Oral Dydrogesterone versus Vaginal Progesterone in Luteal Phase Support in Assisted Reproductive Technique

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**Abstract: Background:** The aim of this study is to compare oral progesterone (Dydrogesterone) with vaginal progesterone suppository for luteal phase support as regard pregnancy rate in ICSI cycles. **Methods:** This is a prospective, randomized clinical trial conducted on (40) females < 40 years old. with Infertility duration less than 5 years with Regular menstrual cycle attends to inpatients and outpatient’s clinic of Obstetrics & Gynecology department, Tanta University Hospitals. Twenty patients received 10 mg dydrogesterone tablet (Tonadogest; Techno pharma; Egypt) four times daily and Twenty patients received 400mg vaginal progesterone suppository (Prontogest; Marcyrl; Egypt) twice daily from the day of oocyte retrieval until a pregnancy test become positive and continue till 10 weeks. **Results:** No difference between oral dydrogesterone and vaginal progesterone in luteal support of IVF/ICSI stimulated cycles according to pregnancy rate and Oral dydrogesterone show better patient satisfaction**. Conclusions:** There is potential benefits for pregnancy and miscarriage rate with both drugs. oral dydrogesterone can be alternative option instead of vaginal progesterone suppository for luteal phase support.

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**Keywords:** Luteal Phase Support, Oral Dydrogesterone, Vaginal Progesterone, Assisted Reproductive Technique

# 1. Introduction

The corpus luteum plays a vital role in maintaining early pregnancy until the luteal–placental shift at 7–9 weeks of pregnancy. For women undergoing assisted reproductive techniques (ART), it is a common practice to over stimulate the ovaries to promote the development of multiple follicles (1,2).

After oocyte aspiration, multiple corpora lutea are formed. However, the supraphysiological estradiol level caused by ovarian stimulation has a negative feedback on the pituitary gland, promoting premature luteolysis and low serum progesterone levels during the luteal phase (2,3).

There is evidence that luteal-phase support (LPS) with progesterone, human chorionic gonadotropin (HCG) or gonadotropin-releasing hormone (GnRH) agonist improves reproductive outcome in women undergoing ART. As the use of HCG is associated with a higher risk of ovarian hyperstimulation syndrome and GnRH agonist has only been tested in addition to progesterone (1,4).

Progesterone seems to be the best option for LPS at present. Progesterone can be administered orally, intramuscularly, vaginally or rectally, with similar efficacy for each route of administration (2,5).

However, Dydrogesterone is an optical isomer of progesterone in which methyl group at carbon 10 is in the alpha position instead of beta position in natural progesterone. Dydrogesterone is an orally active, highly selective progestogen that is similar to endogenous progesterone, but which has a better bioavailability and hence allows administration of lower doses and avoidance of progestogenic side-effects. In contrast to other available synthetic progestogens, it does not cause androgenic side- effects in the mother (e.g. hirsutism, acne) and has no masculinising effect on the female foetus or feminising effect on the male foetus (6)

# 2. Methods

This is a prospective, randomized clinical trial conducted on (40) females who attends inpatients and outpatient’s clinic of Obstetrics & Gynecology department, Tanta University Hospitals from June 2018 till June 2019.

# Inclusion criteria:

* Infertility duration less than 5years.
* Maternal age below 40years.
* Normal levels of hormones, normal transvaginals onography.
* Regular menstrualcycle.

# Exclusion criteria:

* Poor responders (POSEIDON GROUP 4: old patients ≥35years with poor ovarian reserve pre-stimulation parameters AFC<5, AMH <1.2pg/ml).
* High responders (PCOs).
* Abnormal uterus such as sub-mucosal myoma and endometrial adhesion.
* Follicle stimulated hormone (FSH) ≥10mlU/ml.
* Sensitivity to the progesterone products.
* History of dysfunctional uterine bleeding.
* History of recurrent miscarriage (defined as three or more spontaneous miscarriage.

