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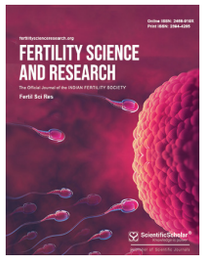

Original Article *Infertility*

Evaluation of Necessity of Routine Luteal Phase Support After Ovarian Stimulation by Oral Ovulogen in Intrauterine Insemination Cycles

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ABSTRACT

Objectives: Assisted reproductive technology aims to achieve superovulation to receive optimum outcomes. Resulting supraphysiological estradiol levels cause luteal phase defect due to feedback inhibition of FSH and LH. During intrauterine insemination, this mechanism is seldom seen. Thus, routine use of progesterone in clinical practice adds to burden of medication and cost without much evidence to recommend it. The objective was to evaluate the clinical utility of luteal support with progesterone in IUI cycles stimulated by oral ovulogens.

Material and methods: A total of 200 women attending infertility OPD were randomly selected as per inclusion criteria (Unexplained infertility, Mild male factor, Donor sperm IUI, PCOD, Coital factors, Mild endometriosis) whereas those with factors like Age more than or equal to 38 years, thin endometrium, previous two or more IUI failures, history suggestive of luteal phase defect-short luteal phase, premenstrual spotting, premature rupture of follicles, presence of structural uterine anomaly, History of endocrine or autoimmune diseases were excluded from the study. After a baseline transvaginal examnination, they underwent ovarian stimulation from day 2 to day 6 by oral ovulogen, letrozole (2.5 mg) followed by Follicular study as per protocol and HCG trigger was given 10000 I.U s/c once dominant follicle develioped and IUI was timed at 36–44 hours after trigger only after confirmation of rupture on USG. Patients divided into two groups. Group A included those with absent luteal support and Group B to receive tab dydrogesterone. Conception, if any, reported by a positive urine pregnancy test kits or confirmed with serum Beta HCG is measured in mIU/ml.

Results: Among cases, 23% had a positive urine pregnancy test.Whereas, in controls 21% had a positive urine pregnancy test, the difference being statistically non-significant with p value = 0.733. Clinical pregnancy rate as a marker of successful outcome of study was present in 22%.Of cases and 21% of controls, although difference was statistically non-significant with p = 0.755.

Conclusion: Luteal phase support with progesterones makes no significant difference in clinical pregnancy rate oral ovulogen stimulated IUI cycles.

Keywords: Clinical pregnancy rate, Intrauterine insemination, Luteal phase defect, Luteal support, Ovulogen

INTRODUCTION

Infertility is defined as the failure to achieve a pregnancy even after twelve months of regular unprotected sexual intercourse.[1] The endometrium modifies itself under the influence of hormones to prepare for implantation of the growing embryo. This is divided into the follicular phase, ovulatory phase, and luteal phase. Luteal phase defect (LPD) was described by Jones in

1949.[2] The luteal phase begins after ovulation and lasts till the onset of the next menstruation and usually lasts 12–16 days. During this phase, the action of the luteinising hormone (LH) causes the corpus luteum to undergo changes known as 'luteinisation' which induces it to become the secretory endometrium.[3] This is to provide a receptive endometrium for the embryo to implant. Failure of which causes defective implantation phase. LPD is a clinical condition characterised by inadequate progesterone secretion in amount or duration to support the endometrium for subsequent implantation, if any.[4] Luteal phase deficiency is clinically defined as an abnormal luteal phase length of ≤10 days. This is possibly due to inadequate progesterone levels or size of exposure or probably endometrial progesterone resistance at the molecular level.[5]

Assisted reproductive technology (ART) includes superovulation to aim at multiple follicles.[6,7] Multifollicular development leads to higher-than-normal Oestradiol levels, which inhibit follicle-stimulating hormone (FSH) and LH, leading to luteal defect through inhibition at the hypothalamic-pituitary axis.[8]

Intrauterine insemination (IUI) is a useful technique for the management of unexplained infertility, endometriosis, and mild male factors in donor sperm cycles. This aims to increase conception chances by maximising the number of healthy sperm to fertilize.[9] The outcome is influenced by many confounding factors, like the quality of the luteal phase.

