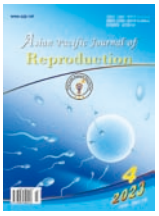

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Pregnancy outcomes following supplementation of single dose GnRH agonist to sustain the luteal phase in antagonist fresh embryo transfer cycles: A multicentric prospective cohort study

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ABSTRACT

Objective: To determine whether a single dose of gonadotropin-releasing hormone (GnRH) agonist administered subcutaneously in addition to the regular progesterone supplementation could provide a better luteal support in antagonist protocol fresh embryo transfer cycles.

Methods: This prospective, multicentric, cohort study included total 140 women, 70 in each group. Controlled ovarian stimulation was carried out as per fixed GnRH antagonist protocol. The trigger was given with hCG. *In vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) was performed and day-3 embryos were transferred. Patients were divided into groups 1 and 2 based on computer generated randomization sheet. Six days following oocyte retrieval, group 1 received 0.2 mg decapeptyl subcutaneously in addition to regular progesterone support while group 2 received progesterone only. Luteal support was given for 14 days to both groups; if pregnancy was confirmed luteal support was continued till 12 weeks of gestation. The clinical pregnancy rate was the primary outcome. The implantation rate, miscarriage rate, live birth delivery rate, and multiple pregnancy rates were the secondary outcomes.

Results: A total of 140 patients were analysed, 70 in each group. Clinical pregnancy rates (47.1% *vs.* 35.7%; *P*=0.17), implantation rates (23.4% *vs.* 18.1%, *P*=0.24), live birth delivery rates (41.4% *vs.* 27.1%, *P*=0.08), and multiple pregnancy rates (21.2% *vs.* 16.0%, *P*=0.74) were higher in group 1 than in group 2. Group 1 had a lower miscarriage rate than group 2 (5.7% *vs.* 8.6%; *P*=0.75). However, these differences were not statistically significant between the two groups.

Conclusions: Administration of a single dose of GnRH agonist in addition to regular natural micronized vaginal progesterone as luteal support in GnRH antagonist protocol cycles marginally improves implantation rates, clinical pregnancy rates, and live birth delivery rates. However, more studies with higher sample sizes are needed before any conclusive statements about GnRH agonist as luteal phase support can be made.

KEYWORDS: GnRH agonist; Triptorelin; IVF; Ovum pick up; Luteal phase support; Antagonist protocol; Cleavage stage; Fresh embryo transfer; Live birth delivery rate

Significance

Luteal phase deficiency is present in all assisted reproductive technology (ART) cycles, so luteal phase support with either progesterone or hCG is a common practice in all ART cycles. This study investigated whether a single dose of GnRH agonist administered subcutaneously in addition to the regular progesterone supplementation could provide a better luteal support in antagonist protocol fresh embryo transfer cycles. This study aided in learning more about the implications of luteal-phase administration of single-dose GnRH agonist on clinical pregnancy, implantation, and live birth rates and demonstrated that progesterone plus GnRH agonist is a more effective luteal phase support regimen than progesterone alone.

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1. Introduction

Luteal phase deficiency is a common problem in current assisted reproduction technology (ART) and has been described in cycles using gonadotrophin-releasing hormone (GnRH) analogues, GnRH agonist as well as GnRH antagonist[1]. In stimulated *in vitro* fertilization (IVF) cycles, the corpus luteum is affected due to: supra-physiological oestradiol levels, aspiration of granulosa cells during oocyte retrieval, and inadequate luteinizing hormone (LH)[2] release during the luteal phase. Therefore, luteal phase support is recommended in ART cycles to improve the embryo implantation rate, clinical pregnancy rate, and delivery rate remarkably[3]. To achieve these aims, two commonly used therapeutic agents for luteal phase support are natural micronized progesterone and human chorionic gonadotropin (hCG). The use of hCG in luteal phase has been associated with a several-fold increase in the risk of ovarian hyperstimulation syndrome and a lack of demonstrated superiority over simple progesterone supplementation in improving implantation and clinical pregnancy rates[4]. The progesterone has therefore been universally adopted for luteal phase support in all ART cycles accompanied by fresh embryo transfers. Oestrogen was also tried for luteal phase support in combination with progesterone, but it was found to be ineffective in improving the implantation and pregnancy rates[5]. Some recent data, however, have suggested a beneficial effect of GnRH agonist administered in the luteal phase on the outcome of ART[6–9]. The mechanism of the presumed beneficial effect of luteal phase agonist administration is poorly defined. It is hypothesized that GnRH agonist acts by supporting the corpus luteum by stimulating the secretion of LH by pituitary gonadotropic cells, acting directly on the endometrium through the locally expressed receptors[10], the direct action of GnRH agonist on the embryo[10].

