Oral Dydrogesterone versus Vaginal Micronized Progesterone in Luteal Phase Support after Controlled Ovarian Stimulation Using Long Gonadotropin-Releasing Hormone Agonist in Women Undergoing in Vitro Fertilization/Intracytoplasmic Sperm Injection

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Abstract

Background: Luteal phase support is indicated after Controlled Ovarian Stimulation (COS) using Long Gonadotropin-Releasing Hormone Agonist (GnRHa) protocol in Women undergoing in Vitro Fertilization (IVF)/Intracytoplasmic Sperm Injection (ICSI). Progesterone is widely used for this indication. Objective: The objective of the current trial is to compare both efficacy and safety of oral dydrogesterone and vaginal micronized progesterone in luteal phase support in women undergoing IVF/ICSI using the long GnRHa protocol. Methods: This open-label randomized controlled study conducted at a private fertility and IVF center in Zagazig, Egypt, during the interval between April 2016 and August 2019. The study included women planned to undergo IVF/ICSI for either male factor infertility, tubal factor infertility, or unexplained infertility. Women with pelvic endometriosis, known reduced ovarian reserve, and women who were known to have poor or high response to ovarian stimulation, as well as women who were stimulated using non-long GnRHa protocol were not included. After embryo transfer, eligible women were randomly allocated into one of the two groups: group I, included women who received oral dydrogesterone 10 mg three times per day; and group II, included women who received vaginal micronized progesterone 400 mg twice per day. The primary outcome was live birth rate. The principal secondary outcome was women satisfaction. Results: Five hundred sixty four women were recruited and randomly allocated into two
groups: group I [Oral Dydrogesterone Group] (n = 284), and group II [Vaginal Progesterone Group] (n = 280). Live birth rates [72 (25.4%) vs 69 (24.6%), respectively, RR 1.03, 95% CI (0.77 to 1.37)], ongoing pregnancy rates [79 (27.8%) vs 81 (28.9%), respectively, RR 0.96, 95% CI (0.74 to 1.25)], clinical pregnancy rates [97 (34.2%) vs 95 (33.9%), respectively, RR 1.01, 95% CI (0.80 to 1.27)] and miscarriage rates (per clinical pregnancy) [18 (18.6%) vs 14 (14.7%), respectively, RR 1.26, 95% CI (0.66 to 2.38)] were all comparable in both groups. The rates of vaginal burning [4 (1.4%) vs 32 (11.4%), respectively, RR 0.12, 95% CI (0.04 to 0.34)], vaginal bleeding [9 (3.2%) vs 26 (9.3%), respectively, RR 0.34, 95% CI (0.16 to 0.72)] and overall dissatisfaction [15 (5.3%) vs 68 (24.3%), respectively, RR 0.22, 95% CI (0.13 to 0.37)] were significantly lower among women of group I when compared to women of group II. **Conclusion:** In conclusion, when compared to vaginal micronized progesterone, oral dydrogesterone seems to be associated with comparable live birth, ongoing pregnancy and clinical pregnancy rates, and significantly lower dissatisfaction and side effects rates, when given as luteal phase support in normal responding women undergoing IVF/ICSI using the long GnRHa protocol.

**Keywords**

Dydrogesterone, Micronized Progesterone, Luteal Phase Support, IVF, ICSI, Pregnancy Rate, Live Birth Rate

