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Case Series

Effective Luteal Support with Dydrogesterone 30 mg SR in Combination with Micronized Vaginal Progesterone in Frozen Embryo Transfer and Severe Endometriosis: Case Series

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Abstract

Luteal phase support is crucial for optimizing outcomes in assisted reproductive technologies, particularly during frozen embryo transfer (FET) cycles, where endogenous progesterone production is insufficient for pregnancy maintenance and endometrial preparation. This report presents two cases: that of a 32-year-old woman with diminished ovarian reserve and that of a 31-year-old woman with severe endometriosis. Both patients underwent FET and received a combination of vaginal micronized progesterone and oral sustained-release dydrogesterone (30 mg). Both patients achieved pregnancy, indicating the effectiveness of combination therapy. The dual regimen may offer a promising approach for enhancing reproductive success in patients with complex fertility issues.

Keywords: Luteal phase support; Progesterone; Dydrogesterone; Frozen-embryo transfer; Assisted reproductive technology

Introduction

Assisted reproductive technology has advanced significantly, particularly with the increased use of frozen-thawed embryo transfer (FET) cycles. Key innovations in in-vitro fertilization (IVF) include routine blastocyst-stage embryo transfer, greater reliance on embryo cryopreservation, preimplantation genetic screening, single embryo transfer, and minimal stimulation protocols [1]. Progesterone plays a crucial role in supporting fertility treatments, particularly during FET cycles because of the insufficiency of an endogenous corpus luteum [2]. Progesterone deficiency is commonly seen in conditions such as luteal phase deficiency, threatened abortion, and recurrent pregnancy loss, often requiring progesterone supplementation [3].

Dydrogesterone is a stereoisomer of progesterone that has a metabolically stable chemical structure. It offers several advantages, including high oral bioavailability, specificity for

progesterone receptors, and a favorable tolerability profile [2]. Oral dydrogesterone is as effective as vaginal micronized progesterone, but evidence comparing the two in assisted reproductive procedures remains inconclusive. The phase 3 Lotus I and II trials demonstrated that oral dydrogesterone is non-inferior to vaginal micronized progesterone capsules and gel, respectively, for luteal phase support (LPS) in FET cycles [4,5]. A prospective, randomized controlled trial (RCT) in 1373 women undergoing IVF showed similar pregnancy (28.7% vs 28.6%) and miscarriage (11.6% vs 13.0%) rates with oral dydrogesterone and vaginal micronized progesterone [6]. Another RCT in 150 women with ≤24 weeks gestation and threatened or recurrent abortion showed significantly lower serum progesterone (21.3 vs 24.1 ng/mL, p=0.001), reduced spotting/bleeding episodes (4.0 vs 7.2, p<0.001), and a lower rate of miscarriage (8.0% vs 20.0%, p=0.034) with oral dydrogesterone compared to vaginal micronized progesterone [7]. Oral dydrogesterone can reduce vaginal irritation and discharge while enhancing patient compliance [6]. Moreover, some studies have highlighted the benefit of combining oral dydrogesterone with vaginal progesterone. A single-center, retrospective cohort study of 391 women undergoing FET (2013–2019) showed that the addition of oral dydrogesterone to vaginal micronized progesterone gel in LPS during artificial FET cycles was associated with significantly higher clinical birth rates than when vaginal progesterone was used alone [8]. The MIDRONE study compared vaginal micronized progesterone and its combination with oral dydrogesterone for LPS in 1364 women undergoing IVF with FET [9]. Although there was no significant increase in live birth rates (41.3% vs 46.3%, p=0.06), miscarriage rates were significantly reduced with the combination therapy (6.6% vs 3.4%, p=0.009). The findings indicate that oral dydrogesterone supplementation may enhance the efficacy of vaginal progesterone in reducing miscarriage rates and improving live birth rates during FET cycles [9]. While both treatments are individually well-studied and effective, the potential synergistic benefits of their combined use remain largely unexplored. However, there is a critical need for more comprehensive studies focusing on the combination therapy of vaginal progesterone and oral dydrogesterone for LPS.

This report presents two clinical cases illustrating the effectiveness of a combination of vaginal micronized progesterone and dydrogesterone sustained release (SR) 30 mg in improving pregnancy outcomes during FET. The first case involves a patient with poor ovarian reserve, and the second case focuses on a patient with grade 4 endometriosis.

Case Series

Case 1: LPS in FET despite poor ovarian reserve

A 32-year-old woman, married for 5 years, presented with a history of obstetric complications, including an intrauterine death at 33 gestation weeks 5 years ago. This complication was attributed to severe pregnancy-induced hypertension and abruptio placenta. During the initial assessment in December 2023, she was found to have endometrial polyps with eumenorrhea and optimal endometrial thickness. Hysterolaparoscopy conducted in January 2024 revealed a right hydrosalpinx, for which salpingectomy was performed, along with excision of endometrial polyps.

