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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ijogr.org

Original Research Article

Marvel drug for infertility!!

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ARTICLE INFO

Article history:
Received 23-06-2023
Accepted 30-10-2023
Available online 22-11-2023

Keywords:
Oral dydrogesterone
Oral sustained release micronized hydroxy-progesterone
Infertility

ABSTRACT

Background: Comparative study of Dydrogesterone versus oral sustained release micronized hydroxy-progesterone for support of luteal phase.
Materials and Methods: A randomized controlled trial, performed from March 2022 to April 2023. 200 women between 18–40 years of age attending infertility OPD at Gandhi hospital were enrolled in this study. Subjects were randomized and were given either oral dydrogesterone or oral sustained release micronized hydroxy-progesterone. Statistical analysis was done accordingly.
Results: In the present study, oral dydrogesterone was demonstrated to be superior than sustained release micronized hydroxy-progesterone, with UPT positive rates being 83% and 30% respectively. Dydrogesterone given orally was tolerated well with similar safety profile to sustained release micronized hydroxy-progesterone.
Conclusion: Our study results depicted the use of dydrogesterone to be effective when compared to oral sustained release micronized hydroxy-progesterone in terms of luteal phase support. Dydrogesterone is hailed to be superior in regards of positive pregnancy rates in the current study.

1. Introduction

People who did not conceive after one year of marital life with regular unprotected intercourse is defined as infertility.[1] 85–90% of young couples conceive within one year.[2]

Progesterone, stimulate the growth of blood vessels that supply the endometrium, helps to secrete nutrients to grow early embryo. PPOS (progesterone primed ovarian stimulation) prevent activation and transmission of Estradiol (E2)-induced LH surges and serves as an alternative to conventional treatment with GnRH analogues.

Ovarian stimulation leads to progesterone deficiency so Luteal phase support is routinely performed during infertility.[3] Use of progestogens in infertility was associated with increased in the live birth rate,[4] a systematic review demonstrated this. Oral progesterone associated with low bioavailability with (due to first pass metabolism) side effects, such as nausea, vomiting, lack of sleep, etc.[5]

Dydrogesterone is a endogenous progesterone with similar molecular structure and pharmacological effects, dydrogesterone is more potent than natural progesterone, with a higher affinity to progesterone receptor than progesterone.[6,7]

Dydrogesterone has more bioavailability than progesterone.[8] Dydrogesterone down regulates cytokines that are detrimental to pregnancy has been proposed and helps in healthy pregnancy;[9] Dydrogesterone shifts Th1 or pro-inflammatory bias towards a Th2 or anti-inflammatory bias, it is an immune-modulator and studies showed that dydrogesterone supplementation is helpful.[10] But it is marginally expensive than other competitive molecules.

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https://doi.org/10.18231/j.ijogr.2023.087

2. Materials and Methods

2.1. Study design

200 women with infertility between 18–40 yr old attending infertility OP at Gandhi Hospital were enrolled in this study. The study period was for 13 months from March 2022 to April 2023 at Gandhi Hospital, after approval from the ethics committee. It was double blind study. Subjects were then randomized into two groups A and B, by using odd-even method. Ovulation induction was done by giving Tab Letrozole 2.5mg BD for five days starting from day 2 of menstrual cycle to day 6 of menstrual cycle in all patients which were comparable in group A and B.

Trans-vaginal sonography was done for all patients from the 6^{th} day of menstrual cycle. Size of follicle was measured on alternate days. At follicular size of 18mm Human Chorionic Gonadotropin (HCG) 5000 IU is administered intramuscularly to trigger ovulation. After ovulation trigger patients were advised to follow timed intercourse on alternate days. Ovulation was confirmed after 36 hrs of Ovulation trigger by performing vaginal ultrasonography and detecting disappearance of dominant follicle and minimal free fluid in POD. Subjects from one of the groups received oral Tablet Dydrogesterone 10mg BD and the other group received oral Cap. Sustained release micronized hydroxy-progesterone 200mg BD after ovulation. Respective drugs were continued in both groups during the luteal phase.