The study aimed to investigate whether subcutaneous administration of a single dose of GnRH agonist in addition to the routine natural micronized progesterone supplementation could provide better luteal support in patients undergoing ART with GnRH antagonist protocol and fresh embryo transfers compared to natural micronized progesterone only.

The primary outcome of the study was to find out the difference in clinical pregnancy rate between the two groups. Secondary outcomes measured were: implantation rate, live birth delivery rate, multiple pregnancy rate, and miscarriage rate.

2. Subjects and methods

2.1. Study design

This was a prospective, multicentric, cohort study conducted at three independent centres from 1st December 2021 to 30th June 2022. A total of 176 antagonist fresh embryo transfer cycles were done at the 3 centres during the study period. The study comprised 140 patients who met the inclusion and exclusion criteria. Patients were then assigned into two groups based on computer-generated randomization sheet before embryo transfer after taking written informed consent. In this study, there was no loss of follow-up of the study participants.

2.2. Inclusion criteria

The study included all the patients who underwent fixed antagonist protocol and received hCG as trigger and underwent fresh embryo transfer during the study period, aged less than 37 years, antral follicular count (AFC) more than 5 & less than 15, anti-Müllerian hormone (AMH) more than 1.2 ng/mL & less than 5 ng/mL, and at least 2 grade A embryos were available for fresh transfer.

2.3. Exclusion criteria

The study excluded: patients who had any uterine or tubal factors affecting implantation like hydrosalpinx, fibroid >4 cm, polyps, stage Ⅲ or Ⅳ endometriosis, Asherman syndrome; patients who had extremes of body mass index (BMI) less than 18 kg/m^2 or more than 30 kg/m^2; patients who were given agonist protocol or received GnRH agonist as the trigger; patients who were hyper responders (when more than 18 oocytes were retrieved or hypo responders when less than 3 oocytes were retrieved) or in whose endometrial thickness less than 7 mm on the day of embryo transfers; patients who underwent frozen embryo transfer cycles and who had male partner with severe oligoasthenoteratozoospermia or for whom surgically retrieved sperms [percutaneous epididymal sperm aspiration (PESA), testicular sperm aspiration (TESA), testicular sperm extraction (TESE), micro TESA] were used for the procedure.

2.4. Study size and power calculation

Previously, Zafardoust *et al*[11] showed that in patients with previous history of IVF/intracytoplasmic sperm injection (ICSI) failure GnRH agonist administration during luteal phase (on day 6 after oocyte retrival), the implantation rates were increased [32.6% *vs.* 12.5%; odds ratio (*OR*) 3.3, 95% confidence interval (*CI*) 1.08-10.40, *P*=0.03]. Based on this published data, power analysis was performed assuming a significance level of 0.05 (2 sided) and power of 80%. It was found that 67 cycles were needed in each group to detect this difference.

2.5. Treatment protocol

2.5.1. Ovarian stimulation

All patients undergoing controlled ovarian stimulation with antagonist protocol meeting inclusion and exclusion criteria were taken. On day 2 or day 3 of the menstrual cycle, a transvaginal scan (TVS), serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and progesterone were done and if serum estradiol was less than 50 pg/mL, serum progesterone less than 1 ng/mL, endometrial thickness less than 5 mm, and no ovarian cyst, ovarian stimulation was started with either recombinant FSH or human menopausal gonadotropin (HMG). The starting dose of gonadotropins for each patient was individualized depending on age, BMI, AMH, and AFC on transvaginal ultrasound (TVS). On day 6 of stimulation, TVS was performed and the antagonist was started at a dose of 0.25 mg of cetrorelix per day as per fixed protocol and gonadotropins were continued. When at least 3 or more follicles reached 17 mm in size, the final oocyte maturation trigger was administered in form of either recombinant hCG 250 mcg subcutaneous or urinary hCG 10000 IU intramuscular.