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**1. Introduction**

Progesterone is a key hormone in the implantation and maintenance of pregnancy [1]. The source of progesterone in women having spontaneous pregnancy or in women undergoing simple ovarian stimulation is from luteinized granulosa and theca cells of the corpus luteum(ei) resulting from ovulation [2]. In women undergoing controlled ovarian stimulation (COS) using the long gonadotropin releasing hormone agonist (GnRHa), however, luteal phase deficiency is evident [3]. The underlying etiology of such luteal phase deficiency includes anterior pituitary gland suppression, supraphysiological levels of estradiol, and aspiration/trauma of granulosa cells during oocyte retrieval [4] [5] [6]. Luteal phase support is, therefore, indicated in women receiving the long GnRHa protocol. Human chorionic gonadotropin (hCG) injection has been shown to be an effective tool for luteal phase support [7] [8] [9]. Nevertheless, the innate risk of ovarian hyperstimulation (OHSS) with hCG limits its use for such an indication. Progesterone supplementation is a more appropriate option, since it does not add to the risk of OHSS [8]. Natural micronized progesterone has been tried using different routes, including intramuscular, vaginal, rectal, oral and, lately, subcutaneous [9] [10]. Oral administration of natural progesterone is associated with a quite low bioavailability (down to 10%) [5]. Meanwhile, parenteral routes...
seem to be inconvenient to many women. Injections are not uncommonly associated with pain and local hematomas or abscesses [11]. Vaginal and rectal routes are associated with local burning and irritation [12]. A well-known, long-used oral semisynthetic progestin (dydrogesterone) has been administered orally in women requiring progesterone supplementation for many indications, since it is not degraded by gastric acidity and skips the first pass metabolism, and, therefore, has a quite high bioavailability [13] [14]. Recently numerous clinical trials have investigated the efficacy of oral dydrogesterone as luteal phase support, in women undergoing *in Vitro* Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) and found comparable efficacy to micronized progesterone [15]-[20]. In addition, a recent systematic review and meta-analysis found similar conclusion [21]. The same systematic review, however, found only two clinical trials which investigated the two medications (dydrogesterone and micronized progesterone) from the side of adverse effects, namely women’s dissatisfaction [21]. The difference between the two medications in these two clinical trials, as regard dissatisfaction rates, was conflicting [3% vs 26%, respectively, p < 0.0001 in one trial] [17], in contrast to 8% vs 9%, respectively, p > 0.05 in the second trial [18]. Therefore, a need for further randomized clinical trials comparing the adverse effects of both medications remains. The objective of the current trial is to compare both efficacy and safety of oral dydrogesterone and vaginal micronized progesterone in luteal phase support in women undergoing IVF/ICSI using the long GnRHa protocol.

2. Methods

The current open-label randomized controlled trial was conducted at a private fertility and IVF center in Zagazig, Egypt, during the interval between April 2016 and August 2019. The study protocol was in agreement to the Helsinki declaration of Ethical Medical Research (last updated in Brazil 2013) and had been approved by the Institutional Review Board of Faculty of Medicine, Zagazig University, Egypt. The study included women planned to undergo IVF/ICSI for either male factor infertility, tubal factor infertility, or unexplained infertility. Women with pelvic endometriosis, known reduced ovarian reserve, and women who were known to have poor or high response to ovarian stimulation, as well as women who were stimulated using non-long GnRHa protocol were not included. All included women underwent luteal phase pituitary down-regulation using triptorelin acetate 0.1 IU [Decapeptyl® 0.1 IU PFS, Ferring Pharmaceuticals, Switzerland] administered subcutaneously every 24 hours from day 21 of preceding cycle till the day of hCG injection for triggering ovulation. COH was started in early follicular phase (day 2 of menstruation following onset of the GnRHs), after ensuring pituitary down-regulation (by quiet ovaries, endometrial thickness < 6 mm, serum LH < 2.0 mIU/ml, and serum estradiol < 50 ng/ml). The initial dose of ovarian stimulation was subcutaneous/intramuscular 225 IU of purified urinary human menopausal gonadotropin (hMG) [Menogon® 75 IU,
Ferring Pharmaceuticals, Switzerland]. Sonographic folliculometry was started 5 - 6 days after onset of ovarian stimulation, then every 2 - 3 days till reaching at least 5 follicles ≥ 18 mm and a trilaminar endometrium with a thickness ≥ 8mm, when hCG [Chorionom® 5000 IU, IBSA, Switzerland] is administered intramuscularly at a dose of 10,000 IU. Oocyte retrieval was performed at 35 - 37 hours after hCG injection. The retrieved oocytes were subjected to either in vitro insemination (if clinical history and semen parameters allow) or ICSI (according the local protocol). Only women who had average response (retrieved 5 - 20 oocytes and had blastocyst-stage embryo transfer) were recruited in the current trial. After embryo transfer, eligible women were approached. Participating women signed informed written consent, and were randomly allocated (using computer-generated system) into one of the two groups: group I, included women who received oral dydrogesterone 10 mg three times per day [Duphason®, Abbott Laboratories, Illinois, US]; and group II, included women who received vaginal micronized progesterone 400 mg twice per day [Prontogest® 400 mg vaginal pessary, IBSA, Switzerland]. Random allocation was concealed and only released after recruitment. Post-embryo transfer allocation reduced the rates of drop out (due to cycle cancelation or poor response) to nil. In all recruited women, either medication was administered till the day of serum pregnancy testing, and continued, in women who had positive pregnancy test, till the luteal-placental shift (12 - 14 weeks of gestation). The primary outcome was live birth rate. The principal secondary outcome was women satisfaction. Satisfaction was measured using the 5-point Linkert’s scale. Women who report “very dissatisfied” or “dissatisfied” were categorized as dissatisfied. Other secondary outcomes included: clinical pregnancy (defined as sonographic detection of viable intrauterine gestational sac), ongoing clinical pregnancy (defined as viability of intrauterine pregnancy beyond 12 weeks of gestation), miscarriage rate, and medication-related adverse effects (nausea, vaginal burning and vaginal bleeding).

