Beyond the uterine first pass: optimizing programmed frozen embryo transfers. A mini-review

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With the greatly increased popularity of segmented in vitro fertilization and frozen embryo transfers, progesterone replacement strategies in programmed cycles are being reexamined. Bidirectionality and the limited capacity of the uterine first pass provide an explanation for disconnects between the endometrial and serum levels when either vaginal or intramuscular progesterone is used alone. Whereas monotherapy departs from the physiology of spontaneous pregnancies, combined therapy provides physiologic replacement while minimizing the number of injections. (Fertil Steril Rep® 2021;2:256–60. ©2021 by American Society for Reproductive Medicine.)

Key Words: Uterine first pass, progesterone replacement, programmed transfer cycles, frozen embryo transfer

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In the United States, transfers of cryopreserved embryos (FETs) are now the most common assisted reproductive technology (ART), accounting for approximately 70% of treatment cycles (1). Many, if not most FETs, are performed in programmed cycles without a corpus luteum following the protocols originally developed for the transfer of fresh embryos created with donor eggs to agonadal women for whom no other options existed. These protocols were widely adopted for FETs in women with ovarian function without specific validation, resulting in satisfactory live birth rates that may mask potential problems. In the absence of a corpus luteum, progesterone (P) replacement presents a clinical challenge on account of both the large quantity of hormone required and the long duration of treatment. In natural conceptions, P production at implantation and in the first trimester is

approximately 50–55 mg/day with circulating levels in the 25–30 ng/mL range (2–4), which represents the physiologic sweet spot for early pregnancy. One might have expected the programmed cycles to aim for these physiologic levels, but this has not been the case. In view of the greatly expanded use of cryopreserved embryos in much more heterogenous origin than just donor eggs, a reexamination of the programmed cycle protocols may be of interest.

REVERSIBILITY AND LIMITED CAPACITY OF THE UTERINE FIRST PASS

In in vitro fertilization (IVF) with transfer of fresh embryos and multiple corpora lutea, luteal supplementation with either vaginal or intramuscular (IM) P is equivalent (5). However, conclusions from ART cycles with a

corpus luteum cannot be extrapolated to programmed FET cycles, which lack this endogenous source of P and are thus entirely dependent on exogenous replacement. The vaginal route of P administration was initially explored with believe in replacing painful IM injections with less invasive formulations, thus lessening the burden of infertility care. The pioneering study by Miles et al. (6) demonstrated that, under steady-state conditions, vaginal administration of micronized P (800 mg/day in 4 doses) resulted in a high endometrial tissue content of 11.5 ng/mL but subphysiologic serum levels of 11.9 ng/mL, whereas IM injections (100 mg/day in 2 doses) achieved a high serum level of 69.8 ng/mL but a lower endometrial content of 1.4 ng/mL. Endometrial biopsies revealed comparable secretory transformation in both groups, reflecting a low threshold for this effect (7–9). The paradoxical mirror-image disequilibria between the endometrial and serum levels arises whenever either the vaginal or the IM route of P administration is employed exclusively, but they have not been adequately explicated in the literature. Instead, a curious dogma proclaiming the irrelevance of the P serum level in ART emerged and

https://doi.org/10.1016/j.xfre.2021.06.008

gained widespread acceptance despite running counter to the physiology of natural pregnancy, which reflects 200×10^6 years of mammalian evolution.

Much of the research on the absorption of vaginal P was undertaken in the late 1990s and early 2000s in connection with the development of proprietary preparations, such as Crinone 8% vaginal gel (Actavis Pharma, Inc., Parsippany, NJ) and Endometrin 100 mg inserts (Ferring Pharmaceuticals Inc., Saint-Prex, Switzerland), and was financed largely by the pharmaceutical industry. A series of elegant studies described a novel gradient-dependent countercurrent passive diffusion system, dubbed the uterine first pass, which was shown to transport P directly from the vaginal venous plexus to the uterine arteries via a countercurrent mechanism (10, 11). Both disconnects between the endometrial and systemic P levels with an exclusive use of either route of administration can be neatly accounted for by the reversibility and limited capacity of the uterine first pass.

