Original Article

Addition of oestradiol to progesterone for luteal phase support in GnRh antagonist IVF/ICSI cycles

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Abstract

Objective: Studies have found conflicting results with respect to the use of progesterone alone or oestrogen and progesterone as luteal phase support for *in vitro* fertilisation (IVF)/ICSI cycles involving use of GnRh antagonist. The purpose of the study is to determine the effect of luteal phase supplementation with oestradiol and progesterone versus progesterone alone in women undergoing IVF/ICSI-Embryo transfer (ET) in relation to the pregnancy rate. **Design:** This was a retrospective observational study spanning 1 year conducted at Medicover Fertility, New Delhi. A sample size of 150 women was taken. **Materials and Methods:** All women underwent controlled ovarian stimulation by gonadotropin and GnRh antagonist protocol. Oocyte retrieval was performed after 34 to 36 hours of hCG trigger and embryos were transferred 3 days after oocyte retrieval. According to luteal phase support protocol, two groups were made: study group (oestrogen plus progesterone, $n = 75$) and control group (progesterone alone, $n = 75$). **Results:** The study and control group did not differ for age, religion, duration of infertility, cause and type of infertility. Out of 75 women in the study group, 31 women conceived, the pregnancy rate being 41%. In the control group, 27 out of 75 women conceived, the pregnancy rate being 36%. Thus, the pregnancy rate was observationally higher in the study group, but the difference was not statistically significant (P value = 0.50). **Conclusion:** Giving oestradiol supplementation along with progesterone in the luteal phase did not improve pregnancy rates significantly. Further, more studies are required to see hormonal profile of oestradiol and progesterone levels during luteal phase and its correlation with pregnancy rate.

Keywords: ICSI, IVF, gnrh analogues, luteal phase support, oestradiol, progesterone

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INTRODUCTION

In vitro fertilisation (IVF) requires the use of GnRH analogues, which prevent the premature surges of endogenous luetinising hormone (LH). Unfortunately, use of Gonadotropin Releasing Hormone (GnRH) analogues also confers harm by inhibiting corpus lutea in these cycles. These analogues either by themselves or in concert with supraphysiological hormonal profiles create an iatrogenic luteal phase defect.[1] As a result, there is dysfunction of corpus luteum and thus the endogenous luteal secretion of oestrogen and progesterone is suboptimal. In presence of suboptimal levels of oestrogen and progesterone in the luteal phase, endometrium is less receptive leading to impairment of implantation and hence decreased pregnancy rate.[2]

Access this article online

Quick Response Code:

Website: www.fertilityscienceresearch.org

DOI: 10.4103/fsr.fsr_25_19

How to cite this article: Munjal R, Gupta S. Addition of oestradiol to progesterone for luteal phase support in GnRh antagonist IVF/ICSI cycles. Fertil Sci Res 2019;6:35-9.

To overcome this iatrogenic luteal phase defect, luteal phase supplementation (LPS) is employed with either single or combined agents, the only consensus being that LPS improves IVF/ICSI outcome.[3] Progesterone supplementation is a routine treatment throughout the world with different doses and routes of administration.[4] The benefit of additional LPS with oestradiol is not clear. Some studies have found administration of oestradiol with progesterone in luteal phase to improve the implantation and pregnancy rates in women undergoing IVF/ICSI as compared to progesterone alone,[4-9] whereas others have found no additional benefit.[10-12,15-17] Thus, effect of addition of oestradiol to progesterone in luteal phase on the pregnancy rate in women undergoing IVF/ICSI is not yet clear.

The study has been attempted to determine the effect of LPS with oestradiol and progesterone versus progesterone alone in relation to the pregnancy rate.

AIMS AND OBJECTIVES

The purpose of the study is to determine the effect of LPS with oestradiol and progesterone versus progesterone alone in women undergoing IVF/ICSI-Embryo transfer (ET) in relation to the pregnancy rate.