2.1. Sample Size Justification

Sample size was calculated using the Online Power and Sample Size Calculator, setting the power (1-β) at 0.8 and the type-1 error (α) at 0.05. Data from a recent meta-analysis [21] showed that the pooled live birth rates were 24% and 25%, respectively. Calculation according to these values, setting the non-inferiority margin at 0.08, produces a minimal sample size of 282 women in each group.

2.2. Statistical Methods

Statistical analysis was performed using MedCalc® version 7.0. Difference between two independent metric variables was analyzed using independent student’s t-test as well as mean difference and its 95% confidence interval. Difference between two categorical variables was analyzed using chi-squared test as well as risk ratio and its 95% confidence interval. Significance level was set at 0.05.
3. Results

Figure 1 shows a flow-diagram of the study course. Five hundred sixty four women were recruited and randomly allocated into two groups: group I [Oral Dydrogesterone Group] (n = 284), and group II [Vaginal Progesterone Group] (n = 280). There were no significant differences between women of both groups regarding the age, body mass index (BMI) or duration of infertility (Table 1). There were no significant differences between women of both groups regarding duration of ovarian stimulation, total dose of gonadotropin given, number of retrieved oocytes, fertilization rate, or number of transferred embryos (Table 2).

On comparison between group I and group II: Live birth rates were [72 (25.4%) vs 69 (24.6%), respectively, RR 1.03, 95% CI (0.77 to 1.37)], ongoing pregnancy rates were [79 (27.8%) vs 81 (28.9%), respectively, RR 0.96, 95% CI (0.74 to 1.25)], clinical pregnancy rates were [97 (34.2%) vs 95 (33.9%), respectively, RR 1.01, 95% CI (0.80 to 1.27)] and miscarriage rates (per clinical pregnancy) were [18 (18.6%) vs 14 (14.7%), respectively, RR 1.26, 95% CI (0.66 to 2.38)]. All these results were comparable in both groups (Table 3, Figure 2).

Figure 1. Flow-diagram of study course.
Excluded for not fulfilling the eligibility criteria.

Figure 2. Bar-chart showing difference between groups regarding pregnancy and miscarriage outcomes. LBR: live birth rate; OPR: ongoing pregnancy rate; CPR: clinical pregnancy rate.
### Table 1. Difference between groups regarding initial characteristics.

|                      | Group I [Oral Dydrogesterone] (n = 284) | Group II [Vaginal Progesterone] (n = 280) | MD (95% CI)   | P<sup>α</sup> |
|----------------------|----------------------------------------|------------------------------------------|----------------|-------------|
| **Age (years)**      | 28.3 ± 4.1                             | 28.5 ± 4.1                               | 0.17 (−0.51 to 0.84) | 0.631       |
| **BMI (kg/m<sup>2</sup>)** | 27.6 ± 5.3                           | 27.5 ± 5.2                               | 0.02 (−0.85 to 1.89) | 0.971       |
| **Duration of Infertility (years)** | 8.4 ± 3.6                             | 8.4 ± 3.6                                | 0.09 (−0.49 to 0.67) | 0.769       |

Data presented as mean ± standard deviation; BMI body mass index (calculated as weight [kg] divided by squared height [m<sup>2</sup>]); MD (95% CI) mean difference and its 95% confidence interval; <sup>α</sup>Analysis using independent student’s t-test.