Pregnancy was determined by positive serum β HCG test on day 22 of cycle and Urine HCG after 5 days of missed period. Pregnancy was confirmed by identifying foetal heartbeats 2 weeks following the positive β HCG.

2.2. Inclusion criteria

All women (18 to 40 years age; BMI ≥18 to ≤ 30kg/m2) with history of infertility according to definition [6 months for women ≥38 years of age].

Women giving informed consent.

2.3. Exclusion criteria

Women with history of intrauterine abnormalities and severe endometriosis.

Women with bilateral tubal occlusion.

Couples with male infertility.

Women with significant endocrine, cardiac, renal, hepatic complicationsand chronic substance abuse.

Patient should not take other progesterone products.

3. Results

In the present study, oral dydrogesterone was demonstrated to be superior than sustained release micronized hydroxy-progesterone, with UPT positive rates being 83% and 30% respectively. Oral dydrogesterone was tolerated well with similar safety to sustained release micronized hydroxy-progesterone. May be vaginal route had different absorption for micronized hydroxyl progesterone.

The statistical analysis comprises the positive pregnancy rate, compliance and tolerance.

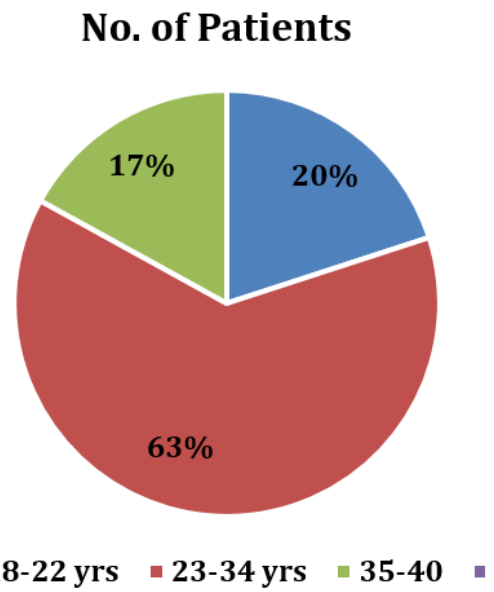

Figure 1: Distribution of patients according to age groups

In this study, majority of patients (63%) belong to the 23-34 yrs. Age group, the youngest being 20 years and the oldest being 36 years.

In our study, majority of patients (69%) had a marital life of less than 5yrs, and the longest marital life being 12 yrs.

Table 1: Distribution of the patients with pregnancy after OI+dydrogesterone

No. of Induction cycles	No. of UPT + ve patients	P ercentage
1 cycle	20	24.09%
2 cycles	39	46.98%
3 cycles	24	28.91%
Total	83	100%

In this study, about 47% of the participants conceived after two cycles of ovulation induction. Only 24% of the participants conceived after one cycle of OI.

In this study, about 73.4% of the participants conceived after two cycles of ovulation induction. Only 10% of the participants conceived after one cycle of ovulation induction.

In this study, on comparing the study groups, subjects UPT +ve after 3 cycles of ovulation induction are significantly higher in Dydrogesterone group.

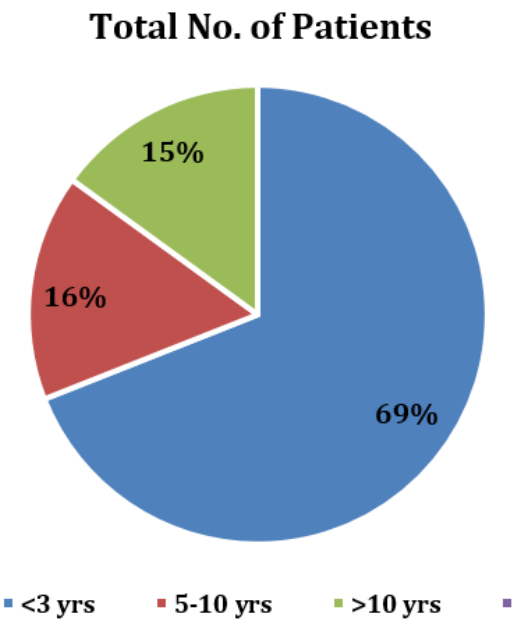

Figure 2: Distribution of patients according to marital life

Table 2: Distribution of the patients with pregnancy after OI+sustained release micronized hydroxy-progesterone