2.5.2. Assisted reproductive technologies

Oocyte retrieval was performed 35-36 h after giving hCG. Conventional IVF or ICSI was performed based on the clinical indication. All fertilized oocytes were cultured in single-step media. All embryos were graded on day 3 according to the Istanbul consensus workshop on cleavage-stage embryo assessment. At least, two or three grade 1 (good) or grade 2 (fair) embryos were transferred under transabdominal ultrasound guidance and the rest of the embryos were frozen for future use.

2.5.3. Luteal phase management

Luteal support was started on the day of oocyte retrieval in all subjects undergoing fresh embryo transfer with micronized vaginal progesterone capsule 400 mg twice daily. On the day of embryo transfer, women were then divided into group 1 and 2 based on computer-generated randomization sheets. GnRH agonist was given to patients in group 1 after taking written informed consent. Group 1 (n=70) received natural micronized vaginal progesterone 400 mg twice daily and triptorelin 0.2 mg *s.c.* 6 days after ovum pick up. Group 2 (n=70) received natural micronized progesterone vaginal progesterone 400 mg twice daily. Serum βhCG was done 2 weeks after embryo transfer. If serum βhCG was positive, luteal support was continued with micronized vaginal progesterone till 12 weeks. TVS was done at 6 weeks of gestation to check for gestational sac, fetal pole, yolk sac, cardiac activity, and to rule out any ectopic gestation or heterotopic pregnancy. All the women who were pregnant received antenatal care and regular monitoring and delivered at our hospital.

2.6. Variables

2.6.1. Primary outcome

The primary outcome was clinical pregnancy rate. The number of clinical pregnancies expressed per 100 embryo transfer cycles. As per the International Glossary on Infertility and Fertility Care: clinical pregnancy[12] is defined as a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy; in addition to intrauterine pregnancy, it includes a clinically documented ectopic pregnancy.

2.6.2. Secondary outcomes

Secondary outcomes included implantation rate, live birth delivery rate, multiple pregnancy rate. As per the International Glossary on Infertility and Fertility Care[12], implantation rate refers to the number of gestational sacs divided by number of embryos transferred, expressed as percentage. Live birth delivery rate refers to the number of deliveries that resulted in at least one live birth, expressed per 100 embryo transfer cycles. Live birth refers to the complete expulsion or extraction from a woman of a product of fertilization, after 22 completed weeks of gestational age; which, after such separation, breathes or shows any other evidence of life, such as heart beat, umbilical cord pulsation or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. A birth weight of 500 g or more can be used if gestational age is unknown. Multiple pregnancy rate (%) refers to number of pregnancies with more than one embryo or foetus by number of pregnancies, expressed as percentage.

2.7. Statistical analysis

The collected data were analysed with IBM SPSS Statistics for Windows, Version 29.0 (Armonk, NY: IBM Corp). The independent sample t-test was used to find the significant difference between the bivariate samples in independent groups. *Chi*-square test was used to find the significance in qualitative categorical data. Similarly, if the expected cell frequency was less than 5 in 2×2 tables, then Fisher's Exact was used. For non-normally distributed (skewed data), Mann-Whitney test was used in all the above statistical tools. To describe the data, descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean and standard deviation (mean±SD) was used for continuous variables. The non-normally distributed data was expressed as median (IQR). P<0.05 was considered as significant.

2.8. Ethics statement

The study was approved by the Office of the Institutional Ethics Committee at Mahatma Gandhi Medical College & Hospital (No./ MGMC&HIEC/ JPR/2021/623).

