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Original Research Article

Real-world observational study to capture practice pattern of controlled ovarian stimulation in the *in vitro*-fertilization and embryo transfer or intracytoplasmic sperm injection-2

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ABSTRACT

Background: The objective of the study was to evaluate the practice patterns of controlled ovarian stimulation (COS) in patients who underwent *in vitro*-fertilization and embryo transfer (IVF-ET) or intracytoplasmic sperm injection (ICSI).
Methods: In REAL-COS (REAL-world observational study to capture practice pattern of COS in IVF-ET/ ICSI cycle) study, data was collected by 138 clinicians across India between April 2021 and March 2022 in a retrospective manner.
Results: Data of 1651 subfertility female patients were evaluated. The mean (SD) age was 31.8 (3.9) years and majority (77.8%) of the patients were aged <35 years. Obese patients constituted 28.1% of the total population. The majority (79.5%) of the patients had primary subfertility and the polycystic ovarian syndrome (PCOS) was the most (27.8%) common cause of subfertility. Nearly equal percent of patients were treated with frozen or fresh embryo transfer. Most (~96%) of the patients received GnRH antagonist protocol wherein cetrorelix acetate was the most common drug (98.7%) while ~4% patients received GnRH agonist protocol wherein luprorelin was the most common one (83%). The most commonly used gonadotropin was recombinant follicle stimulating hormone alone therapy (rFSH, 49.2%). Majority (51.8%) of the patients were initiated at 225 IU dose of gonadotropin for COS. For ovulation trigger, human chorionic gonadotropin (hCG) was used in majority (59%) of the cases. Treatment with rFSH alone therapy resulted in max mean no. of oocytes and mean metaphase-II oocytes as compared with other treatments.
Conclusions: This real-world observational study reports primary subfertility as the major reason for IVF-ET/ICSI in the study population. The GnRH antagonist protocol was followed by most of the clinicians participating in this study. rFSH was the most commonly used gonadotropin. rFSH alone therapy yielded the greatest number of oocytes and metaphase II oocytes versus other treatments.

Keywords: COS, rFSH, In vitro-fertilization, Controlled ovarian stimulation

INTRODUCTION

Infertility is defined as a failure to achieve pregnancy during one year of frequent unprotected intercourse. The etiology of infertility includes male factor infertility, ovarian dysfunction, tubal factor infertility, endometriosis, uterine factor infertility, and cervical factor infertility. At times, the cause is not known and is referred to as "unexplained infertility".[1] Globally, infertility affects approximately 60-80 million couples, of which approximately 15-20 million (25%) are in India alone.[2] Standard treatments for infertility include induction of ovulation, intrauterine insemination (IUI), IVF-ET or intra-cytoplasmic insemination (ICSI).[3]

In IVF, COS is one of the critical steps as it balances risk-benefit of gonadotrophin stimulation in achieving an ideal response. An optimum COS avoids poor ovarian response,

leading to cycle cancellation and prevents excessive response, leading to severe complications such as ovarian hyperstimulation syndrome. Selection of correct type of gonadotropin and its accurate dosage aids in having optimal response.[4] Hence to optimize ovarian response and results of ART, in terms of maximizing chances of pregnancy and eliminating iatrogenic and avoidable risks resulting from ovarian stimulation, individualization of IVF treatment is recommended.[5]

To help optimize ovarian stimulation for ART, it is important to understand the demographic patterns, causes of infertility and practice patterns related to management approach. In the above context, present real-world retrospective study conducted to evaluate practice patterns related to management choices including gonadotropin selection and dosage for ovarian stimulation, choice of ovulation trigger method and mean no. of oocytes/ metaphase II oocytes retrieved in IVF cycles as study end points. Demographic profile of patients and etiology of infertility in patients of IVF-ET/ICSI also analyzed.

METHODS

Study design

This real-world, retrospective, cross sectional, observational REAL-COS (REAL-world observational study to capture practice patterns of COS in IVF-ET/ ICSI cycle) study was conducted at various ART clinics across India between April 2021 and March 2022. A total of 138 clinicians contributed to the study. Retrospective data of female patients who underwent fresh IVF-ET/ ICSI cycle or freeze all cycle was collected by the IVF specialists. Selection of patient was according to treating clinician's discretion and no additional interventions were done.

Study variables

The study variables included demographic details including age, body mass index (BMI), cause of subfertility, ovarian reserve status whether anti-Mullerian hormone (AMH) and/or antral follicle count (AFC), protocols followed for COS, type of gonadotropins used with their starting dose, maximum dose of gonadotropin/ day, whether combination of gonadotropin used, total amount of gonadotropins used (IU), total number of days of ovarian stimulation, the ovulation trigger method used, total number of oocytes retrieved and total no. of metaphase II oocytes retrieved.

