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Progesterone Supplementation in PCOS Women Undergoing Clomiphene Citrate Stimulated IUI may Improve Pregnancy.

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ABSTRACT

Background: To evaluate the efficacy of progesterone supplementation in clomiphene citrate(CC) stimulated PCOS women undergoing intrauterine insemination(IUI) in improving pregnancy outcome **Methods:** This was a prospective observational study conducted on 993 PCOS women undergoing first IUI cycle. Ovarian stimulation was done with 100mg clomiphene from day 3 to day 7. In 860 PCOS women, IUI was performed. They were divided into two groups, the study group (n=442) received 600 mg intravaginal progesterone for luteal phase support (LPS) daily for 14 days and the control group (n=418) did not receive progesterone. Uterine blood flow was assessed on the day of IUI and 14 days after insemination. **Result:** Data from 860 women were analyzed. The pregnancy rate per cycle was higher in progesterone supplemented group than unsupported group. However, miscarriage rate was significantly lower in the study group compared with the control group. Live birth rate was significantly higher in progesterone supported group compared with control subjects. The study group demonstrated significant reduction in resistance index (RI), pulsatility index (PI) and systolic/diastolic (S/D) ratio of uterine artery on day14. **Conclusion:** Progesterone supported IUI cycles demonstrated higher live birth rate in PCOS women stimulated with CC.

Keywords: Luteal phase support, PCOS, clomiphene citrate, progesterone supplementation.

INTRODUCTION

Intrauterine insemination (IUI) is presently one of the most frequently used techniques to achieve conception in infertile couples and Clomiphene citrate (CC) is the most commonly used drug for ovulation induction. Its outcome is influenced by multiple confounding factors, one of which might be the quality of the luteal phase. For normal functioning of luteal phase, optimal pre-ovulatory follicular development and appropriate production of progesterone by corpus luteum is essential.[1]

The benefit of progesterone for luteal phase support in in-vitro fertilization (IVF) cycles has been proved beyond doubt but there is little consensus regarding the use of luteal phase progesterone following ovulation induction (OI) in IUI cycles.[2] It has been shown that in normo-ovulatory patients stimulated with clomiphene for IUI, luteal phase support (LPS) is not associated with a higher pregnancy rate.[3] Polycystic ovarian syndrome (PCOS) is a common female endocrinopathy with estimated prevalence varying from 3–20% depending on the diagnostic criteria used.[4] These patients have irregular menstrual cycles, abnormal follicular development and chronic anovulation or oligoovulation, which may result in insufficiency of corpus luteum. Hence, this group makes an attractive model to study the beneficial effects of progesterone supplementation in luteal phase.

Several studies have reported that endometrial, sub-endometrial, or uterine blood flow may be predictors for pregnancy in IVF cycle. But, there are limited studies regarding the relationship between blood flow and pregnancy after IUI. In the light of above observations, the objective of our study was to elucidate the role of progesterone for LPS and its correlation with uterine blood flow and pregnancy outcome in CC stimulated PCOS women undertaking IUI.

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MATERIALS AND METHODS

This was a prospective, observational study undertaken at the Institute of Reproductive Medicine, Kolkata performed between January 2013 to March 2015. Approval was obtained from the

Institutional Research Ethics Board. Written informed consent was taken from all women included in this study. Total 993 women diagnosed by the Rotterdam criteria as PCOS (Rotterdam consensus, 2004), undergoing their first IUI cycle were included in the study.

All patients included in the study were between the age group of 25 to 40 years. All women had at least one tube patent as demonstrated by HSG or laparoscopy. Women with FSH>12mIU/ml, pre-existing ovarian cyst on day 3, abnormal TSH or prolactin levels and having male partner with poor semen quality (WHO,2010) were carefully identified and excluded.

All patients were stimulated with 100 mg CC from day 3 to day 7. Follicular study was done from day 10 onwards. Ovulation was triggered with 5000 IU hCG, when at least one follicle reached ≥18mm. Single IUI was performed after confirmation of ovulation by transvaginal sonography (TVS). IUI cycle was cancelled in 133 patients. Remaining 860 subjects were divided into two groups. The study group (n = 442) received 600 mg intravaginal progesterone for LPS daily, starting one day after IUI. If the patient conceived, luteal support was continued up to 10th week of pregnancy. Patients in the control group (n = 418) did not receive progesterone following IUI. Pregnancy test was done 14 days after IUI and intrauterine pregnancy was confirmed by using TVS two weeks after a positive pregnancy test.

All scans were done by the same sonologist. Color Doppler in the two-dimensional mode was used to obtain flow velocity waveforms from the ascending main branch of the uterine artery in a longitudinal plane on either side of the cervix. The cursor of the Doppler was positioned to obtain good color signals from the vessels. The pulsatility index (PI), resistance index (RI), and systolic/diastolic (S/D) ratio of the uterine artery were calculated electronically. It was found that there was almost no difference in uterine artery PI, RI, and S/D ratio between the left and right side. On the day of IUI, uterine blood flow was assessed in all 860 patients and repeated after 14 days in 442 patients in the study group and in 418 patients in the control group.