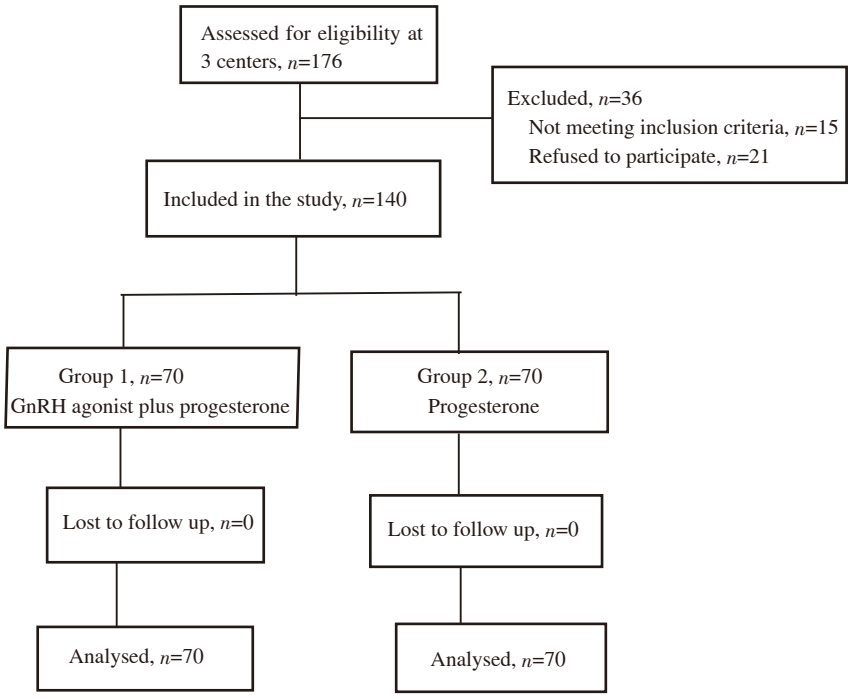

Figure 1. The study flowchart.

3. Results

3.1. Demographic characteristics and baseline characteristics

A total of 176 antagonist fresh embryo transfer cycles were done at the 3 centres during the study period of 7 months and 140 patients who meet the inclusion and exclusion criteria were included in the study. And 36 patients were not included in the study as they did not meet the inclusion criteria or not consented to the study. The study flowchart is given in Figure 1.

The average age of female patients was similar in both groups [(31.6±4.2) years *vs.* (33.1±4.2) years, *P*=0.42]. Similarly, the median duration of infertility [(6.00, 6.00) *vs.* (6.25, 7.00), *P*=0.48], type of infertility [primary (68.6% *vs.* 61.4%), secondary (31.4% *vs.* 38.6%); *P*=0.38] and cause of infertility [female factor (50.0% *vs.* 57.1%), male factor (21.4% *vs.* 17.1%), combined factor (21.4% *vs.* 20.0%) and unexplained factor (7.1% *vs.* 5.7%); *P*=0.85] were also similar in both the groups. Baseline characteristics on day 2 or 3 of the menstrual cycle like FSH, LH, AMH, oestradiol, progesterone, antral follicular count, and baseline endometrial thickness were also similar in both the groups (*P*>0.05) (Table 1).

3.2. Analysis of ovarian stimulation

The number of days of ovarian stimulation, total dose of gonadotropins used, estradiol, progesterone and LH on the day of hCG, median number of follicles more than 14 mm on the day of hCG, and average endometrial thickness on the day of hCG were similar in the two groups (*P*>0.05). IVF was done in 52.9% in group 1 *vs.* 44.3% in group 2, and ICSI was done in 47.1% in group 1 *vs.* 55.7% in group 2 (*P*=0.31). All these parameters were similar in both the groups (Table 2).

3.3. Analysis on the day of oocyte retrieval

The number of oocytes retrieved (8.59±2.75 *vs.* 9.31±2.92, *P*=0.13), number of mature oocytes (5.59±2.78 *vs.* 5.93±2.86, *P*=0.47), number of embryos formed (4.64±2.16 *vs.* 4.84±2.55, *P*=0.62), number of embryos transferred (2.44±0.63 *vs.* 2.29±0.62, *P*=0.14) were also comparable in both the groups (Table 3).

3.4. Comparison of pregnancy outcomes between the two groups

When triptorelin was administered in the luteal phase as a single bolus subcutaneously 6 days after ovum pick up, an increase in clinical pregnancy rate, implantation rate, and live birth delivery rate was seen. Clinical pregnancy rates were 33 (47.1%) using triptorelin single bolus as luteal support compared to 25 (35.7%) in the group with no luteal triptorelin. For this parameter, there was an increase, but it did not reach statistical significance (*P*=0.17). In our study, a total of 171 embryos were transferred in group 1 and a total of 160 embryos were transferred in group 2. The total number of gestational sacs in group 1 was 40 and in group 2 was 29, resulting in an implantation rate of 23.4% in group 1 *vs.* 18.1% in group 2. Even though the implantation rate of group 1 was somewhat greater than group 2, the differences that were noticed were no statistical significance (*P*=0.24). 29 women delivered in group 1 and 19

