Impact of different controlled ovarian stimulation protocols on the physical and psychological burdens in women undergoing *in vitro* fertilization/intra cytoplasmic sperm injection

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ABSTRACT

CONTEXT: Infertility treatment involves a considerable amount of physical and psychological burden which may impact the outcome. **AIM:** The objective was to understand the amount of physical and psychological burden in women undergoing their first *in vitro* fertilization (IVF)/intra cytoplasmic sperm injection (ICSI) cycles. **SETTING AND DESIGN:** Multi-center, prospective, parallel, observational study. **MATERIALS AND METHODS:** The study was conducted across 12 IVF centers in India. A total of 692 women undergoing controlled ovarian stimulation as a part of the first cycle IVF/ICSI completed the trial. Women were recruited in 2 groups based on type of treatment (Group A - gonadotropin-releasing hormone [GnRH] antagonist; Group B - GnRH agonist) and were asked to fill questionnaires during the 2 treatment visits. **RESULTS:** The mean changes between Visit 1 (baseline) and Visit 2 in anxiety and depression (Hospital Anxiety and Depression Scale) scores in Group A for anxiety and depression were −0.5 (3.67), −0.1 (3.57) respectively and for Group B were −0.4 (3.68), 0.1 (3.67) respectively, which was not statistically significant. In Group A, the mean (±standard deviation [SD]) Hopkins Symptom Check List (HSCL) score was 17.9 (±5.17) in visit 1 and 19.1 (±5.45) Visit 2. The change between visits was 1.1 ($P < 0.0001$) with higher score reflecting higher somatic distress symptoms. In Group B, the mean (±SD) HSCL score was 18.2 (±5.19) in Visit 1 and 18.8 (±5.23) in visit 2. The change between visits was 0.6 ($P < 0.0014$). The difference of the mean change in physical burden between Group A and Group B was not statistically significant. **CONCLUSION:** A significant impact in both treatment protocols with respect to the physical burden was found between Visit 1 and Visit 2 but no difference in physical or psychological burden between the two treatment groups was observed.

KEY WORDS: GnRH Agonist, GnRH Antagonist, *In vitro* fertilization, OHSS, physical and psychological burden

INTRODUCTION

Infertility is defined as "a disease of the reproductive system characterized by the failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse."[1] A critical component of reproductive health, which affects men and women globally leading to distress and depression. World Health Organization estimated that approximately 50–80 million couples worldwide suffer from infertility.[2] Infertility is a world-wide problem affecting people of all communities, though the cause and magnitude may vary with geographical location and socioeconomic status. It is estimated that globally between 60 and 80 million couples suffer from infertility every year, of which approximately 15–20 million are in India alone.[3]

Infertile couples experience considerable psychological stress, with low self-esteem, isolation, loss of control, sexual inadequacy and depression. Treatment for infertility depends on its cause, and may include

fertility treatments like ovulation induction and *in vitro* fertilization (IVF) which requires administration of high dose of gonadotropins during controlled ovarian stimulation (COS). IVF has been widely used to treat most causes of subfertility. COS protocols intend to generate multiple oocytes to generate several embryos for transfer into the uterus. In conventional approach, in order to prevent the premature surge of luteinizing hormone (LH), co-treatment with Gonadotropin-releasing hormone (GnRH) agonists is used in COS for IVF. Later, with introduction of GnRH antagonist, it is considered as an alternative to GnRH agonist for prevention of premature LH surge in COS. In contrast with GnRH agonists which down regulate pituitary GnRH receptors, and desensitize gonadotropic cells, GnRH antagonists, directly bind to the pituitary GnRH receptors competitively, and inhibit gonadotropin release. Besides significantly shorter number days of injections, a lower incidence of ovarian hyperstimulation syndrome (OHSS) has been reported which is a major advantage with the use of GnRH antagonists in COS.[4]

