Luteal-phase support in assisted reproduction technology

INTRODUCTION

- Controlled ovarian stimulation (COS) is the single most effective measure ever undertaken for increasing assisted reproduction technology (ART) outcomes. COS, however, disrupts the proper support of the corpus luteum (CL) at the level of the anterior pituitary by altering the pulsatile release of luteinizing hormone (LH) (1). There is now a general consensus professing that progesterone supple- mentation must be provided in ART, at least during the first weeks following oocyte retrieval

LUTEAL FUNCTION IN ART
Physiology of CL function

- After ovulation is induced by the mid-cycle LH surge or a triggering dose of human chorionic gonadotropin (hCG; 5000–10,000 IU), the luteinized granulosa cells collec- tively forming the CL start producing estradiol (E2) and progesterone. The hormonal activity of CL is tightly con- trolled by the pulsatile production of LH by the anterior pituitary. During the mid-luteal phase of the menstrual cycle, the daily production of progesterone is of approxi- mately 25 mg/24 hours. In a seminal study, Filicori et al. reported the results of serial (every 10 minutes) blood sam- pling (2): pulsatile LH secretion (one pulse approximately every 3 hours) is tightly accompanied by a progesterone pulse. Based on these data, the through levels (in between pulses) are of approximately 5 ng/mL (2).

Disruption of CL in ART

- Gonadotropin-releasing hormone (GnRH) analogs, agonists, and antagonists
- Excessive levels of E2 induced by COS The replacement of the LH surge by a triggering dose of hCG
- The net result of these effects is an insufficient pro- duction of progesterone by the CL, which compromises embryo implantation and development

PROGESTERONE ADMINISTRATION
Injectable preparations

- . Injectable proges- terone preparations have existed since pre-ART times .Because progesterone is poorly soluble in water, all prepa- rations available until recently were in an oil base, which mandates intramuscular (i.m.) administration. The latter are notoriously painful and a source of possible sterile abscesses. The oil base—sesame or peanut oil—prepara- tions were put on the market and approved for treating threatened abortions, an indication that does not warrant such treatment anymore. Practically, therefore, all oil base injectable progesterone preparations available are used in ART off-label.
- Injectable progesterone preparations have been vali-
- dated in numerous investigator-initiated trials. Injectable progesterone was found to be effective for LPS in ART and, in case of complete absence of endogenous progesterone, in donor egg and frozen ET (FET) models.

Impossible oral and transdermal progesterone

- Progesterone cannot be administered orally in ART due to intense hepatic metabolism during the first liver pass (7). In micronized form (nowadays, all preparations are micron- ized) progesterone is readily and totally absorbed follow- ing oral ingestion, but is highly metabolized in the liver. Contrary to the situation prevailing with E2, liver metabo- lism effects cannot be overcome by simply increasing the doses of progesterone administered. In the case of E2, daily administration of doses 100-times higher than the daily production by the ovary reliably succeeds in dupli- cating the serum levels and peripheral effects encountered in the menstrual cycle. Oral E2, albeit at increased doses, is therefore usable for E2 administration in ART. This is not the case for progesterone, however. In prior work, oral doses of progesterone of up to 1 g/24 hours failed to reli- ably induce pre-decidual changes in the endometrium,

- as seen in the luteal phase of the menstrual cycle (8). Conversely, however, oral progesterone can be effectively used for preventing endometrial hyperplasia in hormonal treatments of menopause. Indeed, oral progesterone (or its metabolites) effectively exerts anti-proliferative effects on the endometrium. Hence, despite a lack of secretory trans- formation, oral progesterone effectively protects from the risk of endometrial cancer.
- E2 can be successfully administered transdermally using either adhesive systems ("patches") or gel prepara- tions. The advantages of this route of administration—it avoids hepatic metabolism—sparked interest for doing the same with progesterone. Unfortunately, progesterone cannot be administered transdermally and probably never will be. First, the doses that need to be administered for matching CL production (25 mg/24 hours in the mid- luteal phase) are several orders of magnitude larger than the daily production of E2 (from 0.05 to 0.5 mg/24 hours). This would require that skin systems be much too large for any practical application. Second, the skin is rich in 5α-reductase, an enzyme that is capable of inactivating
- progesterone, thus hampering any possible efficacy. While
- transdermal administration of synthetic progestins exists (for contraception), transdermal progesterone is not avail- able for LPS in ART.