However, IUI involves the growth of one or two follicles, which is unlikely to produce the above situation. Hence, in IUI cycles, giving luteal support routinely has become a debatable issue.

Routine use of progesterone in every patient has become a habit, instead of the need, adding to unnecessary doses and cost of medication and cost to the patient.

Till today, only a few studies exist that establish the absolute recommendations of luteal phase support fertility in natural cycles or non-gonadotropin-induced ovulatory cycles.

Objective

To evaluate the clinical pregnancy rates with and without progesterone supplementation in the luteal phase in IUI cycles following stimulation with oral ovulogens.

MATERIAL AND METHODS

Type of Study: Prospective observational randomised comparative study.

Sample size calculation: The study of Müge Keskin *et al.*[5] observed that the clinical pregnancy rate in the control group was 13.9% and in the study group was 6.8%. With these values as a reference, the minimum required sample size with 80% power of study and 5% level of significance was 285 patients in each study group. So the total sample size calculated was 570 (285 patients per group).

$$n > = ((pc^*(1-pc) + pe^*(1-pe))^*(Z\alpha + Z\beta)2)/(pc-pe)2$$

with

pc = clinical pregnancy rate in the control group

pe = clinical pregnancy rate in the study group

Where Z α is the value of Z at a two-sided alpha error of 5% and Z β is the value of Z at the power of 80% calculations:

$$n > = ((0.139^*(1-0.139) + 0.068^*(1-0.068))^*(1.96 + 0.84)^2)/(0.139-0.068)^2$$

$$> = 284.69 = 285 \text{ (approx.)}$$

However, due to limitations in the study period, convenient sampling was done with a study population of 200 women (100 in each group).

Statistical Analysis

Categorical variables were presented in number and percentage and continuous variables were presented as mean ± SD and median. The normality of data was tested by the Kolmogorov-Smirnov test.

Statistical tests applied were as follows:

1. Quantitative variables were compared using an unpaired t-test/Mann-Whitney test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables were compared using the Chi-Square test/Fisher's exact test.

A p-value of <0.05 was considered statistically significant.

The data was entered in an MS EXCEL spreadsheet, and analysis was done using. Statistical Package for Social Sciences (SPSS) version 21.0.

Randomisation: block randomisation.

Methodology: 200 infertile women who attended the infertility outpatient department (OPD) in a level 2 ART centre during a period between November 2021 and July 2022.

All women falling under inclusion criteria (unexplained factors, donor sperm IUI, mild male factor infertility, coital dysfunction, anovulatory infertility, and mild endometriosis) irrespective of body mass index (BMI), racial, or socioeconomic consideration were recruited after written consent. Those with an age more than or equal to 38 years, thin endometrium <7 mm on the trigger day, two or more IUI failures, short luteal phase, premenstrual spotting, and premature rupture of follicles, history of recurrent pregnancy loss (RPL), uterine structural anomaly, and presence of

endocrine or autoimmune disorders were excluded from the study. All the patients underwent complete history evaluation and physical examination. Baseline clinical and hormonal parameters were noted.

Confounding factors: nil.

All subjects underwent baseline transvaginal scans on day 2 of the menstrual cycle, followed by ovarian stimulation from day 2 to day 6 by oral ovulogen, letrozole 2.5 mg (stimucor, 2.5 mg oral, corona, India). Follicular monitoring was done by transvaginal route from day 8/9 onwards to assess the follicles and endometrial thickness. When the follicle reached a size of 18–24 mm with endometrial lining ≥7 mm, human chorionic gonadotrophin (HCG) trigger 10,000 I.U (international units) s/c followed by IUI, timed 36–44 hours after trigger only after confirmation of rupture on ultrasound (USG) was done. After IUI, subjects were randomly allocated to either group A or B, with absent luteal support and others receiving oral dydrogesterone 10 mg (Duphastan, 10 mg oral, Abott, India) twice daily for 17 days following IUI, respectively. Conception, if any, was documented after a positive urine test kit or confirmed with serum beta human chorionic gonadotrophin (HCG) measured in mIU/ml. Patients with positive reports confirming pregnancy were followed by transvaginal ultrasound (TVS USG). The outcomes of the study were measured in terms of clinical pregnancy. Clinical pregnancy is defined as the one with confirmation of cardiac activity on ultrasound.