MATERIALS AND METHODS

This was a retrospective observational study spanning 1 year from April 2018 to April 2019 conducted at Medicover Fertility, New Delhi. A sample size of 150 women was taken.

One hundred fifty women undergoing IVF/ICSI-ET with controlled ovarian stimulation by antagonist protocol were selected, and according to luteal phase support protocol, two groups were made of 75 women each.

Inclusion criteria

(1) Women aged 23 to 35 years of age.
(2) Women receiving controlled ovarian stimulation with gonadotropins and GnRH antagonist.

Exclusion criteria

(1) Serum E2 level more than 6000 pg/mL on day of oocyte retrieval (because of risk of ovarian hyper-stimulation syndrome).
(2) Premature ovarian insufficiency.
(3) Any known medical, endocrine, gynaecological or surgical illness.
(4) Partner with abnormal semen parameters (as per WHO criteria).
(5) Less than two good quality embryos on day 3 after IVF/ICSI.

All the women underwent detailed evaluation; all routine investigations for infertility were done. Based on these investigations, women were being planned for controlled ovarian stimulation (COS)-IVF/ICSI and called on second day of menstrual cycle; day 2 transvaginal ultrasonography (TVS) was done.

All women underwent controlled ovarian stimulation by gonadotropin Recombinant Follicle stimulating hormone/Human Menopausal gonadotropin (rFSH/HMG) and gonadotropin releasing hormone (GnRh) antagonist protocol as determined by primary physician depending on age and ovarian reserve tests. The response was monitored with serial transvaginal ultrasound imaging of ovarian follicles and endometrial thickness. Most women required 9 to 12 days of stimulation. It was aimed to have at least three follicles measuring 17 to 18 mm in mean diameter. Once the targeted thresholds of response were met, hCG (10,000 IU) or 250 mcg recombinant human chorionic gonadotropin (rhCG) was administered to induce follicular maturation. Oocyte retrieval was performed after 34 to 36 hours of hCG trigger, transvaginal ultrasound-guided aspiration under general anaesthesia being the technique. Fertilisation was achieved by IVF/ICSI. Embryo transfer was performed 3 days after oocyte retrieval, transcervical ultrasound guided, using Labotect Embryo Transfer Catheter set.

According to luteal phase support protocol, two groups were made as follows.

Study group: (oestrogen + progesterone)

Oestradiol valerate, 2 mg tablet orally, thrice daily.
(1) Progesterone gel 90 mg (8%), vaginally, once daily and inj. progesterone 100 mg I.M. alternate day.

Control group: (only progesterone)

(1) No oestradiol valerate.
(2) Progesterone gel 90 mg (8%), vaginally, once daily and inj. progesterone 100 mg I.M. alternate day.

Serum beta hCG more than 50 mIU/mL done 14 days after embryo transfer indicated successful implantation. Women with positive beta hCG were referred for early pregnancy scan. Primary outcome studied was pregnancy rate and secondary outcome was implantation rate. Statistical analysis of difference between study and control group was done using Statistical Package for

Social Sciences (SPSS). The two groups were analysed using the Pearson Chi-square test, Mann-Whitney *U* test and Student *t* test, as indicated. The *P* value of less than 0.05 was considered significant.