Statistical analysis

The data collected from all the IVF centers across India was compiled and statistical analysis was performed at Lambda therapeutic research Ltd., Ahmedabad, India. Demographic and baseline characteristics summarized using descriptive statistics. Categorical variables were summarized with frequency and percentage. Continuous variables summarized with count, mean, standard deviation, etc. Graphical presentation of data was done using bar chart as appropriate. Statistical analyses performed using SAS® vers 9.4 (SAS Institute Inc., USA).

Ethics statement

This retrospective study protocol carried less than minimal risk according to the Indian council of medical research 'ethical guidelines for biomedical research on human participants'.[6] The study was conducted after due approval from Bio-smart independent ethics committee, Ahmedabad, India. This was a retrospective study without patient identifiers; hence, the informed consent of patients was not taken. There was no confidentiality breach of the data during its analysis and interpretation.

RESULTS

A total of 1651 subfertility patients from various centres across India were evaluated in this study. Table 1 provides the details of patient characteristics. The mean (SD) age of the patients was 31.8 (3.9) years. The majority (77.8%) of patients were aged <35 years. The mean (SD) BMI was 26.19 (5.62) kg/m^2 and obese patients (BMI ≥30) constituted 28.1% of the total population. The majority of the patients had primary subfertility (79.5%) whereas 20.5% patients had secondary subfertility. Polycystic ovary syndrome (PCOS; 27.8%) was the most common cause of subfertility followed by unexplained infertility (24.8%), endometriosis (11.1%), male factor (10.3%), tubal disease (9.3%) and other ovulatory disorders (4%).

Table 1: Demographic details, (n=1651).

Parameters	N (%)
Age (years), mean (SD)	31.8 (3.9)
Age group (years)	
<35	1284 (77.8)
≥35	367 (22.2)
BMI, mean (SD)* (n=1625)	26.19 (5.62)
<18.5	72 (4.4)
18.5-29.9	1097 (67.5)
≥30	456 (28.1)
Type of subfertility	
Primary	1312 (79.5)
Secondary	339 (20.5)
IVF treatment cycle history	
0	1196 (72.4)
1	259 (15.7)
2	149 (9.0)
3	34 (2.1)
4	11 (0.7)
5	2 (0.1)
AMH levels (ng/ml) (n=1429)**	
<1.2	97 (6.8)
1.2-3.4	658 (46)
≥3.5	674 (47.2)
AFC count# (n=1363)	
<5	206 (15.12)
≥5	1157 (84.88)

About 3/4th of the patients (72.4%) had no previous IVF treatment history, and less than 3% of the patients had undergone more than 2 cycles in the past. The mean (SD) of AMH level was 4.42 (3.14) ng/ml. The majority (93.2%) of patients had normal (adequate) or above normal AMH values (normal AMH value ≥ 1.2 ng/ml). The mean (SD) of AFC was 11.2 (6.78) and majority (84.88%) of the patients had normal (adequate) or above normal AFC (normal AFC value ≥ 5).

Nature of treatment

About half of the patients were treated with frozen embryo transfer (50.1%) and the remaining patients were treated with fresh embryo transfer (49.9%).

Data related to protocol used for the COS was available for total 1312 patients. Most (~96%) of the patients received GnRH antagonist protocol whereas ~4% patients received GnRH agonist protocol. Among patients receiving GnRH antagonist protocol, fixed protocol accounted for 53.7% cases and remaining 46.3% patients received flexible protocol. In patients receiving GnRH antagonist protocol, most (98.7%) patients were prescribed cetrorelix acetate and ganirelix acetate was used in only 1.3% cases. About 3/4th of the patients (71.4%) who were prescribed GnRH agonist were on long GnRH agonist protocols, and luprorelin (83%) was the most common agent used.

Gonadotropin use

rFSH alone therapy was the most commonly used gonadotropin (49.2%) followed by a combination of gonadotropins in 33.3%, and hMG in 10.2% patients (Figure 1).