It has been observed that IVF treatment is often discontinued by the couples before achieving a successful outcome due to the psychological stress.[5,6] The physical and psychological burdens of treatment are the most frequent cause of dropout by women and their partners enrolled in IVF programs, therefore, a reduction of treatment burden may reduce the discontinuation that occurs after an initial failed cycle.[6] Some studies have suggested that elevated anxiety and depression may actually lower pregnancy rates.[7]

This was the first Indian study to understand the physical and psychological burden in women, comparing a GnRH antagonist protocol with the conventional protocol in IVF. The previous studies on IVF have demonstrated that in the women of <35 years of age, the success rate was 21% after 1st cycle and it was increased by 40% by the 5th cycle.[8]

MATERIALS AND METHODS

This was a prospective, noninterventional, observational, two-arm, comparative study designed to compare psychological and physical burden associated with COS among Indian women undergoing first cycle IVF/intra cytoplasmic sperm injection (ICSI) between those using either GnRH antagonist or agonist protocol. An ethical clearance was obtained from the Institutional Review Board/ Independent Ethics Committee in compliance with the local laws, and an informed written consent to participate in the study was obtained from each subject after explaining them study objective. Ethical principles that have their origin in the world medical association declaration of Helsinki, and all applicable local laws, rules, and regulations relating to the conduct of the study were followed.

The study was carried out for a period of 10 months at 12 sites across India. The target was to enrol a total of 669 women aged 18–45 years undergoing COS for first cycle IVF/ICSI using either GnRH antagonist or agonist protocol. The total duration of each subject's participation in the study was 3–6 weeks (after enrolment) based on the treatment protocol the subject was receiving. Subjects who were able to fill the questionnaires and willingly provided the informed consent were enrolled in the study. Subjects who had the prior history of OHSS, who were using depot formulation of GnRH agonist, who were suffering from any neurological or psychiatric illness were excluded in the study.

Physician recruited GnRH antagonist (Group A) and GnRH agonist (Group B) users in a 1:2 ratio respectively. For each subject recruited in the GnRH antagonist regimen, two subjects were recruited in the conventional GnRH agonist regimen from the same study site.

For subjects treated with a GnRH antagonist protocol, Study Visit 1 was scheduled during the last clinical visit prior to start of ovarian stimulation with gonadotropin. For subjects treated with a GnRH agonist protocol, Study Visit 1 was the last clinical visit prior to start of pituitary down-regulation with GnRH agonist. No stratification based on age, or other characteristics was performed. All eligible subjects were asked to fill out baseline (Visit 1) questionnaires: Hospital Anxiety and Depression Scale (HADS)/Hopkins Symptom Check List (HSCL) questionnaires at their respective sites.

Visit 2 for both groups was the day of administration of human chorionic gonadotropin injection or the last day of ovarian stimulation if the treatment cycle was cancelled prior because of premature LH surge or premature ovulation. On this visit, the subjects were asked to fill the HADS, HSCL and Controlled Ovarian Stimulation Impact (COSI) questionnaires.

Instruments used for measuring primary endpoints in the Study were as follows:

Hospital Anxiety and Depression Scale

The HADS is a 14-item scale, designed to evaluate patient's anxiety (HADS-A, 7-item) and depression (HADS-D, 7-item). Each item is answered by the patient on a four-point (0–3) response category so the possible scores range from 0 to 21 for anxiety and 0–21 for depression. The scoring is done by adding the response marks against all questions marked as "A" to give out the anxiety score and against the questions marked as "D" to give the depression score. The score of 0–7 for either subscale could be regarded as being in the normal range, a score of 11 or higher indicating the probable presence of mood disorder, and a score of 8–10 being suggestive of the presence of the respective state.[9-11]

Hopkins Symptoms Checklist (12-item)

The present version of HSCL, which was used in this study is 12-item SOM scale derived from the Hopkins Symptom Checklist (SCL-90).[12,13] Symptom Distress Checklist–SCL-SOM intends to measure self-reported intensity of somatic symptoms. The questions were rated on the four scale ranging from 1 to 4 (1 - Not at all, 2 - a little bit, 3 - quite a bit, 4 - Extremely). Higher scores reflected higher somatic distress symptoms. The total and mean scores of the questionnaire responses from the subjects were analyzed using statistical methods.