RESULTS

The baseline characteristics including age, religion and duration of infertility were similar in two groups. The mean age of women in the study group was 31.62 ± 4.15 years and that in the control group was 30.68 ± 4.01 years (*P* value = 0.16). The two groups were similar with respect to the mean age, age distribution (*P* value = 0.43) and religion (*P* value = 0.28) [Table 1]. There was no significant difference between the pregnant and the non-pregnant women with respect to age (*P* value = 0.32) and religion (*P* value = 0.39). There was no significant difference between the groups in respect to duration of infertility (*P* value = 0.58) [Table 2]. Majority of the women enrolled for the study had primary infertility (74.7%). There was no significant difference in the type of infertility in study group and control group (*P* value = 0.26) and between pregnant and non-pregnant women (*P* value = 0.37) [Table 3]. The aetiological factors of infertility in the women enrolled for the study were compared [Table 4]. The two groups had no significant difference with respect to the cause of infertility (*P* value = 0.17). There was no significant difference between pregnant and non-pregnant women with respect to aetiology of infertility (*P* value = 0.53). Overall, oocyte recovery rate was 86.5% in study population with no significant difference between the two groups. The pregnancy rate in the study was 38.7% (58/150). Out of 75 women in the study group, 31 women conceived, the pregnancy rate being 41%. In the control group, 27 out of 75 women conceived, the pregnancy rate being 36%. Thus, the pregnancy rate was observationally higher in the study group, but the difference was not statistically significant (*P* value = 0.50) [Table 5]. Similarly, implantation rates showed no significant difference between the study group (26.44%) and the control group (25.25%) (*P* value = 0.2). Out of 150 women enrolled for the study, 58 women conceived. Out of 58 women with positive pregnancy test, 15 women (25.86%) have delivered, 21 women (36.2%) have continuing pregnancy, 10 women (17.24%) aborted, 11 women (18.96%) had biochemical pregnancy, one women had tubal ectopic pregnancy (1.72%) which was medically managed and there were two triplet pregnancies (3.44%), for which embryo reduction was done [Table 6].

Table 1: Distribution of women on the basis of demographic details

Characteristics	Study group; N = 75		Control group; N = 75		*P* value*
	n	%	*n*	%	
Age group (years)					
<25	4	5.3	9	12	0.43
25–29	28	37.3	25	33.3	
30–34	28	37.3	30	40	
>35	15	20.1	11	14.7	
Religion					
Hindu	64	85.3	63	84	0.28
Muslim	8	10.7	12	16	
Sikh	2	2.7	0	0	
Christian	1	1.3	0	0	

*Pearson Chi-square test.

Table 2: Duration of infertility in study and control group

	Study group; *N* = 75	Control group; *N* = 75	*P* value*
Duration of infertility (years)	7.98 ± 4.40	8.38 ± 4.10	0.58

*Mann-Whitney *U* test.

Table 3: Type of infertility in study and control group

	Primary	Secondary	*P* value*
Study group; *N* = 75	70.7%	29.3%	0.26
Control group; *N* = 75	78.7%	21.3%	
Total	74.7%	25.3%	

*Pearson Chi-square test.

Table 4: Etiological factors for infertility in study and control group

	Study group; *N* = 75	Control group; *N* = 75	Total
Male factor	37.2%	32.8%	35%
Ovulatory	17.8%	19.7%	18.75%
Tubal factor	12.5%	14.4%	13.45%
Endometriosis	14.8%	11.6%	13.2%
Unexplained	17.7%	21.5%	19.6%
P value*	0.17		

*Pearson Chi-square test.

Table 5: Comparison of pregnancy rates

	Study group; N = 75		Control group; N = 75		*P* value*
	n	%	*n*	%	
Pregnancy rate	31	41.3%	27	36%	0.50

*Pearson Chi-Square test.

Table 6: Outcome of pregnancy among women who conceived

Outcome	Number	Percentage
Delivered	15	25.9%
Aborted	10	17.2%
Continuing pregnancy	21	36.2%
Biochemical pregnancy	11	19%
Ectopic pregnancy	1	1.7%

DISCUSSION

Our findings were comparable to studies done by other authors. In studies by Farhi *et al.*,[5] Chen *et al.*,[7] Lukaszuk *et al.*,[4] Ghanem *et al.*,[8] Elgindy *et al.*,[9] Serna *et al.*[12] and Var *et al.*,[18] there was no significant difference with respect to mean age in study and control group. In the study of Var *et al.*,[18] mean duration of infertility was 8.95 ± 4.97, 8.81 ± 4.97 and 9.21 ± 3.89 years in E + P, hCG + P and only P groups, respectively, comparable to present study, whereas in the studies by Elgindy *et al.*,[9] Farhi *et al.*[5] and Lukaszuk *et al.*,[4] mean duration of infertility was short ranging from 4 to 6 years. In our society, infertility has a lot of social stigma associated with it. Due to this, couples are reluctant to discuss and approach earlier for infertility management. Thus, the greater duration of infertility in our study can attributed due to the social stigma associated with infertility in our society.[13]