With the vaginal route, the quantity of P delivered achieves a high tissue content within the endometrium but is insufficient to achieve physiologic serum levels in the much greater volume of distribution of the systemic circulation. With IM P administration, the surprisingly low endometrial content despite high circulating levels arises from reversal of the gradient with consequent reversal of diffusion from the uterine artery with high P levels to the vaginal veins, which now carry blood depleted of P after passage through the vagina (Table 1). In addition, limited capacity results in the blunted dose response of P levels with the vaginal route: serum levels do not rise proportionately to doses ranging from 180 mg/day to 800 mg/day but instead remain stubbornly capped at 10–15 ng/mL (5, 10, 12). From a practical point of view, this means that increasing the vaginal dose cannot raise the circulating levels into the physiologic range, and that lower doses achieve the same systemic effects as higher doses. In marked contrast to P, vaginal estradiol, which is given at 100-fold lower doses of 2–8 mg/day, produces supraphysiologic serum levels, because this quantity of hormone falls within the carrying capacity of the uterine first pass (13).

The physiologic range for early pregnancy has been defined for serum levels, but the qualitative endometrial effect of secretory transformation is not quantifiable (3, 5, 6, 9). Studies of spontaneous viable pregnancies and clinical abortions established the mean physiologic P levels at 25.5 and 14.1 ng/mL, respectively. These studies constitute the biologic bedrock for defining three ranges of circulating P levels in early pregnancies as physiologic (20–30 ng/mL), subphysiologic (<20 ng/mL), and supraphysiologic (>30ng/mL) (Table 1). Although subphysiologic levels are of clinical concern because of the risk of pregnancy loss, supraphysiologic levels raise no such concern, because once all the receptors are saturated, the additional hormone exerts no further effect. Supraphysiologic levels on a constant replacement protocol indicate nascent placental secretion, which allows tapering of the exogenous support.

Archer et al. (12), employing vaginal suppositories, which are notorious for rapid dissolution and leakage, postulated that vaginal absorption is the rate-limiting step in the uterine first pass. This hypothesis, however, is inconsistent with Buletti et al.'s (14) observations in an ex vivo uterine perfusion model, which demonstrated avid vaginal absorption. In the uterine perfusion model, the vaginal cuff attached to the extirpated organ was covered with P in oil. Under steady-state conditions, samples of the myometrium, endometrium, and vagina revealed P contents of approximately 2.6, 1.8, and 60 ng/mg of tissue, respectively. Because the vaginal tissue content was 23 times higher than the myometrial content and 33 times higher than the endometrial content, these results lend further support to our hypothesis that the limited capacity of the uterine first pass is because of the countercurrent mechanism itself rather than because of limited vaginal absorption. Limited vaginal absorption in addition fails to account for the low endometrial tissue level when IM P is given alone (6).

BEYOND THE ENDOMETRIUM

Because circulating P levels as low as 0.9 ng/mL induces secretory changes in the endometrium, why does P rise to as high as 180 ng/mL at term? (2–4, 7–9). Most ART studies focused on embryo implantation and the endometrium with little attention to other target organs for P such as the myometrium, placental blood vessels (15), and extrapelvic tissues including the immune system (16). After implantation, however, P's major role is to induce myometrial quiescence so as to permit a >400-fold growth in uterine size during pregnancy without provoking uterine contractions, which risk expulsion of the conceptus (2). To do so, P, aided by relaxin from the corpus luteum, must counterbalance the stimulatory effects of not just estradiol but in addition oxytocin and prostaglandins. Whereas the secretory transformation of the endometrium is irreversible, and once it occurs, it leads either to implantation or menstruation but cannot revert to proliferation, the myometrial contractility depends on a dynamic balance between stimuli and inhibitors, a balance that changes during the menstrual cycle and in the course of pregnancy. The stimuli of contractility peak during coitus and orgasm at ovulation, inducing frequent strong uterine contractions that aid in the ascent of sperm within the female reproductive tract, including preferential entry into the oviduct ipsilateral to the dominant follicle (17). The long-standing posttransfer advice for patients to refrain from orgasm, which is associated with the release of oxytocin and vigorous uterine contractions, as well as ejaculation, which deposits prostaglandin-laden semen in the vagina, aimed to minimize these known stimuli of myometrial contractility in the periimplantation period.

In traditional IVF with transfer of fresh day 2 embryos, the pregnancy rates correlated directly with the circulating P levels and inversely with the frequency of uterine contractions (18). The average frequency of uterine contractions two days after retrieval was 4.3/minute while, with multiple corpora lutea, the P serum level was supraphysiologic at 68–111 ng/mL without exogenous supplementation. Three days later, during transfer of fresh day 5 blastocysts, the frequency of uterine contractions was markedly reduced to 1.5/

TABLE 1

The progesterone levels in the serum and the endometrium with the vaginal and parenteral routes of administration in programmed frozen embryo transfer cycles and in natural pregnancy.

