximately 25 mg) into the bloodstream daily. Progesterone's effects extend beyond the uterus to include immunomodulatory effects that likely induce tolerance to the developing gestation. In terms of achieving these proposed extrauterine benefits of progesterone, many routes, dosages, and combinations of progesterone administration remain underexplored in ART. For instance, a well-powered and methodologically sound RCT by Wang et al. (5) found that micronized vaginal progesterone combined with oral dihydrogesterone yielded results comparable with IM progesterone in programmed FET cycles. Although dihydrogesterone is not currently available in the United States, and the study population by Wang et al. (5) and practice patterns differed significantly from those of the United States, the study points to the possibility that more patient-friendly modes of programmed progesterone administration may yet supplant the IM route.

Looking ahead, the anticipated introduction of SubQ progesterone in the United States offers a promising alternative. Assisted reproductive technology professionals must rigorously evaluate whether SubQ progesterone can match the reliability of IM progesterone in terms of systemic absorption and clinical outcomes. Until its efficacy is confirmed (relative to the gold standard of IM progesterone), practitioners should continue to prescribe IM progesterone in programmed FET protocols. Thankfully, a combined protocol of vaginal progesterone supplemented with IM every third day was noninferior to daily IM progesterone in terms of live birth and was preferred by patients (2).

As ART practices evolve, alternative routes such as SubQ progesterone or oral formulations combined with vaginal progesterone hold promise. However, clinical protocols must continue to prioritize systemic delivery of progesterone for programmed FET, as validated by the existing level I evidence. Specifically, until robust RCTs confirm the efficacy of alternative routes of delivery, IM progesterone remains the standard of care. At this point in the history of ART, one thing is clear—progesterone plays a vital role in sustained implantation, not

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only by direct induction of endometrial receptivity, but also via extrauterine effects.

Given that most of our patients experiencing infertility would do nearly anything to improve their probability of having an infant, every third day administration of IM progesterone is warranted, based on current level I evidence. We strongly desire to improve our patients' experience, which is why we have chosen to study alternative regimens to daily IM progesterone. That said, a successful outcome—taking home an infant—will improve their experience the most. To guide change in clinical protocols, Medicine, and particularly reproductive medicine, still relies primarily on the clarity provided by high-quality RCTs.

The Sustain study was an example of how an RCT can help to resolve longstanding uncertainties to benefit patients. The study not only highlighted the importance of systemic progesterone in programmed FET protocols, it also set a precedent for rigorously examining emerging alternatives such as SubQ progesterone. Moving forward, practitioners and researchers must continue striving to make RCTs more accessible and feasible, ensuring they remain the foundation on which medical advancements are built.

The lesson is clear: robust RCTs are not just tools for validating treatments—they are the cornerstone of meaningful progress in medicine, providing patients with the best chance of success and practitioners with the confidence to implement proven strategies.

CRediT Authorship Contribution Statement

Allison A. Eubanks: Writing – original draft. **Dominique de Ziegler:** Conceptualization, Writing – review & editing. **Kate Devine:** Conceptualization, Writing – review & editing.

Declaration of Interests

A.A.E. has nothing to disclose. D.d.Z. has nothing to disclose. K.D. has nothing to disclose.

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