The results in our study were comparable to the study by Farhi *et al.*,[5] in which majority of the women had primary infertility (60% and 61% in the study and control group, respectively) and there was no significant difference between the study and the control group. In the study of Farhi *et al.*,[5] the most common indication for IVF was male factor (54% in the study group and 43% in the control group), followed by tubal factor (27% in study group and 32% in control group). Similarly, in the study by Var *et al.*[18] and Elgindy *et al.*,[9] most common cause was found to be male factor, followed by ovulatory dysfunction, unexplained and tubal factor. The results in our study were comparable to these studies.

In the present study, the pregnancy rate was observationally higher in the study group, but the difference was not statistically significant. In the study by Var *et al.*,[18] significantly higher pregnancy rates were seen in women who received E + P (40.6%) as compared to those who received only P (21.6%) or hCG + P (38.9%). Elgindy *et al.*[9] also found highest pregnancy rate in the group receiving progesterone + vaginal E (45.56%) and it was significantly higher than the women receiving only P (30%). Ghanem *et al.*[8] found higher pregnancy rate in the women receiving progesterone + oestrogen compared to those receiving only P or P + hCG (40.9%, 20.4% and 29.5%, respectively), and the difference was statistically significant (*P* value = 0.02). Many other studies have reported significantly higher pregnancy rates like Farhi *et al.*,[5] Gorkemli *et al.*[6] and Chen *et al.*[7] In a dose-finding RCT, Lukaszuk *et al.*[4] reported highest pregnancy rate in the group treated with progesterone + 6 mg oestrogen (51.3%), compared to the group receiving only progesterone (23.1%) and progesterone + 2 mg oestrogen (32.8%) (*P* value < 0.001). In contrast to the above-mentioned studies, other studies have failed to find any benefit of LPS with oestradiol. The recent RCT by Lin *et al.*[20] failed to show any benefit of oestradiol to progesterone as luteal phase support. The pregnancy rate was similar in estrogen + progesterone and progesterone only groups (50.9% and 58%, respectively). Also, in the study by Moini *et al.*,[19] no significant difference in the pregnancy rates was found between women receiving oestrogen + progesterone and those receiving only progesterone. Smitz *et al.*[10] reported similar pregnancy rate (29%) whether or not oestradiol valerate was added as luteal phase support. Engmann *et al.*[14] reported that there was no significant difference in pregnancy rate in women who received oestrogen + progesterone (50%) and those who received only progesterone (63.4%). Serna *et al.*[12] found out that the pregnancy rate was 41.8% in oestrogen + progesterone group and 42% in only progesterone group, no significant difference was found between the two groups.Hence in our study, we found that the pregnancy rate was observationally higher in the study group (LPS with oestradiol valerate 6 mg/day + progesterone) compared to the control group (LPS with progesterone alone), but the difference was not statistically significant.

CONCLUSION

The limiting factor in the success of IVF/ICSI is implantation, which involves two major participants, embryos and endometrium. To overcome the iatrogenic luteal phase defect in IVF cycles with use of GnRh analogues, LPS with progesterone is employed as a routine treatment with different doses and routes of administration.[7] The effect of addition of oestradiol to progesterone, as luteal phase support, on the pregnancy rate in women undergoing IVF/ICSI is not yet clear. We found that pregnancy rate was observationally higher in LPS with oestradiol valerate along with progesterone compared to LPS with progesterone alone, but the difference was not statistically significant.

Hence, we conclude that oestradiol supplementation in the luteal phase did not improve pregnancy rates significantly. Although more studies are required to see hormonal profile of oestradiol and progesterone levels during luteal phase in control and study group and its correlation with pregnancy rate.

Financial support and sponsorship
Nil.

Conflicts of interest

There are no conflicts of interest.

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