# Methods:

## All cases were subjected to the following:

* 1. Written informed consent from every patient included in this study. The consent was proved by the medical ethical committee of Tanta University Hospital.
	2. Full history was taken with attention on:
		+ Age: maternal age less than 35 years old.
		+ Duration of infertility less than 5years.
		+ Menstrual cycle was regular and no history of dysfunctional uterine bleeding.
		+ Obstetric history: no congenital uterine anomalies or history of recurrent abortion.
		+ Medical history: no sensitivity to progesterone.
	3. Full general and abdominal examination was done.
	4. Local examination: Patients underwent a detailed clinical examination including per vaginal examination.
	5. Investigations were done include:
		+ Laboratory investigations include (Serum progesterone in mid-luteal phase-AMH- FSH–LH-TSH-Prolactin).
		+ Radiological investigation includes (Ultrasonography to exclude congenital anomalies or sub-mucosalmyoma).
		+ Other routine investigations include (Complete blood picture- coagulation profile-random blood sugar, and tests for thrombophlebitis). All patients underwent transvaginalsonography examination using Samsung ultrasound machine, model H60, USS- H60NF4K/WR (Samsung, Korea) with 3.5-MHz and 5-MHz convex probes (Figure9).

6-Then appropriate drugs had been be administrated for ovulation stimulation according to long protocol.

In the long protocol, GnRH agonist is started on day 21 of the cycle preceding treatment and continued in a constant dose until the day of HCG administration. It is continued in parallel with gonadotropin treatment which is usually started on the first days of an ensuing menstruation, after two weeks of agonist treatment or following demonstration of pituitary down regulation by measuring low (<50 pg/ml) estradiol levels.

Transvaginalsonography will be repeated for each patient every other day to follow up follicle growth and endometrial thickness. When at least three follicles reach adiameter of 18-24 mm, 10000IU HCG had been intramuscularly injected and oocyte retrieval (Ovum Pick Up) had been performed under transvaginal ultrasound guidance. Then successful fertilization (ICSI) then the two best available embryos are selected and transferred into uterine cavity at day 3 or day 5. Embryos had been transferred to patients with various number and grades after 48-72 hours or at blastocyst stage. βHCG test was done at 14-17days after embryo transfer and cardiac pulsation is visible on sonography 2 weeks later.

# Patients were randomly assigned into two equal groups by simple randomized alternating method:

**Group A:**

Twenty patients received 10 mg dydrogesterone tablet (Tonadogest; Techno pharma; Egypt) four times daily from the day of oocyte retrieval until a pregnancy test become positive and continue till 10 weeks.

# Group B:

Twenty patients received 400mg vaginal progesterone suppository (Prontogest; Marcyrl; Egypt) twice a day from the day of oocyte retrieval until a pregnancy test become positive and continue till 10 weeks.

Both groups received folic acid 400 microgram/day.

**Patient satisfaction** to oral Dydrogesterone and vaginal Progesterone were investigated by questionnaire according to price, convenience and different side effects that the supplements could cause as vaginal Bleeding, Vaginal irritation, Nausea, Epigastric pain, Change in appetite and Weight gain. Satisfaction score was assessed by 5-point scale (with 1 being „„ absolutely dissatisfied‟‟ and 5 being„„ absolutely satisfied‟‟).

# Statistical analysis:

Quantitative data were described as mean ± standard deviation (SD) and range and were compared by Student’s T test. Qualitative data were described as frequencies (number of cases) and percentages (%) and were compared by Chi-square test. Pvalue<0.05 is considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) program release 25 for Microsoft Windows.

**Outcome:**

Success rate of ICSI protocol (pregnancyrate).

Patient satisfaction.

Side effects of drugs.

## Potential risks

* + No potential risks are considered by using Oral Dudrogesterone or vaginal Progesterone.
	+ Side effects of both drugs include: hypotension, headache and drowziness.
	+ Any unexpected risks appeared during the course of the research will be cleared to participants and thee thical.

committee on time.

## Ethical committee

* + - The study was started after medical ethical committee approval.
		- Written consent from all included patients.
		- All included patient knows about the aim of present study, risk factors, possible complications and risk of failure.

## Provision of privacy

There are adequate provisions to maintain privacy of participants and confidentiality of the data, the patient name was replaced by serial number and her address kept confidential. There is no conflict of interest. Authors don‟t receive any fund from any institute. Authors didn't give any compensation to the participant. Authors didn't represent anyrisk to the environment. Authors took verbal and written consent from the participants. The work is stopped if the patient refuses to continue. No differentiation between patients according to religion and race.

# 3. Results

This study was carried on (40) females presented by infertility (demographic and characteristic data of studied women as regard, age Infertility duration, Prior IVF cycles, BMI (Kg/m2), Type of infertility and Parity show no statistical significant difference between studied group comparison between the two studied groups regarding baseline hormonal level (FSH-LH-AMH-Prolactin –E2 –TSH ) in both groups and antral follicular count by ultrasound before IVF. We found that no significant difference between both groups.