RESULTS

Out of 200 patients, infertility was selected as per inclusion or exclusion criteria. After intrauterine insemination, they were further randomly allocated into two groups of 100 subjects each, depending upon no luteal phase support or receiving it, respectively.

The mean age among subjects in Group A was 31.05 ± 4.78 years, and Group B was 31.2 ± 4.44 years, respectively with no statistically significant difference [Table 1].

Among the patients recruited, primary infertility was present in 74% of Group A and 72% of Group B. 26% of Group A and 28% of Group B had secondary infertility [Table 2].

Among oral ovulogens, letrozole 2.5 mg was prescribed once a day from day 2 to day 6 of menses. As the dominant follicle grew 18–24 mm, with endometrium more than 7 mm, an HCG 10,000 I.U. trigger was given.

Mean endometrium thickness (ET) on the trigger day of Groups A and B were 8.46 ± 1.36 mm and 8.44 ± 1.17 mm, respectively.

After the trigger, mono-follicular development was observed in 55% of Group A and 71% of Group B. And two follicles seen in 45% of Group A and 29% of Group B [Table 3].

Table 1: Baseline age characteristics between study groups.

Age (years)	Group A	Group B	Total
<=30 years	42% (42/100)	35% (35/100)	77 (38.50%)
>30 years	58% (58/100)	65% (65/100)	123 (61.50%)
Mean ± SD	31.05 ± 4.78	31.43 ± 4.09	31.24 ± 4.44

Table 2: Comparison of diagnosis between study groups.

Diagnosis	Group A (n = 100)	Group B (n = 100)	Total
Primary Infertility	74 (74%)	72 (72%)	146 (73%)
Secondary Infertility	26 (26%)	28 (28%)	54 (27%)
Total	100 (100%)	100 (100%)	200 (100%)

Table 3: Comparison of distribution of follicles in study groups.

ET on trigger (mm)	Group A (n = 100)	Group B (n = 100)	Total	
Mean ± SD	8.46 ± 1.36	8.44 ± 1.17	8.45 ± 1.26	p = 0.916
Follicles on the day of trigger	Group A (n = 100)	Group B (n = 100)		
1	55 (55%)	71 (71%)	126 (63%)	p = 0.019
2	45 (45%)	29 (29%)	74 (37%)	
Total	100 (100%)	100 (100%)	200 (100%)	

Table 4: Comparison of urine pregnancy test between cases and controls.

Urine pregnancy test	Group A (n = 100)	Group B (n = 100)	Total
Negative	77 (77%)	79 (79%)	156 (78%)
Positive	23 (23%)	21 (21%)	44 (22%)
Total	100 (100%)	100 (100%)	200 (100%)

Table 5: Clinical pregnancy rates among study groups.

Clinical pregnancy	Group A	Group B	Total
No	77% (77/100)	79% (79/100)	156 (78%)
Yes	22% (22/100)	21% (21/100)	43 (21.5%)
Ectopic/abortion	1% (1/100)	0%	0.5%

Intrauterine insemination was performed after 36–44 hours of trigger, after confirming rupture on ultrasound. Patients were randomly allocated to cases, in whom with tab dyrogesterone 10 mg twice a day for 17 days after the procedure. Conception was tested by urine pregnancy test (UPT) kits.

In Group A, 23% had a positive urine pregnancy. Whereas, in Group B, 21% had a positive test, the difference statistically non-significant with p-value = 0.733 [Table 4].