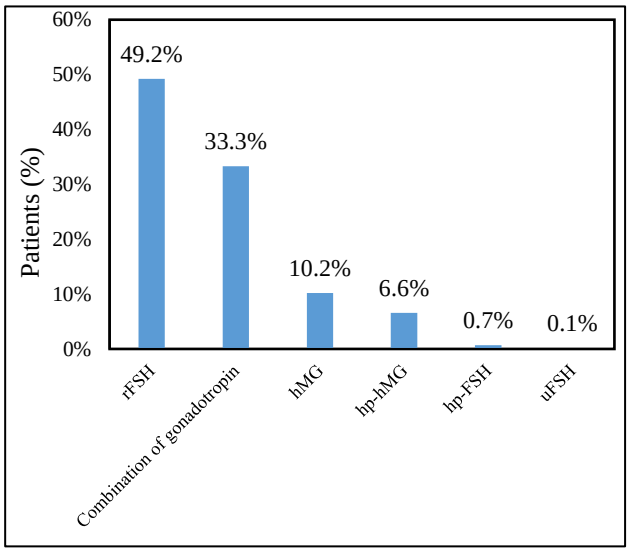

Figure 1: Gonadotropins used.

hMG-Human menopausal gonadotropins; hp-hMG-highly purified human menopausal gonadotrophin; hp-FSH-highly purified follicle stimulating hormone; rFSH-Human recombinant follicle stimulating hormone; uFSH-urinary follicle stimulating hormone.

Starting daily dose of gonadotropins

Majority (51.8%) of the patients were initiated at 225 IU dose of gonadotropin whereas 26%, 12.7% and 9.5% patients were initiated on 300 IU, 150 IU and other doses, respectively (Figure 2). Among those who were prescribed combination of gonadotropins, rFSH in combination with hp-hMG in the dose of 225-300 IU was used in 35% cases. The maximum dose of gonadotropins used per day was 225 IU (79.1%) followed by 450 IU (11.1%).

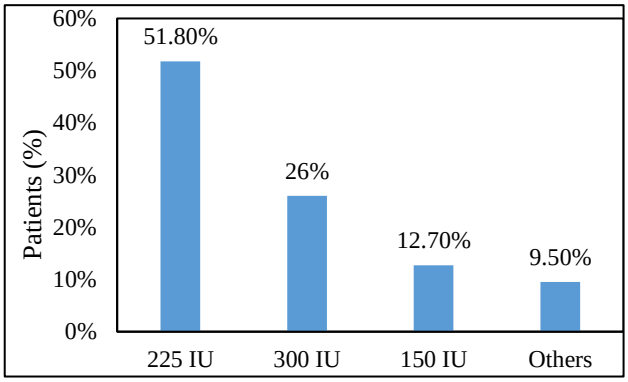

Figure 2: Starting daily dose of gonadotropins.

Mean number of days of ovarian stimulation and dose of gonadotropin used

The mean number of days of ovarian stimulation was 10.4 days irrespective of age, which varied from 10-10.5 days among various treatment protocols. Patients aged ≥35 years had a high mean total dose (3016.6 IU) of gonadotropin as compared with patients aged <35 years (2670.5 IU). Mean total dose of gonadotropin used was highest for hp-hMG (3148.7 IU) followed by hMG (3042.9 IU), hp-FSH (3020.5 IU), combination of gonadotropins (2947.9 IU), rFSH (2494.8 IU) and uFSH (2250 IU).

Choice of ovulation trigger method

In majority (59%) of the cases, hCG was used (10000 IU dose: 55.5% cases and 5000 IU dose: 3.5% cases) for ovulation trigger while in remaining cases (41%) GnRH agonist was used (Figure 3).

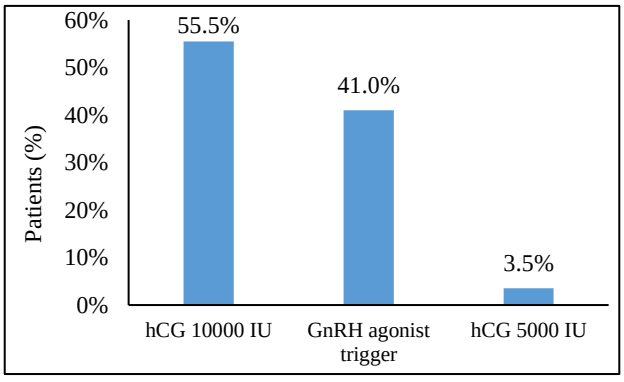

Figure 3: Choice of ovulation trigger method.

Mean number of follicles with ≥17 mm size on the day of hCG

The mean number of follicles with ≥17 mm size on the day of hCG 5000IU injection was 20.9 and hCG 10000IU injection was 20; the overall mean number of follicles ≥17 mm size on the day of ovulation trigger was 20.3.