 From table 1 authors conclude that no statistical significant difference according to Characteristics clinical outcome of drugs in both groups according to endometrial thickness with P-value**0.20**), oocyte number (**0.87)**, fertilized ovum (**0.24)**, fresh embryo transferred (**0.82)**, frozen embryo (**0.54).**

**Table (1):** Characteristics clinical outcome of drugs in both groups:

|  |  |  |
| --- | --- | --- |
| **U/S** | **Group** | **p-value** |
| **A** | **B** |
| **Endometrial****thickness (mm)\*** | Range | 8-14 | 9-12 | **0.20** |
| Mean ± SD | 9.25±0.71 | 9.35±0.75 |
| **Oocyte number** | Range | 5-10 | 6-12 | **0.87** |
| Mean ± SD | 6.2 ±3.2 | 8.4±2.8 |
| **Fertilized ovum** | Range | 4-9 | 4-11 | **0.24** |
| Mean ± SD | 6.3±1.23 | 7.1±1.34 |
| **Fresh Embryo** | N | 2 | 2 | **0.82** |
| **Frozen embryo** | Range | 0-7 | 1-9 | **0.54** |
| Mean ± SD | 4.3±1.173 | 6.1±1.244 |

**Table (2):** Side effects of both drugs:

|  |  |  |
| --- | --- | --- |
| **Side effects** | **Group** | **p-value** |
| **A** | **B** |
| N | % | N | % |
| **Vaginal bleeding** | 4 | 21.05 | 8 | 42.1 | **0.17** |
| **Nausea** | 4 | 21.05 | 1 | 5.2 | **0.15** |
| **Epigastric pain** | 4 | 21.05 | 1 | 5.2 | **0.15** |
| **Change in appetite** | 8 | 42.1 | 7 | 36.8 | **0.75** |
| **Weight gain** | 4 | 21.05 | 8 | 42.1 | **0.38** |
| **Vaginal irritation** | 1 | 5.2 | 8 | 42.1 | **0.007\*** |

Among the 40 patients who were initially enrolled, two could not follow the study protocol and were excluded from the final analysis: one patient **from group A showed bad response to ovarian stimulation**, one patient **from group B lost in follow up.**

From table 2 authors conclude that no significant statistical difference between both groups regarding side effect except for vaginal irritation. comparison between two groups according to incidence of each side effects in both groups such as Vaginal bleeding with P-value (0.17), Nausea (0.15), Epigastric pain (0.15), Change in appetite (0.75), Weight gain (0.38) and Vaginal irritation with significant P-value (0.007).

From Table 3 authors conclude that patient satisfaction to oral Dydrogesterone was better than that of vaginal Progesterone with a significant P-value 0.010.

From table 4 authors conclude that no statistical significant difference between both groups according to pregnancy rate with P-value 0.27.

**Table (3):** Patient satisfaction of both drugs:

|  |  |  |
| --- | --- | --- |
| **Side effects** | **Group** | **p-value** |
| **A** | **B** |
| N | % | N | % |
| **Scale 1****(absolutely dissatisfied)** | 0 | 0 | 0 | 0 | **0.010\*** |
| **Scale 2****(dissatisfied)** | 0 | 0 | 2 | 10.5 |
| **Scale 3****(Neither dissatisfied nor satisfied)** | 2 | 10.5 | 4 | 21.1 |
| **Scale 4 (satisfied)** | 2 | 10.5 | 8 | 42.1 |
| **Scale 5****(absolutely satisfied)** | 15 | 78.9 | 5 | 26.3 |

# Table (4): Outcome of treatment:

|  |  |  |
| --- | --- | --- |
|  | **Group** | **p-value** |
| **A** | **B** |
|  | **N** | **%** | **N** | **%** |  |
| **Outcome of****treatment** | Get pregnant | 6 | 31.5 | 5 | 26.3 | 0.27 |
| Failed | 13 | 68.5 | 14 | 73.7 |

**4. Discussion**

Recent years have witnessed a substantial progress in the treatment of infertility and assisted reproductive techniques. The ultimate goal of these therapies is to achieve pregnancy and a healthy baby. Luteal phase support is one of the factors affecting the probability of pregnancy. Historically, luteal phase support in assisted pregnancy techniques is an important issue among researchers. Recently, progesterone supplementation has achieved improved results during ART cycles. Dydrogesterone is a retro-progesterone with a good oral bioavailability which is an active biological metabolite of progesterone. (7)