Progesterone level site	Vaginal progesterone only	Parenteral progesterone only	Combined protocol	Natural pregnancy
Serum	Subphysiologic	Supraphysiologic	Physiologic	Physiologic
Endometrium	Supraphysiologic	Physiologic	Physiologic	Physiologic
Uterine first pass: direction of diffusion	From the vaginal venous plexus to the uterine arteries	From the uterine arteries to the vaginal venous plexus	Variable	Not applicable

Chetkowski. Uterine first pass. Fertil Steril Rep 2021.

minute from a peak of 4.4 contractions/minute on the day of human chorionic gonadotropin (hCG) trigger (19). At blastocyst transfer, the mean P level was in addition supraphysiologic at 134.5 ng/mL without supplementation. These stratospheric P levels in the early luteal phase of traditional IVF cycles with hCG trigger raise the question of whether exogenous supplementation needs to be started as early after retrieval as is commonly done, or whether it can be added later in the luteal phase to counteract the precipitous fall in endogenous production in treatment employing gonadotropin-releasing hormone analogs. The inverse correlation between the embryo implantation rate and the frequency of contractions was recently confirmed in programmed FET cycles (20). The observation that a significant decrease in the frequency of contractions does not occur until five days after egg retrieval is consistent with the relatively slow mechanism of action of steroid hormones, which require both genomic transcription and translation, and correlates better with the total exposure over time, expressed as the area under the curve, than with the instantaneous levels (8).

Vigorous uterine contractions at transfer might expel the embryo from the endometrial cavity, particularly if the procedure is technically difficult (21). Whereas all the studies of uterine contractility to date selected young subjects with normal uteri, age-associated uterine abnormalities, such as fibroids and adenomyosis, are likely to exacerbate myometrial irritability and interference with embryo implantation in older women. After nidation, excess contractility might contribute to abnormal placentation, pregnancy loss, abnormal bleeding, and other obstetrical and perinatal complications observed in ART pregnancies (22).

The ability of the vaginal route of administration to deliver a sufficient quantity of P to saturate the myometrial receptors and to induce uterine quiescence remains uncertain. In premenopausal women, the mean volume of the myometrium is 14.4 to 25.6 times greater than that of the endometrium, depending on the phase of the menstrual cycle and the method of measurement (23). Whereas in the ex vivo uterine perfusion model, the myometrial P content was higher than that of the endometrium, but that level was achieved gradually after several hours (14). In addition, the uterine perfusion model is liable to overestimate the myometrial content, because only the uterine vessels are cannulated in the extirpated organ, whereas in situ the uterus receives blood not just from the uterine arteries but in addition from the uterine branches of the ovarian arteries, which together form a dense anastomotic network in the mid-corpus. Thus, in the living uterus, P delivered by the uterine arteries through the uterine first pass is diluted by blood from the ovarian arteries, which do not partake in the uterine first pass (10). It has been hypothesized that, in programmed cycles, vaginal P might not suppress uterine contractions as efficiently as parenteral hormone (24). However, this intriguing inkling did not survive a recent randomized controlled trial (RCT) that found a comparable frequency of contractions with both routes of administration (20).

IS VAGINAL PROGESTERONE ALONE REALLY ADEQUATE FOR REPLACEMENT?

Despite the widespread use of vaginal P alone, particularly in Europe, reports of its clinical efficacy are at best mixed. Vaginal-only protocols and the dogma of the irrelevance of the P serum levels to treatment outcomes have recently come under assault on several fronts. Measurement of the P level before embryo transfer in programmed cycles appears

TABLE 2

Self-pay unit prices for progesterone preparations at four retail pharmacies in May 2020 in the United States.

Medication	Average price ($)	Price range ($)	Replacement dose	Average cost for 60 Days ($)
Crinone 8% (90 mg) vaginal gel	35.42	30.50–42.00	One, twice per day	4,250.40
Endometrin 100 mg	7.50	6.10–8.15	One, three times per day	1,350.00
Prometrium 200 mg	17.38	3.19–26.45	Two, twice per day	4,171.20
Generic micronized P 200 mg	1.66	0.98–3.59	Two, twice per day	398.40
progesterone in sesame oil 50 mg/mL (1 mL)	4.82	4.40–4.99	1 mL, once per day	290.40

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to be of value with both the vaginal and parenteral routes of administration (25–28). These studies indicated that from 30% to 50% of women have suboptimal P serum levels before the embryo transfer and compromised outcomes (26–27). Furthermore, a recent prospective cohort study provided evidence of patients using the vaginal-only protocol who had suboptimal P serum levels one day before FET benefited from the addition of just 25 mg of subcutaneous P daily with normalization of pregnancy and live birth rates (28). In a well-designed, three-armed RCT of blastocyst-stage FETs, a planned interim analysis demonstrated that women conceiving on Endometrin (200 mg twice per day) experienced a higher pregnancy loss rate and lower ongoing pregnancy rate than those of women conceiving on either IM or combined vaginal/IM P (29). Consequently, the vaginal-only arm of the study was discontinued early.