Mean number of oocytes and metaphase II oocytes retrieved

The mean number of oocyte retrieval was highest with rFSH (12.1) followed by hp-FSH (11.6), hp-hMG (11.5), combination of gonadotropins (11.1), hMG (10.5) and uFSH (6.5). Similarly, the number of mean metaphase-II (M-II) oocytes was maximum with rFSH (8.5) followed by hp-hMG (8), hMG (7.8), hp-FSH (7.3) and combination of gonadotropins (6.9) (Figure 4).

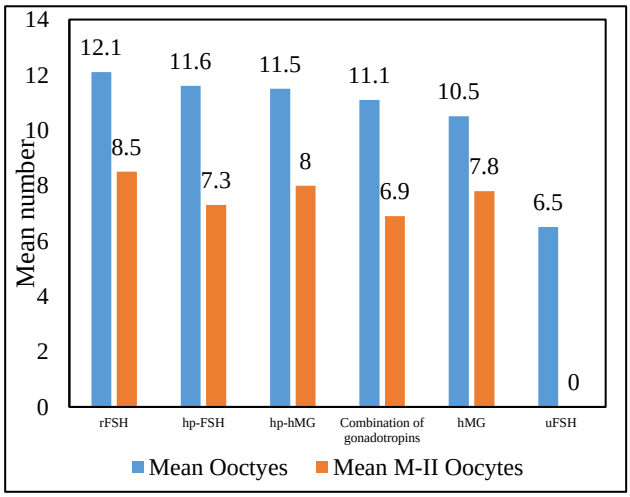

Figure 4: Mean number of oocytes and metaphase II oocytes retrieved.

DISCUSSION

The problem of infertility confronts millions of people worldwide.[7] Slightly over half of all infertility cases are a result of female conditions, while sperm disorder or unknown factors are associated with the rest of the causes.[8] This cross sectional observational real world study on 1651 subfertility female patients was conducted to evaluate the practice patterns related to management choices, gonadotropin selection and dosage for ovarian stimulation and oocyte retrieval.

The study reported that majority (77.8%) of patients were aged <35 years and majority patients had primary subfertility (79.5%) while only 20.5% had secondary subfertility. In an Indian study conducted on 120 couples visiting an infertility clinic for evaluation and treatment, the prevalence of primary infertility was 57.5% versus 42.5% of secondary infertility.[9] Worldwide studies have reported a higher incidence of primary infertility than secondary infertility.[10-12] Prevalence of primary infertility increases by age, higher BMI, irregular menstrual pattern, family history of infertility and delayed age at marriage.[13-15] Obesity, which is associated with hormonal imbalance and menstrual dysfunction, is a risk factor for infertility.[16] In the present study, obese patients constituted 28.1% of the total study population. The WHO universal criteria for obesity 2021 was considered for the evaluation in this study.[17] An important determinant of spontaneous pregnancies as well as pregnancies from assisted reproduction is the age of female. The average age of female partners coming for infertility treatment in this study was 31.8 (±3.9) years. Fecundity starts declining in the fourth decade and fertility starts declining as early as 32 years, and hence, late childbearing is often defined after the age of 35 years.[18] In the present study, PCOS was the most common cause of subfertility followed by unexplained infertility, endometriosis, male factor, tubal disease and other ovulatory disorders. Numerous studies worldwide have shown that the main female factor causing infertility is PCOS.[19-22] Unexplained infertility is a diagnosis of exclusion wherein after evaluation of the male and female factors the clinician fails to identify a specific cause for infertility. The incidence of unexplained infertility is quoted to be around 30%.[23] According to Gelbaya et al even after doing standard fertility tests, in 15-30% of couples, no causes were identified.[24] In the current study, approximately 25% patients had unexplained infertility.

Important predictors of ovarian reserve including AFC and serum AMH concentration can be used as predictors of ovarian responses to gonadotropin stimulation during IVF treatment.[25,26] In the present study, majority of patients had normal (adequate) or above normal AMH and AFC values.

ARTs are most frequently performed secondary to infertility. In patients with tubal factor infertility, male factor infertility, diminished ovarian reserve, ovarian failure (with donor eggs), ovulatory dysfunction, and unexplained infertility ARTs are frequently performed.[27] Several protocols are available for IVF-ET. GnRH antagonists in IVF inhibit premature luteinizing hormone (LH) rise. GnRH antagonists compete directly with endogenous GnRH for receptor binding and therefore rapidly inhibit secretion of gonadotropin and steroid hormones.[28] GnRH antagonists induce a shorter and more cost-effective ovarian stimulation compared to the long agonist protocol. However, a better synchronization of follicular recruitment and growth occurs with GnRH agonists than GnRH antagonists.[29] GnRH agonists have been used for controlled ovarian hyperstimulation for several decades, but in the recent times the use of GnRH antagonist has been widely adopted.[30] In the present study, most (~96%) of the patients received GnRH antagonist protocol of which 53.7% underwent fixed protocol, and remaining 46.3% patients received flexible protocol. Contradictory observations exist comparing fixed and flexible protocols. Four randomized controlled trials (RCTs) comparing a fixed (on day 6) versus a flexible (by a follicle diameter of 14-15 mm) protocol of GnRH

