The Future of Luteal Phase Support in ART and the Role of Dydrogesterone

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INTRODUCTION

In vitro fertilization (IVF) treatment routinely involves ovarian stimulation (OS) with gonadotropins in combination with GnRH analogs to prevent premature luteinization and ovulation (1). However, it is well-established that the use of GnRH analogs during OS may impair corpus luteum function, resulting in suboptimal endometrial receptivity (2). Thus, luteal phase support (LPS) with progestins is an essential part of IVF treatment and is mandatory to support implantation and to increase pregnancy rates after fresh embryo transfer (3).

TYPE OF PROGESTERONE AND ROUTE OF ADMINISTRATION

Progestins can be administered using various routes, either vaginally, intramuscularly (IM), rectally, orally, or subcutaneously, with differential impact on the pharmacokinetics of progestins. Indeed, serum progesterone (P) levels are higher when progestins are administered using the IM route compared to the vaginal one. On the other hand, although micronized P capsules had initially been developed for oral use, they can be administered vaginally, offering an effective alternative to oral and IM injections: serum P concentrations may be lower after vaginal compared to IM administration, but endometrial P levels are higher because of the uterine first pass effect, while several disadvantages of the IM route (i.e., injection site pain and discomfort, risk of infection) are avoided (4). On a similar note, vaginal micronized P is preferred over oral administration due to the rapid absorption and avoidance of the first-pass metabolism (5, 6). However, there are a number of downsides to the vaginal route of P administration, since vaginal irritation, discharge and bleeding may occur (7). Furthermore, suboptimal serum P levels in a subgroup of women who are prescribed vaginal P may be associated with reduced pregnancy rates (8). Therefore, vaginal micronized P administration should not be seen as a panacea.

In this regard, the concept of oral progestin administration in assisted reproduction technology (ART) has recently been revitalized, given that dydrogesterone (6-dehydro-retroprogesterone) has been extensively used for the treatment of other conditions associated with P deficiency since the 1960s (9). Dydrogesterone is a stereo-isomer of P, with an additional double bond between carbons 6 and 7, characterized by a better oral bioavailability and higher specificity for P receptors compared with oral micronized P (10, 11). A recent study demonstrated that after natural conception dydrogesterone supplementation from 6 to 20 weeks of gestation significantly reduced the incidence of preeclampsia (PE) in high-risk patients (12), while these findings were replicated by...
another retrospective study showing a reduction in PE rate after dydrogesterone supplementation in assisted reproductive techniques and intra-uterine insemination (13).

Clinical Studies Evaluating Dydrogesterone in Fresh Cycle IVF
Several small-scale clinical studies have shown that oral dydrogesterone is at least as efficacious as micronized vaginal progesterone in supporting pregnancy following fresh embryo transfer (14–16). These findings revived the interest in oral dydrogesterone for LPS and paved the way for large Phase III prospective RCTs (Lotus I and Lotus II studies), which led to the recent approval of oral dydrogesterone for LPS in IVF–ART.

In particular, Lotus I was an international Phase III non-inferiority RCT including 1,034 patients undergoing IVF and fresh embryo transfer, which showed that dydrogesterone 30 mg (10 mg three times daily) resulted in comparable ongoing pregnancy rates (pregnancy rates at 12 weeks' gestation of 37.6 and 33.1% in the oral dydrogesterone and micronized vaginal P group, respectively) compared to vaginal micronized P 600 mg (200 mg three times daily) (17). Similarly, Lotus II RCT compared oral dydrogesterone 30 mg (10 mg three times daily) with 8% micronized vaginal P gel (90 mg once daily) and demonstrated non-inferiority, with ongoing pregnancy rates at 12 weeks' gestation of 38.7% in the oral dydrogesterone group and 35.0% in the micronized vaginal progesterone gel group (18). The main conclusion of the two RCTs was that oral dydrogesterone is safe (no evidence for an increased risk for fetal malformation), well-tolerated and as efficient as vaginal P.