### Table 2. Difference between groups regarding IVF/ICSI cycle outcomes.

|                      | Group I [Oral Dydrogesterone] (n = 284) | Group II [Vaginal Progesterone] (n = 280) | MD/RR (95% CI) | P<sup>1</sup> |
|----------------------|----------------------------------------|------------------------------------------|----------------|-------------|
| **Duration of Stimulation (days)** | 15.1 ± 1.9                             | 15.03 ± 2.2                              | −0.02 (−0.35 to 0.3) | 0.886       |
| **Total Gonadotropin Dose (IU)** | 2772.1 ± 1273.8                       | 2856.4 ± 1372.3                         | 84.3 (−134.6 to 303.3) | 0.449       |
| **No. of Retrieved Oocytes** | 14.02 ± 6.4                           | 14.4 ± 6.9                               | 0.4 (−0.69 to 1.5) | 0.470       |
| **Fertilization Rate** | 0.66 ± 0.14                           | 0.64 ± 0.15                              | −0.02 (−0.04 to 0.004) | 0.099       |
| **No. of Transferred Embryos** | 140 (49.3%)                           | 139 (49.6%)                              | 0.99            | 0.934       |
| 2                    | 141 (50.7%)                           | 141 (50.4%)                              | (0.84 to 1.17)   |             |

Data presented as mean ± standard deviation; or frequency (percentage); MD/RR (95% CI) mean difference/risk ratio and their 95% confidence interval; <sup>1</sup>Analysis using independent student’s t-test; <sup>2</sup>Analysis using chi-squared test.

### Table 3. Difference between groups regarding pregnancy and miscarriage outcomes.

|                      | Group I [Oral Dydrogesterone] (n = 284) | Group II [Vaginal Progesterone] (n = 280) | RR (95% CI) | P<sup>α</sup> |
|----------------------|----------------------------------------|------------------------------------------|-------------|-------------|
| **LBR**              | 72 (25.4%)                            | 69 (24.6%)                               | 1.03 (0.77 to 1.37) | 0.846       |
| **OPR**              | 79 (27.8%)                            | 81 (28.9%)                               | 0.96 (0.74 to 1.25) | 0.842       |
| **CPR**              | 97 (34.2%)                            | 95 (33.9%)                               | 1.01 (0.80 to 1.27) | 0.955       |
| **Miscarriage Rate** | 18 (18.6%)                            | 14 (14.7%)                               | 1.26 (0.66 to 2.38) | 0.478       |

LBR live birth rate; OPR ongoing pregnancy rate; CPR clinical pregnancy rate; Data presented as frequency (percentage); RR (95% CI) risk ratio and its 95% confidence interval; <sup>α</sup>Analysis using chi-squared test; <sup>2</sup>Miscarriage rate per clinical pregnancy.
The rates of nausea were higher in women of group I when compared to women of group II; the difference, however, did not each statistical significance [10 (3.5%) vs 4 (1.4%), respectively, RR 2.46, 95% CI (0.78 to 7.27)].

The rates of vaginal burning [4 (1.4%) vs 32 (11.4%), respectively, RR 0.12, 95% CI (0.04 to 0.34)], vaginal bleeding [9 (3.2%) vs 26 (9.3%), respectively, RR 0.34, 95% CI (0.16 to 0.72)] and overall dissatisfaction [15 (5.3%) vs 68 (24.3%), respectively, RR 0.22, 95% CI (0.13 to 0.37)] were significantly lower among women of group I when compared to women of group II (Table 4, Figure 3).