women delivered in group 2, resulting in a live birth delivery rate (41.4% *vs.* 27.1%), but the differences were no statistical significance (P=0.08). 22 of the 29 deliveries in group 1 resulted in singletons, while 7 of the deliveries were twins. Group 2 had 19 deliveries, 15 of which were singletons and 4 of which were twins, resulting in multiple pregnancy rates were 21.2% in group 1 and 16.0% in group 2, respectively (P=0.74). There were 4 miscarriages in group 1, one of which was ectopic, and the rest were missed abortions, while in group 2 there were 2 ectopic pregnancies, 1 foetus was terminated as it had increased nuhcal translucency and the fluorescence in situ hybridization (FISH) performed on chorionic villus sample confirmed Downs syndrome, and rest 3 were missed abortions. Miscarriage rates across the two groups did not differ significantly (5.7% *vs.* 8.6%) despite being lower in group 1, there was no statistically significant difference in miscarriage rates between the two groups (P=0.75) (Table 4).

Table 1. Demographic and baseline characteristics (day 2 or 3 of the menstrual cycle) of the study population.

Characteristics	Group 1 (n=70)	Group 2 (n=70)	P-value
Female partner age, years	31.6±4.2	33.1±4.2	0.42
Male partner age, years	34.9±4.6	36.3±4.8	0.75
Duration of infertility, years[#]	6.00 (6.00)	6.25 (7.00)	0.48
Type of infertility[*], n (%)			0.38
Primary infertility	48 (68.6)	43 (61.4)	
Secondary infertility	22 (31.4)	27 (38.6)	
Cause of infertility[*], n (%)			0.85
Female	35 (50.0)	40 (57.1)	
Male	15 (21.4)	12 (17.1)	
Combined	15 (21.4)	14 (20.0)	
Unexplained	5 (7.1)	4 (5.7)	
FSH (D2 or D3), mIU/mL	5.4±2.0	5.6±1.9	0.59
LH (D2 or D3), mIU/mL	3.5±1.9	3.5±1.7	0.90
Oestradiol (D2 or D3), pg/mL	51.29±27.52	44.95±16.33	0.10
Progesterone (D2 or D3), ng/mL	0.5±0.2	0.5±0.2	0.64
AMH, ng/mL	2.66±1.30	3.03±1.77	0.20
Endometrial thickness (D2 or D3), mm	3.2±0.9	3.1±0.8	0.62
AFC (D2 or D3)	11.19±3.00	10.79±3.11	0.44

Continuous data are expressed as mean±SD and unpaired sample t-test is used; categorical data (*) are expressed as n (%) and Chi-square test is used; non-normally distributed data (#) is expressed as median (IQR) and Mann-Whitney test is used. Group 1 receives 0.2 mg decapeptyl subcutaneously in addition to regular progesterone support, while group 2 receives progesterone only. FSH: follicle-stimulating hormone, LH: luteinizing hormone, AFC: antral follicular count, AMH: anti-Müllerian hormone, D: day.

Table 2. Analysis of ovarian stimulation.

Characteristics	Group 1 (n=70)	Group 2 (n=70)	P-value
Duration of stimulation, days	9.8±1.8	10.4±1.7	0.63
Total dosage of gonadotropins, IU	2 481.96±982.21	2 683.75±1 188.98	0.28
Estradiol on the day of hCG, pg/mL	2 551.21±1 327.77	2 375.81±1 471.58	0.46
Progesterone on the day of hCG, ng/mL	0.91±0.54	1.08±0.50	0.06
LH on the day of hCG, mIU/mL[#]	1.37 (1.31)	1.42 (1.70)	0.30
Number of follicles greater than 14 mm on the day of hCG[#]	7.00 (5.00)	6.00 (3.25)	0.04
Endometrial thickness on the day of hCG, mm	9.22±1.60	8.94±1.60	0.31
Procedure done			0.31
IVF[*], n (%)	37 (52.9)	31 (44.3)	
ICSI[*], n (%)	33 (47.1)	39 (55.7)	

Continuous data are expressed as mean±SD and unpaired sample t-test is used; categorical data (*) are expressed as n (%) and Chi-square test is used; non-normally distributed data (#) is expressed as median (IQR) and Mann-Whitney test is used. LH: luteinizing hormone, hCG: human chorionic gonadotropin, IVF: *in vitro* fertilization; ICSI: intracytoplasmic sperm injection.