No. of Induction cycles	No. of UPT +ve patients	Percentage
1 cycle	3	10%
2 cycles	22	73.33%
3 cycles	5	16.67%
Total	30	100%

Table 3: Distribution of the patients with pregnancy after OI+sustained release micronized hydroxy-progesterone v/s OI+dydrogesterone

No. of Induction cycles	No. of UPT +ve patients after OI+sustained release micronized hydroxy-progesterone	No. of UPT +ve patients after OI+dydrogesterone	Total
1 cycle	3 (2.65%)	20 (17.69%)	23
2 cycles	22 (19.46%)	39 (34.51%)	61
3 cycles	5 (4.54%)	24 (21.23%)	29
Total	30 (26.65%)	83 (73.45%)	113

$\chi 2$=6.273; P<0.05.

4. Discussion

Dydrogesterone is an oral progesterone approved for the treatment of miscarriages associated with progesterone deficiency and infertility due to luteal phase insufficiency.[11] Progesterone is a product of choice for luteal support[12,13] as shown in studies done by Daya S., Gunby, J., et al. (2004) and van der Linden, Michelle et al., when compared to hCG with lower rates of OHSS.

Dydrogesterone stands out for its unique pharmacological profile, binding exclusively to the progesterone receptor without exhibiting estrogenic, androgenic, or glucocorticoid activity, setting it apart from other progestogens.[14] Because of better bioavailability progesterone like activity of the main metabolites, the equivalent dose of dydrogesterone is 10-20 times lower than that of oral micronized progesterone.[14]

In the present study no side effects like drowsiness, nausea and vomitings were identified with dydrogesterone and sustained release micronized hydroxy-progesterone which was comparable to studies done by Salehpour et al(2013).,[15] and Wagh et al. (2021).[16] Similar results were obtained in an RCT done by Herman Tournaye et al. and others.[11]

In the present study the results obtained proved the use of dydrogesterone for luteal support is beneficial as data depicted in Table 3.

Previous studies conducted for luteal phase support in infertility treatment, the daily dose of dydrogesterone ranged from 20 to 30 mg; however, 10 mg twice daily was shown to have reduced endometrial development compared with 200 mg vaginal micronized hydroxyprogesterone TID.[17]

But in our study it shows dydrogesterone shows increased endometrial development compared to micronized hydroxy progesterone.

Oral dydrogesterone is equally efficient as the micronized hydroxy progesterone in luteal support of infertility treatment with higher satisfaction and better tolerability. Oral dydrogesterone is effective drug, tolerated well can be used for routine luteal support in infertility treatment.[18]

Oral dydrogesterone and vaginal progesterone are similarly effective. And oral dydrogesterone is superior with improved clinical pregnancy rate compared to vaginal progesterone capsules. However, in that study data is sufficient to conclude that dydrogesterone does not cause a clinically relevant reduction on ongoing and clinical pregnancy rates.[19]

In our study dydrogesterone is superior to micronized hydroxy progesterone in luteal phase support and achieving clinical pregnancy rate.

5. Conclusion

Dydrogesterone emerges as a commendable choice for luteal phase support in infertility treatment. Its demonstrated superiority when compared to oral micronized hydroxy-progesterone in achieving positive pregnancy rates. Both medications demonstrated good tolerability with minimal side effects. Dydrogesterone can be a promising asset in the realm of reproductive medicine. Its unique pharmacological attributes, devoid of estrogenic, androgenic, or glucocorticoid effects, underscore its suitability for this critical phase of assisted reproduction. Dydrogesterone's potential to enhance successful outcomes in infertility treatment merits its strong consideration as a valuable adjunctive therapy during luteal phase.

6. Source of Funding

None.

7. Conflict of Interest

There is no conflict of interest between the authors.

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Cite this article: Vellanki J, Sravani E. Marvel drug for infertility!!. *Indian J Obstet Gynecol Res* 2023;10(4):456-459.