Patients with positive reports confirming pregnancy were followed by transvaginal ultrasonography. Outcomes noted as positive clinical pregnancy described as the presence of an intrauterine sac with cardiac activity. Clinical pregnancy as a marker to project a successful outcome of the study was present in 22% in Group A and 21% in Group B, although statistically non-significant with p = 0.755 [Table 5].

DISCUSSION

Today, intrauterine insemination is among the most prescribed procedures during infertility management. Its success rate depends on numerous factors such as indication, optimal procedures for sperm preparation, insemination timing, preventing premature LH surges, and the quality of the luteal phase.[10] The term, LPD refers to an abnormal luteal phase causing failure to develop a fully mature secretory endometrium. The pathological basis of this is insufficient progesterone production in quantity or duration leading to impaired implantation and early pregnancy loss. This clinical entity may be seen in normally menstruating fertile women and in certain medical conditions such as advanced age, eating disorders, stress, obesity, polycystic ovary syndrome, hyperprolactinemia, endometriosis, and hypothyroidism.

Luteal support refers to luteal phase administration with exogenous progesterone to support the endogenous hormone. During assisted reproductive technology protocols, multi-follicular development leads to supraphysiological oestrogen levels that disrupt the hypothalamic-pituitary axis, leading to a short luteal phase. Hence requiring luteal support. Fatemi *et al.* in 2007 have advocated milder stimulation protocols to eventually overcome the luteal phase defect.[11] However, in transvaginal ultrasonography with oral agents, only one or two dominant follicles may form, hence virtually negating the above requirement.

Studies conducted by various authors have incorporated ovulation induction by gonadotropins with or without clomiphene citrate. Our study has mentioned the effects of progesterone supplementation in oral form, i.e., dydrogesterone. It is a retro progesterone with oral bioavailability and has an anti-oestrogenic effect on the endometrium, achieving the desired secretory transformation. Studies pioneered by Chakravarty BN in 2005 and Taş M in 2019 observed an equal efficacy of both oral dydrogesterone and micronised progesterone with similar rates of successful pregnancies in intrauterine insemination as well as ART cycles.[7,8] Considering ease, comfort, and tolerability profile, we incorporated oral progesterone for luteal support.

Kyrou D *et al.* 2010 conducted a prospective randomised controlled trial to assess the role of micronised progesterone in clomiphene citrate-stimulated IUI in normovulatory patients. There was no difference in ongoing pregnancy between cases and controls (8.7% vs. 9.3%, p = 0.82; difference −0.6%, 95% confidence interval (CI). Although it was the first RCT to test the necessity of luteal support with clomiphene citrate-induced intrauterine insemination cycles, it is underpowered to confirm a difference in the ongoing pregnancy rate of 5%, which was clinically significant.[12]

Letrozole is an aromatase inhibitor that augments FSH release from the hypothalamus and increases the sensitivity of developing follicles to FSH. Letrozole may act to increase mid-luteal progesterone levels after ovulation. In comparison to natural cycles, letrozole was demonstrated to significantly increase mid-luteal progesterone levels and support the luteal endometrium. Progesterone supplementation, if any, would be only additive, not necessary.

To date, almost no literature exists for studying the requirement of the luteal phase in letrozole-stimulated IUI cycles. Except for a few, like Montville *et al.* who in 2010 conducted a retrospective analysis in letrozole-stimulated IUI cycles and observed clinical pregnancies were documented in 21.1% of cycles in the progesterone group, compared versus none in the non-progesterone group.[13] They hence recommended progesterone support in letrozole cycles. Whereas, in our study, a positive clinical pregnancy rate as a marker of the successful outcome of the study was present in 22% of cases and 21% of controls, although the difference was statistically non-significant with p = 0.75.