Given her poor ovarian reserve, with an antral follicle count of seven, she was counseled for IVF. In March 2024, ovarian stimulation was initiated with human menopausal gonadotropins (HMG) 450 IU. Seven mature metaphase II oocytes were retrieved, of which six were fertilized, resulting in two blastocysts: one fully expanded blastocyst (grade AA) and one early blastocyst (grade BB). FET was planned, and hormone replacement therapy was started. A single depot intramuscular injection of gonadotropin-releasing hormone (GnRH) agonist (3.75 mg) was administered on day 2 of the patient's menstrual cycle, followed by confirmation of ovarian downregulation, with reduction in estradiol (<100 pg/mL) and luteinizing hormone (LH, <5 mIU/mL) levels. Transvaginal ultrasound revealed an absence of endometrial growth.

The endometrial thickness during ovarian stimulation was 7 mm. Therefore, estradiol hemihydrate was administered in incremental doses ranging from 4–24 mg/day over a prolonged period of 40 days, helping to achieve an endometrial thickness of 10.2 mm. Sub-endometrial blood flow was assessed, with a peak systolic velocity of 17.91 cm/s indicating favorable conditions for embryo transfer.

LPS was provided using a combination of vaginal micronized progesterone capsule (400 µg, thrice daily), oral dydrogesterone SR (30 mg; Dydroboon 30 SR, once daily), and intramuscular progesterone (100 mg for 6 days). On day 7 of progesterone supplementation (June 2024), a single-thawed blastocyst was transferred. Thirteen days post-transfer, the serum beta-human chorionic gonadotropin (beta-hCG) level was 764 IU/L, and it increased to 2100 IU/L after 4 days. Transvaginal ultrasound at 7 weeks of gestation confirmed a single live intrauterine pregnancy.

Administration of vaginal micronized progesterone capsule and oral dydrogesterone was continued until week 10 (12 weeks of gestation). There has been no episode of threatened abortion, indicating that progesterone levels were adequately maintained. The most recent follow-up in August 2024 revealed ongoing pregnancy.

Case 2: LPS in FET despite operated grade 4 endometriosis

A 31-year-old female, married for 1.5 years, with a 2-year history of endometriosis presented with primary infertility. In January 2022, she received a depot intramuscular injection of leuprolide (11.25 mg) for ovarian downregulation. Although her menstrual cycle was regular, she experienced prolonged bleeding (8–10 days) and severe dysmenorrhea. In June 2022, she underwent

laparoscopic excision of a 4–5 cm endometriotic cyst in the left ovary. However, during her visit in March 2023, both ovaries were deemed non-approachable due to recurrent endometriosis, and an endometriotic cyst (6 cm) was detected in the left ovary.

Owing to the challenging position of the ovaries for oocyte retrieval, a second laparoscopic surgery was performed in March 2023 to facilitate ovarian mobilization. Intraoperative findings included left hydrosalpinx (which was managed with salpingectomy), recurrence of extensive endometriosis, and a nodule on the sigmoid colon, which was excised. The ovaries were then mobilized and placed appropriately in the pelvic cavity for oocyte retrieval.

For ovarian stimulation, HMG 450 IU was initiated in antagonist protocol in September 2023. Eleven cumulus-oocyte complexes were retrieved, yielding eight mature metaphase-2 oocytes. Two blastocysts (grade AA and BB) were obtained after 5 days of culture and vitrified for future FET.

The first FET, using a hormone replacement protocol, resulted in a negative beta-hCG test. The patient underwent a second ovarian stimulation cycle in March 2024, yielding 12 cumulus-oocyte complexes, eight mature oocytes, and two blastocysts. LPS was administered using a combination of vaginal micronized progesterone capsule (400 mg thrice daily), oral dydrogesterone SR (30 mg; Dydroboon 30 SR once daily), and intramuscular injection of progesterone (100 mg for 6 days). A single blastocyst was transferred, resulting in a positive beta-hCG test 13 days post-transfer. Subsequently, ultrasonography confirmed a single uterine pregnancy at 7 weeks. LPS was continued until week 10 (12 weeks of gestation), with no episode of threatened abortion. Ultrasound examination showed good sub-endometrial blood flow with adequate endometrial growth (**Figure 1**). As of September 2024, the pregnancy had completed 24 weeks of gestation.