In the absence of luteal-phase support, the area under the curve for progesterone is suboptimal and accompany by premature luteolysis, short luteal phase and early bleeding. Progesterone is necessary for implantation and for the early development of the fertilized ovum. In response to progesterone, the glands become tortuous and secretory and there is an increase in stromal vascularity, thus making the endometrium both morphologically and functionally well prepared for implantation. (8)

**Salehpour et al** (9), show that oral dydrogesterone is as effective as vaginal progesterone for luteal-phase support in women undergoing IVF. This was prospective, randomized trial conducted on 80 Women with a history of male factor infertility undergoing controlled ovarian stimulation for IVF treatment (fresh cycle) randomly were divided in two groups (group A or oral dydrogesterone group and group B or vaginal progesterone group). The inclusion criteria were the use of GnRH analogue down- regulation and age less than 40 years old with regular menstrual cycles that similar to our trial. All women were euthyroid and normoprolactinemic. Group A (n=40) received 10 mg dydrogesterone QID (40mg daily) and group B (n=40) received 400 mg suppository vaginal progesterone (cyclogest) twice per day (800 mg daily). And the result was Clinical pregnancy rate in cyclogest group was higher than dydrogesterone group but the difference was not significant (p=0.52), furthermore the miscarriage rate in two group was the same. The difference between two groups regarding antral follicle and base line hormonal levels were not significant (p>0.05) and this also support our result.

**Zargar** et al (10). This research reported that no statistically significant difference between groups by P= 0.3. The aim of this study was to compare oral dydrogesterone with vaginal suppository (Cyclogest) and progesterone ampule (progestin) for luteal phase supportin ART cycles. This was a randomized double blinded clinical trial conducted on 612 infertile women who were candidate for IVF or ICSI Research Centre during April 2014 to March 2015. The patients were randomly assigned into three groups according to the administration of the medications as: oral dydrogesterone (30 mg), vaginal progesterone suppository (800 mg) or progesterone ampule (100 mg). Inclusion criteria were infertility duration less than 5 years, maternal age below 40 years, normal levels of hormones, normal transvaginalsonography, and regular menstrual cycles as in our study. The pregnancy was observed in 53 patients (25%) of 212 in the dydrogesterone group, in 53 cases (26.5%) of 200 patients in the cyclogest group, and 53 patients (26.5%) of 200 in the ampule group. Moreover, the miscarriage was occurred in 3 patients (5.6%) of 53 in the dydrogesterone group, in 2 cases (3.8%) of 53 patients in the cyclogest group, and 2 patients (3.8%) of 53 in the ampule group.

**Ganesh** et al (11) supported our results. The aim of this study was To compare the efficacy of oral [dydrogesterone](https://www.sciencedirect.com/topics/medicine-and-dentistry/dydrogesterone) with that of micronized vaginal P gel and micronized P capsule for luteal [supplementation.](https://www.sciencedirect.com/topics/medicine-and-dentistry/supplementation) This was prospective, randomized clinical study conducted on 1,373 infertile women undergoing IVF participated and gave that result: The overall pregnancy rate and miscarriage rate were similar in the three groups. Oral dydrogesterone seems to be a promising drug for luteal support in woman undergoing IVF.

According to patient satisfaction, there are many trials support our result as **Chakravarty et al (12).** this prospective, randomized study was to compare the efficacy, safety and tolerability of vaginal micronized progesterone with oral dydrogesterone as luteal phase support after in-vitro fertilization (IVF). A total of 430 women underwent IVF/intracytoplasmic sperm injection (ICSI) treatment. Patients were randomized to luteal supplementation with either intravaginal micronized progesterone 200 mg three times daily (n = 351) or oral dydrogesterone 10 mg twice daily (n = 79). In cases of a positive pregnancy test, luteal support was continued for 12 weeks. Both dydrogesterone and micronized progesterone were associated with similar rates of successful pregnancies. Vaginal discharge or irritation were reported by 10.5% of patients given micronized progesterone. Significantly (p < 0.05), more patients given dydrogesterone than micronized progesterone were satisfied with the tolerability of their treatment. There were no differences between the treatments with regard to liver functiontests.