Table 3. Analysis on the day of oocyte retrieval.

Outcomes	Group 1 (n=70)	Group 2 (n=70)	P-value
Number of oocytes retrieved	8.59±2.75	9.31±2.92	0.13
Number of mature oocytes	5.59±2.78	5.93±2.86	0.47
Number of embryos formed	4.64±2.16	4.84±2.55	0.62
Number of embryos transferred	2.44±0.63	2.29±0.62	0.14

Data are expressed as mean±SD and unpaired sample t-test is used.

Table 4. Comparison of pregnancy outcomes between the two groups.

Outcomes	Group 1	Group 2	*OR* (95% *CI*)	*P*-value
Clinical pregnancy rate*	47.1% (33/70)	35.7% (25/70)	1.61 (0.82-3.16)	0.17
Implantation rate*	23.4% (40/171)	18.1% (29/160)	1.38 (0.81-2.36)	0.24
Miscarriage rate**	5.7% (4/70)	8.6% (6/70)	0.65 (0.17-2.40)	0.75
Live birth delivery rate*	41.4% (29/70)	27.1% (19/70)	1.90 (0.93-3.86)	0.08
Multiple pregnancy rate**	21.2% (7/33)	16.0% (4/25)	1.41 (0.36-5.49)	0.74

Data are presented as % and analyzed using *Chi* square test* and Fisher exact test**. Difference between two groups is expressed as odds ratio (*OR*) and 95% confidence interval (*CI*).

4. Discussion

The landmark paper by Tesarik *et al*[13] utilizing GnRH agonist as luteal phase support 6 days after ICSI in fresh transferred cycle revealed a significant improvement in the implantation and live birth rate by restoring significant serum LH levels during the luteal phase as well as having a direct beneficial effect on embryo development potential. The majority of earlier trials that used 0.1 mg of injection decapeptyl (GnRH agonist) for luteal phase support found a considerable improvement in the overall success rate of IVF. Zafardoust *et al*[11] were able to demonstrate an increase in the biochemical pregnancy rate (32.6% *vs.* 12.5%, *P*=0.03) which was statistically significant and Davar *et al*[14] showed a substantial rise in the clinical pregnancy rate (26% *vs.* 21%, *P*=0.40) using 0.1 mg of decapeptyl as luteal phase support in addition to progesterone. In this study, 0.2 mg of decapeptyl was used instead of the usual 0.1 mg dose to observe the impact of increasing the dosage of GnRH agonist and how that affected IVF success. In our study population, we observed, doubling the GnRH agonist dosage up to 0.2 mg led to a higher clinical pregnancy rate (47.1% *vs.* 35.7%, *P*=0.17) and live birth delivery rate (41.4% *vs.* 27.1%, *P*=0.08) in group 1 compared to group 2, but these differences were statistically insignificant, and there was no significant doubling in the outcome.

Our findings are comparable to the study conducted by Abu *et al*[15] using 0.2 mg decapeptyl, which revealed higher biochemical pregnancy rates (47.7% *vs.* 44.4%, *P*=0.38), clinical pregnancy rates (25.7% *vs.* 23.4%, *P*=0.50), and livebirth rates (24.3% *vs.* 22.2%, *P*=0.49), respectively in the group supplemented with agonist but not statistically significant. Various luteal phase protocols were available with relation to the timing of GnRH agonist administration, but taking into consideration the direct effect of GnRH agonist on embryo and endometrium[10] we preferred to give agonist 6 days following ovum pick-up. We achieved higher clinical pregnancy rates (47.1% *vs.* 35.7%, *P*=0.17) in our study but were statistically insignificant. Similarly, the clinical pregnancy rates were higher (38% *vs.* 31%, *P*<0.23) in Benmachiche *et al*[16] study using GnRH agonists administered 6 days after oocyte retrieval, but these differences were also not statistically significant.