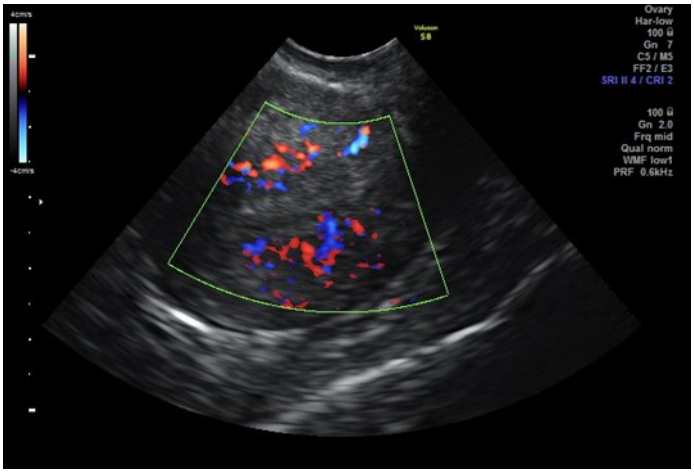

Figure 1: Ultrasound (Color Doppler) examination showed good sub-endometrial blood flow with adequate endometrial growth

Discussion

This report presents two cases where the addition of oral dydrogesterone SR 30 mg to vaginal micronized progesterone led to successful pregnancies in patients with a challenging reproductive history – one patient had a poor ovarian reserve and another had grade 4 endometriosis.

The outcomes in Case 1 offer initial evidence to support the combination vaginal micronized progesterone and oral dydrogesterone as a viable option for patients with significant reproductive challenges. The patient had a history of obstetric complications and a low ovarian reserve. In IVF cycles, retrieving 15–20 oocytes is recommended to achieve a 70–80% chance of having at least one baby in women younger than 38 years [10,11]. In this case, FET was planned following endometrial preparation cycle with hormone replacement therapy. A successful pregnancy depends on two key factors: a high-quality, chromosomally normal blastocyst and a receptive uterine endometrium [12]. The timing of embryo implantation must be synchronized with the optimal window of endometrial receptivity. Ovarian response is typically assessed based on antral follicle count, anti-mullerian hormone level, and basal follicle-stimulating hormone level [13]. The estradiol and LH levels of patient 1 were reduced after 11 days after an intramuscular injection of a GnRH agonist depot 3.75 mg.

Combined therapy with vaginal micronized progesterone and dydrogesterone SR was effective in this case in achieving and maintaining an ongoing pregnancy post-FET. The hormonal regimen effectively supported endometrial thickening and satisfactory beta-hCG levels without a threatened abortion, indicating adequate progesterone levels during LPS. This case highlights the potential for successful pregnancy outcomes in women with low ovarian reserve on using the described combination therapy.

In Case 2, the patient had severe (grade 4) endometriosis, which is known to significantly and adversely impact fertility [14]. More than 10% of women of reproductive age are diagnosed with endometriosis, and more than 38%–50% of infertility cases among women are due to endometriosis [15,16]. A systematic literature review of 19 studies suggests that dydrogesterone is a safer alternative to gestrinone for managing pelvic pain and dysmenorrhea in women of reproductive age, with improved pregnancy rates and potentially fewer side effects. The review supported the favorable therapeutic profile of dydrogesterone compared to that of gestrinone, GnRH agonists, and other treatments in managing endometriosis [17]. However, the difference was not statistically significant. Moreover, few studies have examined the efficacy of combining vaginal micronized progesterone with oral dydrogesterone in patients with severe endometriosis.

Before her successful FET pregnancy, the patient in our second case underwent multiple surgeries, including salpingectomy and

laparoscopic excision of recurrent endometriotic cysts. Ovarian stripping and surgical excision of endometriotic cysts can compromise ovarian vascularity and result in local inflammation and thermal damage, thereby reducing the ovarian reserve [15]. Although the number of antral follicles in the second case are unknown, combining vaginal micronized progesterone and oral dydrogesterone led to a successful intrauterine singleton pregnancy.

Managing LPS in endometriosis can be challenging due to the complex nature of the disorder, often involving inflammation and reduced endometrial receptivity [15]. Reduced endometrial receptivity, can be treated through prolonged progesterone supplementation and/or increasing serum progesterone levels [18]. Substantial variability has been reported in the amount of progesterone absorbed through the vagina [19]. Vaginal progesterone administration may have local adverse effects, such as vaginal bleeding, irritation, and discharge, potentially impacting patient comfort and sexual function [2]. Therefore, increasing the duration of progesterone administration using vaginal progesterone alone may not be practical from a patient's perspective [18]. In this context, combining oral dydrogesterone with vaginal progesterone seems promising. Moreover, women with endometriosis often require multiple daily doses of dydrogesterone, which can be inconvenient. Oral dydrogesterone 30 mg SR tablets offer a more convenient treatment option with once-daily dosing, reducing pill burden and improving treatment adherence.

Conclusion

The two cases presented herein highlight the effectiveness of combining vaginal micronized progesterone with oral dydrogesterone 30 mg SR in fertility treatments. This approach has shown promise in providing adequate LPS and improving pregnancy outcomes for patients with poor ovarian reserve undergoing FET and those with severe endometriosis.

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Ethical considerations

Both patients provided informed consent for the use of anonymized images from their diagnosis and treatment for research purposes, ensuring that all identifying information would be removed. Written informed consent was obtained from both the patients described in this case series.

Conflict of interest

The authors declare no conflicts of interest.

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