Clinical Studies Evaluating Dydrogesterone in Frozen Embryo Transfer Cycles
Frozen-thawed embryo transfer (FET) has become an increasingly important part of IVF treatment, with large clinical trials and meta-analyses demonstrating similar live birth rates to those associated with fresh embryo transfer (19). To date, several methods of endometrial preparation for FET have been developed, with hormone replacement therapy (HRT)-FET cycles being the most commonly used, in view of the reduced need for treatment monitoring and easier scheduling. In HRT-FET cycles estrogen and progesterone are administered consecutively, in order to mimic the endocrine conditions of the endometrium of a normal menstrual cycle. However, from a physiological point of view, LPS in HRT-FET is completely different compared to LPS in a fresh IVF cycle due to the lack of

TABLE 1 | Overview of evidence of dydrogesterone use in HRT-FET cycles.

| Study                  | N   | Study design | LPS in HRT-FET                                                                 | Embryo stage                                      | Outcome                                                                 |
|------------------------|-----|--------------|-------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------|
| Zarei et al. (22)      | 400 | RCT          | 400 mg MVP 2x/d vs. 10 mg DYD 2x/d vs. 10 mg DYD 2x/d + 0.1 mg GnRHa vs. 10 mg DYD 2x/day + 1500 IU hCG | Cleavage stage                                    | CPR, 20, 9, 25, and 17% (p = 0.03)                                      |
|                        |     |              |                                                                               |                                                   | OPR, 18, 9, 3, and 17% (p = 0.07)                                      |
|                        |     |              |                                                                               |                                                   | MR, 18.1, 35.7, 14.8, and 19.1% (p = 0.84)                               |
| Alahmad et al. (24)    | 314 | Retrospective | MVP 600 mg/day of 90 mg vs. DYD 10 mg 3x/day                                 | 2PN                                               | Cumulative CPR: Difference: 1.4%, 95% CI: (−9.4 to 12.6), p = 0.80        |
|                        |     |              |                                                                               |                                                   | CPR of first FET: Difference: −3.2%, 95% CI: (−12.8 to 7.4), p = 0.54    |
| Guo et al. (21)        | 529 | Retrospective | DYD 10 mg 4x/day vs. IM P4 60 mg/day                                         | Cleavage stage/blastocyst                         | CPR, IR, MR, EPR, CPR, DR                                               |
|                        |     |              |                                                                               |                                                   | no significant difference                                              |
| Rashidi et al. (23)    | 180 | Pilot RCT    | IM P4 50 mg 2x/d vs. DYD 20 mg 2x/d vs. MVP 400 mg 2x/d                     | 95% cleavage stage                                | CPR, MR, LBR                                                           |
|                        |     |              |                                                                               |                                                   | no significant difference                                              |

LPS, luteal phase support; HRT, hormone replacement therapy; FET, frozen embryo transfer; RCT, randomized controlled trial; MVP, micronized vaginal progesterone, DYD, dydrogesterone; GnRHa, gonadotrophin releasing hormone agonist; hCG, human chorionic gonadotrophin; IM P4, intramuscular progesterone; PN, pronuclei; CPR, clinical pregnancy rate; OPR, ongoing pregnancy rate; MR, miscarriage rate; IR, implantation rate; EPR, ectopic pregnancy rate; DR, delivery rate; LBR, live birth rate.
ovulation and absence of endogenous corpora lutea, suggesting that transformation of the endometrium into a receptive state for the implanting embryo is completely dependent on exogenous P supplementation (20).

While there is robust evidence demonstrating the efficacy of oral dydrogesterone for LPS in fresh IVF cycles as mentioned above, very few small studies using inconsistent doses have evaluated the role of dydrogesterone in HRT-FET cycles ([21–24]; Table 1). In the only RCT performed up to date, Zarei et al. (22) reported lower pregnancy rates in the oral dydrogesterone group compared to the micronized vaginal P group, using doses of 20 and 800 mg, respectively. However, the lack of data with regard to the optimal dosing of oral dydrogesterone in FET-HRT, highlights the need for further studies. In view of the advancing understanding of the impact of an absent corpus luteum in FET-HRT cycles and the associated elevated risk for PE (25), dydrogesterone with its potential immunomodulatory effects (26) represents an interesting research track. Of great importance will be the development of a clinically applicable dose monitoring test for dydrogesterone and/or its metabolites, as an optimal LPS presumably lies in its individualization (8).

CONCLUSION

Collectively, there is evidence that dydrogesterone has high oral bioavailability and specificity for P receptors (27), suggesting that it is effective at a dose 10–20 times lower than that of micronized P (25). Dydrogesterone has a good safety and tolerability profile with few side effects, making the ideal candidate for LPS in ART. Oral dydrogesterone is as effective as vaginal progesterone for LPS in women undergoing fresh IVF, whilst more evidence is warranted for its use in HRT cycles. The well-known widespread preference of women for an oral compound may pave the way for dydrogesterone to become the new standard. Furthermore, preliminary observations showing a decreased risk of PE after dydrogesterone supplementation in natural and intrauterine insemination cycles (12, 13) may be of paramount value in HRT-FET cycles, which are known to have a higher incidence of PE (28).

AUTHOR CONTRIBUTIONS

All authors contributed to this work and approved the final version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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