Also, **Barbosa** et al (2). This trial is to compare the effects of oral Dydrogesterone and vag. Progesterone for luteal‐phase support (LPS) in women undergoing assisted reproductive techniques (ART). There was no relevant difference between oral dydrogesterone and vaginal progesterone for LPS with respect to rate of ongoing pregnancy, clinical pregnancy or miscarriage Two of the three studies reporting on dissatisfaction of treatment identified lower levels of dissatisfaction among women using oral dydrogesterone than among women using vaginal progesterone (oral dydrogesteronevs vaginal progesterone capsules: (2.5%) vs (25.6%), respectively); (oral dydrogesteronevs vaginal progesterone gel: (4.6%) vs (18.0%), respectively ). The third study showed no difference in dissatisfaction rate (oral dydrogesteronevs vaginal progesterone capsules: (8.3%) vs (7.0%), respectively).

Also, **Khosravi** et al (6). This prospective, randomized, double blind study was performed in a local infertility center from May 2013 to May 2014. It consisted of 150 infertile women younger than35years old undergoing ovarian stimulation for IUI cycles. They underwent ovarian stimulation with oral dydrogesterone (20 mg) as group A and vaginal cyclogest (400 mg) as group B in preparation for the IUI cycles. Clinical pregnancy and abortion rates, mid luteal progesterone (7daysafter IUI) and patient satisfaction were compared between two groups and there result was The mean serum progesterone levels was significantly higher in group A in comparison with group B (p=0.001). Pregnancy rates in group A was not statistically different in comparison with group B (p =0.58). Abortion rate in two groups was not statistically different (p =0.056). Satisfaction rates were significantly higher in group A compared to group B (p<0.001).

**Tomic** et al 13). This is Randomized controlled trial. A total of 853 infertile women undergoing IVF/ICSI treatment in University Hospital Center “Sisters of Mercy”, Zagreb, Croatia. [Luteal support](https://www.sciencedirect.com/topics/medicine-and-dentistry/luteal-support) was provided as Crinone 8%® vaginal progesterone gel (90 mg) administered daily, or oral dydrogesterone Duphaston® (2× 10 mg) administered two times daily. Progesterone was administered from the day of [oocyte retrieval](https://www.sciencedirect.com/topics/medicine-and-dentistry/oocyte-retrieval)(day 0) till test or in a case of pregnancy, until week 10. And the result was that the on-going pregnancy rates were insignificantly different. Overall satisfaction and tolerability were significantly higher in the dydrogesterone group than in the Crinone group. [Vaginal bleeding,](https://www.sciencedirect.com/topics/medicine-and-dentistry/vagina-bleeding) interference with [coitus](https://www.sciencedirect.com/topics/medicine-and-dentistry/coitus) and local adverse side effects such as vaginal irritation and discharge occurred significantly more in Crinone group than in dydrogesterone group.

Our data were contradictory with the results of the study by **Patkiet** et al (14). The aim of the present study was to evaluate dydrogesterone for luteal-phase support in assisted reproductive technologies (ART) and to compare it with micronized vaginal progesterone. All patients underwent long-term downregulation with gonadotropin- releasing hormone agonists. In phase I, 498 patients were divided into three groups: long protocol and not at risk of ovarian hyperstimulation syndrome (OHSS) (group A); long protocol and at risk of OHSS (group B); and those in a donor oocyte program (group C). All patients received micronized progesterone 600 mg/day, vaginally. They were also randomized to dydrogesterone 20 mg/day (n = 218) or placebo (n = 280). The pregnancy rate was higher with dydrogesterone than with placebo in group A (33.0% vs. 23.6%), group B (36.8% vs. 28.1%) and group C (42.9% vs. 15.6%; p < 0.001). In phase II, 675 patients were divided into the same three groups (groups D, E and F) and were randomized to dydrogesterone 30 mg/day (n = 366) or micronized progesterone 600 mg/day (n = 309). The pregnancy rate was significantly higher with dydrogesterone than with progesterone in group D (39.1% vs. 26.7%; p <0.01), group E (41.2% vs. 35.6%; p < 0.01) and group F (48.2% vs. 33.9%; p < 0.001). In conclusion, dydrogesterone is effective in luteal-phase support in ART.

**Conclusion:**

From the results of the present study, it was found that, there was no statistically significant difference between oral dydrogesterone and vaginal progesterone in luteal support of IVF/ICSI stimulated cycles according to pregnancy rate but slightly higher rate with oral dydrogesterone.

Oral dydrogesterone show better patient compliance than vaginal progesterone. Interference with coitus and local adverse side effects such as vaginal irritation and discharge with vaginal progesterone could be avoided with the use of oral dydrogestero.

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