Vaginal progesterone

- Starting from the early days of ART, progesterone has been administered vaginally primarily for avoiding the side effects of i.m. injections (9). With the oral and trans- dermal administration of progesterone not being possible, the vaginal route indeed appeared to be the only practical alternative remaining.
- Early work with vaginal progesterone demonstrated the great efficacy of its endometrial effects. Despite relatively low plasma levels being achieved (8,9), biop- sies reliably showed complete pre-decidual changes of the endometrial stroma (8). The high efficacy of vaginal progesterone led to its widespread use for LPS and FET preparation in ART.
- Over the years, various vaginal progesterone prepa- rations were developed and approved for use for LPS in ART, and for priming endometrial receptivity for FETs

New subcutaneous progesterone preparation

- The search for practical options that avoid the painful i.m. progesterone injections while retaining reliable efficacy led to the development of what was seemingly impos- sible: an aqueous progesterone preparation. Indeed, an aqueous progesterone preparation available for subcu- taneous administration was developed by encapsulating progesterone in cyclodextrin .Cyclodextrin, a starch residue commonly utilized in the pharmaceutical and food industry, enhances the polarity—and hence water solubility—of substances. Upon entering the body, cyclo- dextrin is readily digested, liberating free progesterone .The product developed, Prolutex®, is now commer- cially available in numerous countries and constitutes a new therapeutic alternative to i.m. injections and vaginal

DURATION OF PROGESTERONE TREATMENT

Onset of treatment

- The impairment of progesterone production encountered in COS used in ART primarily affects the mid-to-lateluteal phase. Early in the history of ART, certain authors had claimed that LPS could therefore be initiated only a few days after oocyte retrieval. The recommendation for late onset of LPS was also motivated by the fear in these authors' mind that early LPS might advance the secretory transformation of the endometrium, causing an early closure of the window of receptivity). Today, these fears— however intellectually founded—have been proven not to be realized practically in everyday ART.
- There is now a general consensus for favoring an early onset of LPS in ART on the evening of oocyte retrieval or the day after. This is in part motivated by the fact that the uterus-relaxing properties of progesterone tend to reduce uterine contractions (UCs) at the time of ET .

Termination of treatment

- The prevailing hypothesis for the patho-physiology of luteal-phase dysfunction and hence the need for LPS in ART contends that it is the normal pituitary support of CL that is disrupted. Following this principle, LPS would only need to be administered until the positive pregnancy test. Later, it is indeed the hCG produced by the developing embryo, not the anterior pituitary, that sus- tains proper CL function. In spite of this seemingly sim- ple principle, it has been common practice for most ART centers to continue LPS until 10 weeks of pregnancy

E2 ADMINISTRATION

- E2 pretreatment is mandatory, however, for priming endometrial receptivity for FET .Decades of ART and donor egg ART activity have revealed that E2 administra- tion is relatively simple, effective, and extremely forgiving. The daily oral administration of 4–8 mg of E2 reproduces the serum levels and peripheral effects of E2 as seen in the menstrual cycle. The liver, however, is exposed to mark- edly higher quantities of E2, as it sees the whole amount administered, which far exceeds what is normally pro- duced in the menstrual cycle. The excess liver exposure due to the first liver pass effect inherent to oral adminis- tration may cause problems in certain individuals, nota- bly in women at higher risk of veno-thromboembolism accidents. In these individuals, E2 should not be adminis- tered orally if at all possible and/or preventive medication (e.g., low-molecular-weight heparin) should be provided simultaneously.