But for today's practitioners, it has become routine to prescribe progesterone in every luteal phase, irrespective of the protocol applied, adding to the huge burden of expenses on the patient's side. Maher MA in 2011 conducted a prospective randomised trial on 71 patients using recombinant FSH followed by IUI and further subdividing it into two groups receiving vaginal progesterone support versus not.[14] Their findings were in favour of luteal support since the clinical pregnancy rate per patient was more for supported cycles (54.92% vs. 35.21%, respectively; p = 0.016).[13] Agha-Hosseini M conducted a prospective randomised control trial in 2012 on 148 patients having unexplained or male factors undergoing IUI after controlled ovarian stimulation. Luteal support was provided by vaginal

suppositories. Their findings supported that per-cycle rates of clinical pregnancy were higher in those receiving luteal support (24.3% vs. 14.1%, p = 0.027).

Miralpeix E *et al.* 2014[2] conducted a systematic review and meta-analysis with five randomised controlled trials (RCT) and observed that that luteal support with vaginal progesterone achieved significantly higher live birth rate (RR 1.94, 95% confidence interval [CI] 1.36 to 2.77), and clinical pregnancy rate (RR 1.41, 95% CI 1.14 to 1.76). In the subgroup analysis, this beneficial effect of receiving progesterone was only observed in the group stimulated with gonadotropins (RR 2.28, 95% CI 1.49 to 3.51), compared to the group stimulated with clomiphene citrate (CC) (RR 1.30, 95% CI 0.68 to 2.50).

In 2013, Micah J. Hill conducted a systematic review and meta-analysis evaluating the outcome of progesterone supplementation with gonadotropins versus clomiphene citrate.[6] Their findings were similar to results in other studies that higher clinical pregnancy rates of progesterone were supplemented cycles (OR 1.77, 95% CI 1.20–2.6). However, clomiphene citrate-stimulated cycles showed no difference in clinical pregnancy (OR 0.89, 95% CI 0.47–1.67). This probably is attributed to inherent increased LH levels in clomiphene cycles and an improved corpus luteal function. Clomiphene citrate induces ovulation by blocking the hypothalamic oestrogen receptors. This leads to an increase in GnRH (gonadotropin-releasing hormone). As a result, FSH and LH secretion are increased during clomiphene citrate.

Müge Keskin, in 2020, conducted a prospective controlled randomised study on 87 patients to observe the necessity of vaginal progesterone on gonadotropin-stimulated IUI cycles. Their assessment was not in favour of luteal phase support, as clinical pregnancy and rates were comparable (6.8% in cases vs. 13.9% in controls = 0.48).

Limitations

Due to the limited study period and restricted sample size, the results need to be observed for a larger population over time for correct statistical inference. Furthermore, data inference on live birth rates wasn't feasible due to the limited study period and could be observed and noted with prospective study patterns.

CONCLUSION

Luteal phase defect has multiple aetiologies. Assisted reproductive techniques involving superovulation and subsequent negative feedback on the HPO axis are among the known indications of supporting the luteal phase. Presently, in IUI cycles there is a reflex to routinely prescribe progesterone for luteal phase support. Our study has attempted to identify that unless indicated, luteal support with progesterone has no significant effect on clinical pregnancy in IUI cycles. To date, no previous studies have incorporated oral progesterone for use and study efficacy for routine luteal phase support. Moreover, with limited literature on the use of letrozole as an oral ovulogen, our study could be a basis for future research and practice development. Currently, there is a growing awareness that even with mild/minimal stimulations with few follicles developing, routine luteal progesterone support does not seem to improve outcomes significantly. In the future, inferences of current research need to be expanded over mild ART stimulations so that habitual progesterone overprescription and its costs may be avoided.

Abbreviations

ART: Assisted reproductive technique, BMI: Body mass index, ET: Endometrial thickness, FSH: Follicle stimulating hormone, HCG: Human chorionic gonadotropin, IUI: Intrauterine insemination, LH: Luteinising hormone, LPD: Luteal phase defect, PCOS: Polycystic ovarian syndrome, TVS: Transvaginal sonography, UPT: Urine pregnancy test.

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Author contribution

PR, RS, FR, AG: Patient analysis, performing IUI and result analysis were entirely conducted by esteemed coauthors and embryology team.

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