Different GnRH agonists were utilized in several earlier studies, which produced results that were similar to those of ours. All these findings are consistent with Tesarik *et al*[13] observation's that regardless of the ovarian stimulation protocol utilized, the luteal-phase GnRH agonist group demonstrated significantly higher rates of implantation, clinical pregnancy, and live birth. Even though Benmachiche *et al*[16] in their study showed a preference for using GnRH agonist as luteal phase support in GnRH agonist triggered IVF cycles due to its detrimental effect on corpus luteum, thus affecting the overall pregnancy outcome. But in line with Tesarik *et al*[10] study, our study also used hCG as a triggering agent and showed positive clinical pregnancy outcomes. The implantation rate in our study was (23.4% *vs.* 18.1%, *P*=0.24) which is statistically insignificant but Zafardoust *et al*[12] was able to demonstrate significant improvement in implantation (27.1% *vs.* 17.4%, *P*<0.05) in their study.

In our study, there were fewer miscarriages in the GnRH agonist group than in the control group (5.7% *vs.* 8.5%, *P*=0.75), and this difference was not statistically significant. Our results corroborate those of Abu *et al*[15] which showed the rate of miscarriage among the study group was lower (4.5% *vs.* 9.4%, *P*=0.009) compared to the progestogen alone group which was statistically significant in their study. Qublan *et al*[7] found that the rate of miscarriages was low in the GnRH agonist group (5%) and high in the control group (8.3%) but it was also not statically significant. Finally, arriving upon convincing evidence, according to the Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD009154[17], six studies involving 1 646 women were conducted to compare the effectiveness of progesterone alone *versus* progesterone combined with a GnRH agonist for luteal phase support. These studies evaluated various outcome measures, including live birth rate, clinical pregnancy rate, and ongoing pregnancy rate. The findings indicated a potential advantage of using progesterone in combination with a GnRH agonist, as the rates of live birth, clinical pregnancy, and ongoing pregnancy were significantly lower in the group receiving progesterone alone. The Peto odds ratio for the live birth rate was 0.40 (95% *CI* 0.26-0.61), for the clinical pregnancy rate was 0.74 (95% *CI* 0.60-0.90), and for the ongoing pregnancy rate was 0.76 (95% *CI* 0.60-0.97). However, no notable differences were observed between the two groups in terms of miscarriage and multiple pregnancy rates based on the findings of this review.

However, the current clinical practice Guideline of the European

Society of Human Reproduction and Embryology ovarian stimulation for IVF/ICSI[18,19] states that a GnRH agonist bolus, in addition to progesterone for luteal phase support in hCG triggered cycles is appropriate for usage in a clinical trial setting only. Reviewing the literature for safety issues regarding GnRH agonist administration, several observational clinical studies have examined the effects of unintentionally administering a GnRH agonist during the luteal phase. Except for one author[20], all authors concur that the administration of luteal phase GnRH agonists do not jeopardize the continuation of ART pregnancy; rather, it appears to support the implantation[21,22]. Up to 1998, it was documented that accidentally administering GnRH agonists during the mid-luteal phase resulted in more than 340 unexpected spontaneous pregnancies[23]. A congenital defect incidence of 2.5% and a pregnancy loss of 15% were observed among them, which was similar to what had been observed in the general spontaneous population and during IVF[23–25].

The main strengths of this study were prospective nature of the study with good patient compliance, simple regimen and improvement in pregnancy rates. We were able to track all the pregnancies until they resulted in delivery or ended otherwise and recorded perinatal outcomes. But the limitation of the study was the small sample size. Though there was an increase in clinical pregnancy rates, implantation rates and live birth delivery rates, our results could not reach statistical significance.

In conclusion, this study indicates that the addition of GnRH agonist to the luteal phase in antagonist ART cycles results in a modestly greater clinical pregnancy rate and live birth delivery rate, although it is not statistically significant. Therefore, more studies with higher sample sizes are necessary before any conclusive statements about GnRH agonist as luteal phase support can be made.

Conflict of interest statement

The authors have disclosed no conflicts of interest.

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Authors' contributions

The study was designed by Dr. Tatapudi S V Parvathi Devi and Dr. Alka Gahlot. Data collection was carried out by Dr. Tatapudi S V Parvathi Devi and Dr. Ravikant Soni. Dr. Tatapudi S V Parvathi Devi and Dr. Meeta Sharma wrote the initial manuscript. Dr. Tatapudi S V Parvathi Devi, Dr. Sangita Sharma, and Dr. Manisha Choudhary analyzed and interpreted the scientific data/results. All authors thoroughly reviewed and provided their approval for the final manuscript.

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