In addition to supporting more physiologic P replacement protocols in programmed cycles, this important RCT bridged the artificial gap in the literature between ART and early pregnancy care. Progesterone plays a key role in evolving pregnancies long after embryo transfer. A Cochrane review of P support indicated that it was beneficial in women with threatened abortion (30). Patients with unexplained recurrent pregnancy losses had improved birth rates with a midluteal injection of hCG to boost P production by the corpus luteum (31).

Choice of a Vaginal Preparation

Most studies compared a vaginal preparation with IM injections, which remain the de facto gold standard. In the absence of randomized head-to-head comparisons between different vaginal products, clinics have no rational basis for requiring patients to use a particular preparation. Without randomization, even the exact same protocol leads to contradictory conclusions. A retrospective cohort study of women undergoing transfer of day 3 cryopreserved embryos found lower pregnancy and live birth rates with Crinone 8% vaginal gel twice per day compared with those of IM P (50 mg/day) (32). However, a second cohort study using the exact same protocols with vitrified/warmed blastocysts found no differences in pregnancy, spontaneous abortion, and live birth rates (33). In the absence of valid efficacy data, patients act rationally when they base their choice on price. Table 2 lists the average retail costs of P preparations currently available in the United States at four infertility pharmacies. The unit prices range from $1.66 for generic micronized P capsules to $35.42 for Crinone 8% vaginal gel. With common replacement dosages, the total average cost for 60 days ranges from $290.40 to $4,250.40. For the two most expensive vaginal preparations, the medication cost for 60 days exceeds the cost of a FET in our program.

OPTIMIZING PROGRAMMED FET CYCLES

Although we harbor no illusions that a single best P replacement protocol will ever be devised, let alone adopted universally, combining vaginal and parenteral P seems more likely than monotherapy to meet the twin goals of emulating physiology and lessening the burden of care.

The short half-life (6–8 hours) and variable absorption of most vaginal preparations together with the limited capacity of the uterine first pass all lead to subphysiologic serum levels, which impact target organs other than the endometrium. With its reliable absorption and long half-life of 22–24 hours, P in oil constitutes an excellent complement to vaginal preparations in as much as it provides a "floor" below which tissue levels do not fall while vaginal P helps space out the painful injections. Addition of IM P to vaginal P (Endometrin) improved FET outcomes (34), whereas older donor egg recipients may benefit from addition of vaginal P to IM injections (35).

The optimal dose and minimum frequency of parenteral P in combined protocols have not been established. First order kinetics dictate that 50% of the IM dose is eliminated in 24 hours, 75% in 48 hours, and 87.5% in 72 hours. At Alta Bates, our current protocol consists of P in oil (75 mg [1.5 mL]) every 48 hours with micronized P (200 mg three times per day), which reduces the number of injections by 50% but the dose by only 25% compared with the standard protocol of 50 mg (1.0 mL) daily. The just published online second report from Devine et al.'s (36) RCT demonstrated comparable live birth rates with a combined protocol using P in oil (50 mg every 72 hours) and an all IM protocol of P (50 mg/day), both of which were superior to a vaginal-only protocol. Alvarez et al. (28) used just 25 mg/day of aqueous P to normalize the live birth rates in women who had low circulating P level with a vaginal protocol. A subcutaneous P (Prolutex, IBSA, Lugano, Switzerland) awaits approval in the United States but will offer a welcome alternative to IM injections. With a half-life of 17.2 hours, or 6 hours shorter than that of IM P in oil, Prolutex may require more frequent injections than P in oil, but they may be more convenient and better tolerated (37). Considering the large quantity and long duration of P replacement, having multiple complementary routes of administration appears advisable.

CONCLUSION

Finally, programmed cycles may well benefit from the addition of posttransfer monitoring, which can provide for evidence-based dose adjustment and timely termination of the replacement on detection of adequate placental production of P. Rather than following a "one-size-fits-all" approach with a single protocol, the replacement can be tailored to an individual patient's characteristics including her age, weight, genetic profile, hormone metabolism, and even personal preferences. More than one in three women conceiving through FET in programmed cycles at Alta Bates prefer IM injections to micronized P capsules. Although implementation of more personalized protocols is time-consuming and will no doubt meet with resistance by many clinics, it in addition holds the promise of improved outcomes for mothers and their offspring.

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