antagonist administration did not show any significant difference.[31] However, few published studies have shown a lower pregnancy rate in the flexible as compared to the fixed protocol.[32] Majority of the patients (98.7%) receiving GnRH antagonist protocol, were prescribed cetrorelix acetate while only 1.3% were given ganirelix in this study.

rFSH, hMG or combination of gonadotropins are widely used in the IVF-ET/ICSI for COS.[33] In the current study, the most commonly used gonadotropin was rFSH alone therapy followed by a combination of gonadotropins, and hMG. The starting daily dose of gonadotropins was 225 IU in about half of the patients whereas 300 IU and 150 IU were used in 26% and 12.7% patients, respectively. A dose of 100-225 IU is considered the standard gonadotropin daily dose.[34]

GnRH agonists have been used to trigger final oocyte maturation in GnRH antagonist cycles.[35] As per existing literature, a lower probability of pregnancy is expected when a single dose of GnRH agonist is used instead of hCG for triggering final oocyte maturation.[36] Replacing hCG with GnRH agonist reduces the risk of developing ovarian hyperstimulation syndrome (OHSS).[37] In the present study, in majority of the cases, hCG was used for ovulation trigger and GnRH agonist was used in remaining cases. The mean number of days of ovarian stimulation was 10.4 days in this study, which is consistent with the published literature.[38]

The mean total dose of gonadotropin for hp-HMG was 3148.7 IU, for hMG was 3042.9 IU, and for rFSH was 2494.8 IU in our study, which is comparable to the doses reported by Esteves and colleagues in which the total dose for hMG was 2685 IU, HP-hMG was 2903 IU and r-hFSH was 2268 IU.[39] In our study, the total dose of rFSH was lower than hMG, which is in accordance with a previous report, and indicates a lower total dose requirement with rFSH versus hMG.[39]

Age is a predictive variable for gonadotropin dose in COS.[40] In our study, patients aged ≥35 years had a high mean total dose (3016.6 IU) of gonadotropin as compared with patients aged <35 years (2670.5 IU). In a retrospective study, Tabata et al reported a lower dose of gonadotropin in patients aged <35 years as compared with patients aged >35 years.[41] La Marca et al reported a starting dose <225 IU in 50.2% of patients aged <35 years and 18.1% of patients aged >35 years, respectively.[42]

The mean number of oocyte retrieval and the metaphase-II oocytes was highest with rFSH (12.1 and 8.5). The mean number of oocytes retrieval with rFSH was 13.1 and 11.4 with urinary FSH in a study by Schats et al.[43] In a meta-analysis, Lehert and colleagues reported that hMG resulted in significantly fewer oocytes than rFSH (mean 9.4±6.3 versus 10.9±6.6).[44] In a subsequent meta-analysis, there were no significant differences in the number of oocytes retrieved between the rFSH + recombinant human LH versus r-hFSH (weighted mean difference: -0.03; 95% CI: 0.41 to 0.34).[45] In a study by Lenton et al, the mean number of oocytes and metaphase II oocyte retrieval with rFSH were 10.2 and 8, and with urinary FSH was 10.8 and 6.9, respectively.[46] In a study by Tabata et al the number of oocytes with FSH and FSH in combination with hMG were 9.6 and 8.5, respectively; metaphase-II oocytes were 5.7 and 5.3, respectively.[41]

The study limitations included retrospective nature of the study, and unavailability of the pregnancy outcomes. Further, due to retrospective nature of the study, data collected from few patient records were not complete and missing for some parameters.

CONCLUSION

This retrospective, observational study reports the real-world data on practice pattern of COS in IVF-ET / ICSI cycles in India. The study showed that majority of the patients were aged <35 years. Also, primary subfertility was the reason for IVF-ET/ICSI in majority of the patients. PCOS was the most common cause for subfertility. In most of the patients GnRH antagonist protocol was used, cetrorelix being the most common. For ovarian stimulation, rFSH alone therapy was used and the starting dose of gonadotropin was 225 IU per day in about half of the patients. In more than half of the patients, hCG was used with 10000 IU dose being the most common. The maximum number of oocytes and metaphase II oocytes were retrieved with rFSH alone therapy.

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