Cycle characteristics of patients in terms of number of follicles >14mm, size of follicle on day of hCG, day of hCG trigger and endometrial thickness (ET) were compared. Pregnancy rate per completed cycle, miscarriage rate and live birth rate were compared between the two groups. Clinical pregnancy was defined as presence of viable fetus on TVS. Pregnancy was followed by regular antenatal care till delivery. Live birth was defined as having a live baby at delivery.

The primary outcome measures were pregnancy rate and live birth rate and secondary outcome measures were miscarriage rate and uterine blood flow. This study was adequately powered. Data were statistically analyzed using the SPSS 'computer package (SPSS version 20, SPSS Inc., Chicago, IL) with the student's t-test and Chi-square test. Results were expressed as mean and standard error of mean. P<0.05 was considered statistically significant.

RESULTS

Initially 993 PCOS women undergoing first IUI cycle with CC were included, out of which IUI was cancelled in 133 women. Major cause of cancellation was inadequate response (n=113). Other reasons for IUI cancellation were luteinized unruptured follicle, failed semen collection and on demand cancellation.

Demographic and baseline hormonal profile were comparable in both groups [Table 1]. There was no statistically significant difference between the two groups in terms of cycle characteristics like number of follicles >14mm, size of follicles on day of hCG, day of hCG trigger and endometrial thickness (ET) [Table 2].

Table 1: Demographic and baseline hormonal profile

Variables	Study Group	Control Group	P Value
Age (Years)	29.2±3.9	28.9±4.1	NS
BMI	24.4±4.1	24.9±3.9	NS
FSH (IU/L)	5.9±1.6	6.0±1.2	NS
LH (IU/L)	5.5±1.4	5.7±1.4	NS
E2 (Pg/ml)	42.9±18.1	45.2±14.6	NS

Table 2: Cycle characteristics

Variables	Study Group	Control Group	P value
No. of follicles >14mm	2.09±0.4	2.1±0.4	NS
DF (cm)	1.9±0.62	2.0±0.65	NS
ET (mm)	7.9±0.52	8±0.58	NS
Day of hCG trigger	121.7±1.1	12.8±1.1	NS

DF- dominant follicle, ET endometrial thickness

Out of 860 patients, 132 patients conceived; out of which 108 ended in live birth including one twin delivery in the study group. Twelve pregnancies ended in miscarriage. The pregnancy rate per cycle was found to be higher in the study group as compared to the controls (19% vs 12.4%), though it did not reach significant levels (p=0.11).The

miscarriage rate was, however, significantly lower in the study group (10% vs 30.7%, p=0.05). The live birth rate was significantly higher in the study group when compared to control group (16.2% vs 8.61%, p=0.02) [Table 3].

Table 3: Results

Variables	Study Group	Control Group	P value
Total No. Of Patients	442	418	-
Pregnancy Rate	80 (18%)	52 (12.4%)	p= 0.11
Miscarriage Rate	8 (10%)	16 (30.7%)	p=0.05*
Live Birth	72 (16.2%)	36 (8.61%)	p=0.02

There was no difference in the uterine blood flow parameters (RI, PI, S/D ratio) between the study and control groups on the day of IUI. In the progesterone supported group, significant reduction in RI, PI and S/D ratio was seen after 14 days of IUI. In control group, there were no significant changes in RI, PI and S/D ratio on the day of IUI and 14 days afterwards [Table 4].

Table 4: Doppler indices of study group and control group on day of IUI and 14 days after insemination

Variables	Study Group			Control Group		
	Day of IUI	14 days following IUI	P value	Day of IUI	14 days following IUI	P value
RI	0.67 ± 0.05	0.70 ± 0.08	0.001	0.67 ± 0.05	0.67 ± 0.06	0.22
PI	1.30 ± 0.20	1.30 ± 0.30	0.001	1.30 ± 0.21	1.3 ± 0.22	0.65
S/D	3.20 ± 0.48	3.30 ± 0.65	0.002	3.20 ± 0.51	3.20 ± 0.52	0.88

DISCUSSION

To the best of our knowledge, this is the first study which shows the role of progesterone in LPS and its correlation with uterine blood flow and pregnancy outcome following ovulation induction with CC in PCOS women in IUI cycles. There was significant reduction in the miscarriage rate in the progesterone group with a significant improvement in the live birth rate as well. Although statistically not significant, PCOS women in the study group showed a trend towards higher pregnancy rate. Uterine blood flow demonstrated significant improvement following progesterone supplementation. Thus, the present study suggests that uterine blood flow and pregnancy outcome can be improved following luteal phase progesterone supplementation in women with PCOS following ovulation induction with CC in IUI cycles.