FROZEN ETs
The donor egg lesson

- Today, we know that the endometrium primed by E2 and progesterone only is as receptive as it possibly gets, with implantation rates that can be equaled in the natural cycle, but never surpassed. This indicates that everything else produced by the ovaries during the menstrual cycle (peptides, androgens, etc.) either does nothing or possibly harms endometrial receptivity.
- The donor egg model laid out the groundwork that allowed us to understand and apply practically the prin- ciples governing the hormonal control of endometrial receptivity. From the early days of donor egg ART, one has been struck by the fact that recipients of donor egg ART generally had better results than their counterparts under- taking regular ART. This has led us to suspect that COS used in ART exerts negative effects on endometrial recep- tivity not seen in donor egg ART.

Estrogen priming and progesterone-driven receptivity

- Endo- metrial receptivity depends on two necessary hormonal effects:
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- *Estrogen priming*: This is necessary for allowing the indispensable endometrial proliferation and the E2-dependent development of progesterone receptors. *Time-related, progesterone-induced secretory changes of the endometrium*: The secretory transformation of the endometrium is induced by progesterone. From the early days of reproductive endocrinology, we know that these changes—taking place in the endometrial glands and later stroma—are time dependent and relatively progesterone dose and serum level independent.
- A wealth of data that accumulated through four decades of ART activity have by and large confirmed and expanded upon these early but still valid concepts

No need for ovarian suppression

- When E2 and progesterone replacement cycles were intro- duced for priming FETs (based on the strong results of donor egg ART), ovarian function was commonly sup- pressed using a GnRHa (25). Later, it became evident that E2 alone sufficed if initiated early enough (on cycle day 1 or, even better, a few days before menses) for suppress- ing the inter-cycle follicle-stimulating hormone elevation and preventing follicular recruitment (26,27). Today, most centers use E2 and progesterone treatment regimens for planning FETs, as these have been found to be equiva- lent yet simpler than timing FETs in the menstrual cycle. Generally, FET priming implies an E2 priming phase of two to three weeks followed by timed progesterone admin- istration. In principle, a single clinical control is necessary at the end of the E2-only priming phase. This is done for asserting proper estrogenization (endometrial thickness ≥7 mm) and ensuring that no exposure to progesterone had taken place (plasma progesterone ≤1.5 ng/mL). The timing of ETs is scheduled on the third to fourth day and fifth to sixth day of progesterone exposure for cleaving- stage and blastocyst transfers, respectively. We personally prefer edging on the early side—the third and fifth days of progesterone exposure for cleavage-stage and blastocyst transfers, respectively—as this was found to be equally effective and possibly more forgiving.

The window of endometrial vulnerabilitY

- Possible negative effects of COS on the endometrium were first suggested by witnessing higher pregnancy rates in donor egg ART as compared to the fresh ET counterparts. Today, we realize that there is more to these effects of COS on the endometrium than merely a decrease in embryo implantation rates. Indeed, alterations of endometrial development may exert durable effects on the quality of placentation and, in turn, obstetrical development of the fetus. In rat models, poor placentation generated by trans- ferring blastocysts in a hyperstimulated endometrium led to lower-weight pups and placentas

CONCLUSION

- LPS has been proven to be necessary in ART. LPS is ideally started early, on the day of oocyte retrieval or the day after, as this minimizes the risk that UCs adversely affect ART outcome. LPS consists of delivering supplemental doses of progesterone either by injectable preparation or vagi- nal administration. The recent availability of an aqueous progesterone preparation allowing self-administration by subcutaneous injections provides women who dislike vaginal administration with an alternative. It has been amply documented that LPS can be stopped after the first positive ultrasound finding or even positive pregnancy test. Yet many groups continue to prescribe LPS for longer than necessary, in part because this is necessary in FETs, as many fear that having two distinct regimens for fresh ART and FET might cause confusion.