Controlled ovarian stimulation impact questionnaire

The COSI questionnaire consists of six questions (Q1-Q6) with one or more item (s) per question. With a total of 28-item, the questionnaire addresses affects (9-item), anxiety on injection (4-item), convenience (1-item), life management (5-item), adverse events (AE) from injection (5-item), and difficulties relating to injections (4-item). Once tested against other psychological measurement tools, it was found to have acceptable psychometric properties. The questions are organized into 4 domains: (1) Psychological health, (2) interference with daily life, (3) injection burden and (4) compliance worry.[14] The answers from the COSI items are combined into a single total score per question that ranges from 9 to 45 (Q1), 4–20 (Q2), 1–5 (Q3), 5–25 (Q4), 5–25 (Q5), 4–20 (Q6), with a higher score reflecting a lower treatment impact on patients' daily life and well-being. To assess the impact of ovarian stimulation, the endpoints of the current study are defined in 3 categories: (1) Psychological burden, (2) The combined domains of interference with daily life and injection burden and (3) handling of medication which can lead to compliance worry. Psychological burden was assessed using the COSI psychological impact domain and handling of medication was used using the COSI compliance worry domain. Two COSI domains (interference with daily life and injection burden) were combined as one predesignated endpoint of interference with daily life as injection burden can interfere with daily life. Psychological burden, interference with daily life, and handling of medication were assessed using the total calculated score of Q1 (range: 9–45), Q4+Q5+Q6 (range: 10–70), and Q2+Q3 (range: 5–25), respectively.

Statistical analysis and sample size determination

The analysis was done on all the subjects allocated to any treatment arm in the study and was considered as safety population. All hypothesis testing for this study was done using two-sided, 0.05 level tests. The missing data was not imputed. Change was calculated only for subjects with nonmissing data at both the time points. The statistical analysis for the safety data was done using the software SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Psychological burden (anxiety, depression) was analyzed using HADS. Chi-square test/Fisher's exact test was used to compare the HADS response between treatment groups in each visit. HADS score between the two treatment groups was compared and analyzed using Mann–Whitney U-test by visit and for the change from Visit 1. The HADS scores were summarized using number of subjects (*N*), mean, median, minimum and maximum. Wilcoxon Signed Rank test was used to calculate the significant change from Visit 1 in HADS score for each treatment group.

Physical burden was analyzed using HSCL scale. HSCL score between the two treatment groups was compared and analyzed using Mann–Whitney U-test by visit and for change from Visit 1. The HSCL scores were summarized using number of subjects (*N*), mean, median, minimum and maximum.

Wilcoxon Signed Rank test was used to calculate the significant Change from Visit 1 in physical burden using HSCL score in each treatment group. The difference in physical burden using HSCL scale between treatment groups was summarized for each question by number (*n*) and percentage (%) and was compared using Chi-square Test/Fisher's exact test.

The comparison of the psychological burden, interference with daily life, and handling of medication between the two treatment groups at the end of GnRH agonist or antagonist administration was analyzed using the Mann–Whitney U-test. The endpoints were summarized using number of subjects (*N*), mean, median, minimum and maximum.

The number (*n*) and percentage (%) of subjects with at least one AE or serious adverse event (SAE) were presented for the two groups. Number of subjects with at least one AE or SAE were compared between the two groups using Chi-square test/Fisher's exact test. The incidence of OHSS was presented using number (*n*) and percentage (%) of subjects with OHSS for the two groups. Incidence of OHSS was compared between the two groups using Chi-square test/Fisher's exact test.

It was planned to enroll a total of 669 (including dropout rate) subjects in the study. Assuming a 10% of difference in scale of anxiety, depression and physical discomfort would be of clinical significance, for 80% power with 5% significance and with 20% additional for incomplete data, the total subjects planned to be enrolled in Group A was 222 and Group B was 447. A total of 692 subjects were actually enrolled in the study (in Group A 232 and in Group B 460 subjects were enrolled) to yield approximately 671 evaluable subjects (Group A 230 and in Group B 441) in the per protocol population.