4. Discussion

The current trial showed similar efficacy of both oral dydrogesterone and vaginal micronized progesterone in terms of comparable rates of live birth, ongoing pregnancy, clinical pregnancy and miscarriage pregnancy in normal-responding women undergoing IVF/ICSI using long GnRHα protocol. Meanwhile, oral dydrogesterone was associated with slightly higher rates of nausea; yet significantly lower rates of vaginal burning, vaginal bleeding and overall women’s

Table 4. Difference between groups regarding adverse effects.

|                  | Group I [Oral Dydrogesterone] (n = 284) | Group II [Vaginal Progesterone] (n = 280) | RR (95% CI) | P*          |
|------------------|----------------------------------------|------------------------------------------|-------------|-------------|
| Nausea           | 10 (3.5%)                              | 4 (1.4%)                                 | 2.46 (0.78 to 7.27) | 0.110       |
| Vaginal Burning  | 4 (1.4%)                               | 32 (11.4%)                               | 0.12 (0.04 to 0.34) | <0.001      |
| Vaginal Bleeding | 9 (3.2%)                               | 26 (9.3%)                                | 0.34 (0.16 to 0.72) | 0.003       |
| Dissatisfaction  | 15 (5.3%)                              | 68 (24.3%)                               | 0.22 (0.13 to 0.37) | <0.001      |

LBR: live birth rate; OPR: ongoing pregnancy rate; CPR: clinical pregnancy rate; Data presented as frequency (percentage); RR (95% CI) risk ratio and its 95% confidence interval; *Analysis using chi-squared test; †Miscarriage rate per clinical pregnancy.

Figure 3. Bar-chart showing difference between groups regarding adverse effects.
dissatisfaction. The results of the current trial went in agreement with the results of previously published literature. In the largest trial (LOTUS I) [19], 1301 cycles were randomly allocated to either oral dydrogesterone (30 mg per day on three divided doses) or micronized vaginal progesterone (200 mg suppository). The LOTUS I trial showed that oral dydrogesterone is non-inferior to micronized vaginal progesterone as regard live birth rate [34.6% vs 29.8%], ongoing pregnancy rate [37.6% vs 33.1%], clinical pregnancy rate [47.1% vs 45.5%].

The current trial results also come in agreement to two systematic reviews. The first a Cochrane systematic review published in 2015, on 94 randomized trials comparing different luteal phase support regiments. The meta-analysis of this review found a significantly higher clinical pregnancy rate with oral dydrogesterone when compared to both oral and vaginal micronized progesterone [22]. In a more recent systematic review published in 2018 on 8 trials, the rates of live birth, ongoing pregnancy and clinical pregnancy were comparable with either oral dydrogesterone or vaginal progesterone [21].

One of the apparent limitations in the current trial is absence of blinding of both interventions to the patient and the investigator. In the LOTUS I trial [19] oral placebo was added to the vaginal group and a vaginal placebo was added to the oral group. Such blinding was not adopted in the current trial, as the principal secondary outcome was women’s satisfaction. We already know that vaginal route of the medication in the second route per se and its possible consequences of bleeding or irritation contributes in a substantial way to this principal secondary outcome. Therefore, we intentionally restricted the routes of administration to the oral route in group I and the vaginal route in group II. On the other hand, the LOTUS I trial was not concerned about the possible women’s dissatisfaction linked to the vaginal administration of progesterone. The current trial made use of concealed allocation in order to overcome the inevitable lack of blinding and reduce the risk of selection bias.

Another limitation of the current trial was lack of data regarding the potential risk of congenital malformations. Results from the LOTUS I study found comparable rates of congenital malformations in both interventions [19]. In addition, both dydrogesterone and micronized progesterone are long-studied and well-known medications with a high safety profile [15] [16] [17] [23].

A third limitation of the current trial is restricting the assessment of efficacy of oral dydrogesterone in women undergoing ovarian stimulation using the long GnRHa protocol and in normal-responding women. Further clinical trials are needed to assess the efficacy of dydrogesterone in poor- and high-responders, and in women undergoing ovarian stimulation using other protocols.

5. Conclusion

In conclusion, when compared to vaginal micronized progesterone, oral dydrogesterone seems to be associated with comparable live birth, ongoing pregnancy and clinical pregnancy rates, and significantly lower dissatisfaction and
side effects rates, when given as luteal phase support in normal responding women undergoing IVF/ICSI using the long GnRHα protocol.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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