It has been well established that there is deficient luteal phase in stimulated in-vitro fertilization / intra-cytoplasmic sperm injection cycles. In controlled ovarian stimulation, it is suggested that high serum steroid concentrations might negatively affect LH secretion via feedback mechanisms, which results in premature luteolysis and defective secretion of progesterone.[5] However, in the stimulated IUI cycles the quality of the luteal phase still remains obscure.

Normal luteal phase plays a crucial role in the establishment of pregnancy. Conception cycles are associated with more rapid rise of progesterone and higher mid-luteal estrogen and progesterone levels compared to cycles which do not result in pregnancy. This supports the need for adequate progesterone during the luteal phase for normal implantation and successful pregnancy.[6] Luteal phase deficiency (LPD) has been described as a condition in which endogenous progesterone is not sufficient to maintain a functional secretory endometrium and allow normal embryo implantation and growth. At present there is no single test which can establish LPD. Probably the only practical way to define or diagnose a LPD is to demonstrate that luteal support itself increases pregnancy and live birth rates.[7] In the present study, luteal phase progesterone support in PCOS women showed significant improvement in live birth rate. So, we can speculate that PCOS woman are probably associated with higher incidence of luteal phase insufficiency, which can be corrected by progesterone support.

Various studies have shown that in PCOS women, progesterone production by granulosa cells is abnormal.[8] Granulosa cells may have inherent defects in both the response to gonadotropin action and steroidogenesis in women with PCOS.[9] Endometrial development and endometrial receptivity in PCOS may be abnormal due to high androgen levels.[10,11] It has also been reported that the miscarriage rate in women with PCOS is higher than that in the general population and abnormal progesterone production has been implicated as the cause.[12,13] Progesterone, by downregulating endometrial androgen receptors,[14] may improve implantation. It also induces decidualization, upregulates insulin like growth factor II and modulates expression of insulin-like growth factor binding proteins which are abnormally expressed in women with PCOS and thus may improve pregnancy outcome.[15] The present study supports that progesterone supplementation for LPS in PCOS in CC stimulated IUI cycle helps to improve implantation and reduce miscarriage rate by correcting associated luteal phase abnormalities.

Progesterone upregulates endothelial nitric oxide synthase (eNOS) expression in uterine and spiral

arteries necessary for implantation.[16] It is well known that nitric oxide (NO) helps in vasodilatation, decidua formation, endometrial remodeling during trophoblast invasion.[17] NO regulates endometrial functions such as receptivity and implantation.[18,19] In the present study, following progesterone supplementation significant change in uterine artery doppler indices was noted, thereby enhancing pregnancy outcome.

The duration of luteal phase support in ART cycles is a matter for debate. There are reports suggesting no benefit of LPS beyond positive pregnancy test. In the present study, LPS was continued up to 10 weeks if the patient conceived, as the continuation of pregnancy is independent of corpus luteal function beyond 8 to 10 weeks of gestation and the hormone production is entirely taken over by placenta after 10 weeks of pregnancy.[20]

A recent systematic review and meta-analysis suggest that the clinical pregnancy and live birth in IUI cycles improved with luteal phase progesterone support with gonadotropin induction rather than with CC. The authors stated that this discrepancy could have been due to protocol used for ovulation that resulted in the differences in the endogenous luteal phase functioning.[21] However, this meta-analysis has only included patients with unexplained infertility. The present study included PCOS women who are more likely to be affected by luteal phase abnormalities due to abnormal follicular development. In these patients, even after CC stimulation, a significant beneficial effect of progesterone on live birth rate was observed in this study.

A study done by Montville et al. shows higher pregnancy rates following luteal supplementation with progesterone in women with PCOS using letrozole for ovulation induction, while no positive effect of progesterone on those stimulated with clomiphene citrate. The author explained the cause may be due to less number of cycles in CC group to reach statistical significance.[22] Another randomized study conducted on 110 CC resistant PCOS, undergoing gonadotropin ovulation induction in IUI/ovulation induction cycles. With luteal phase progesterone supplementation, a trend towards higher clinical pregnancy rate and live birth rate was seen, though statistically not significant.[23] In our study, clinical pregnancy rate was higher in progesterone group even though it did not reach statistical significance. However significantly lower miscarriage rate and higher live birth rate was observed in the progesterone group.

The present study includes a good sample size and we have also evaluated live birth rate which was not analysed in other studies. The limitation of our study is that it was a non randomized study.

CONCLUSION

The present study suggests that use of progesterone supplementation for luteal phase in PCOS woman in CC stimulated IUI cycles is beneficial. It reduces miscarriage and significantly improves live birth rate. We recommend adequately powered large randomized controlled trials before advocating routine use of progesterone in PCOS women following clomiphene stimulation.

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