RESULTS

The disposition of subjects in this study is summarized in flow chart in Figure 1 and subject assignment to treatment protocols is described in Figure 2. In Group A 232 and in Group B 460 subjects were enrolled with mean (±standard deviation [SD]) age of 30.6 (3.83) and 30.7 (4.21) years, in each group respectively. Majority (Group A 55.6%; Group B 55.2%) subjects belonged to the city where the study center was situated [Table 1].

Primary endpoints of this study were analyzed as given below:

Change in psychological burden (anxiety, depression) using Hospital Anxiety and Depression Scale

The mean (±SD) change in the anxiety score from Visit 1 to Visit 2 for Group A and Group B was −0.5 (±3.67) and −0.4 (±3.66) respectively. The mean (±SD) change in depression score from Visit 1 to Visit 2 for Group A and Group B was −0.1 (±3.57) and 0.1 (±3.67), respectively. The change from Visit 1 to Visit 2 between Group A and Group B was not statistically significant for anxiety ($P = 0.9552$) as well as depression ($P = 0.3562$) [Table 2].

Change in physical burden using Hopkins Symptom Check List scale

In Group A, the mean (±SD) HSCL score in Visit 1 and Visit 2 was 17.9 (±5.17) and 19.1 (±5.45). The mean change in the HSCL score from Visit 1 to Visit 2 was statistically significant ($P < 0.0001$). In Group B, the mean (±SD), HSCL score in Visit 1 and Visit 2 was 18.2 (±5.19) and 18.8 (±5.23). The mean change in the HSCL score from Visit 1 to Visit 2 was statistically significant ($P < 0.0014$) [Table 3]. The mean change in HSCL score was not statistically significant ($P = 0.1431$) when compared between two groups [Figure 3].

Psychological burden, interference with daily life, and handling of medication using controlled ovarian stimulation impact questionnaire

In Visit 2, the total scores for psychological burden, interference with daily life and handling of medication was compared between the two treatment groups using the domains of the COSI questionnaire as described in the Material and Methods Section. The mean (±SD) score of "psychological burden," "interference with daily life" and "handling of medication" in subjects of Group A was 19.8 (±6.35), 25.0 (±9.64) and 14.8 (±5.37), and of Group B was 19.2 (±6.12), 23.8 (±8.98) and 14.4 (±5.62), respectively. The differences between the groups were not statistically significant [Table 4].

Safety assessment

Extent of exposure

Subjects were enrolled only after the treatment decision (for either GnRH agonist or antagonist protocol) had been made by the investigator. The mean duration of medication taken by the subjects in Group A and Group B was 10.5 (±1.37) and 21.1 (±4.15) days, respectively.

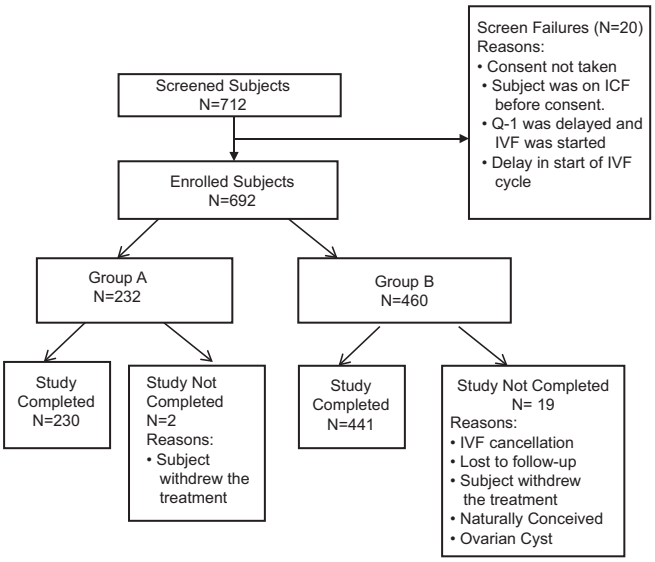

Figure 1: Subject disposition

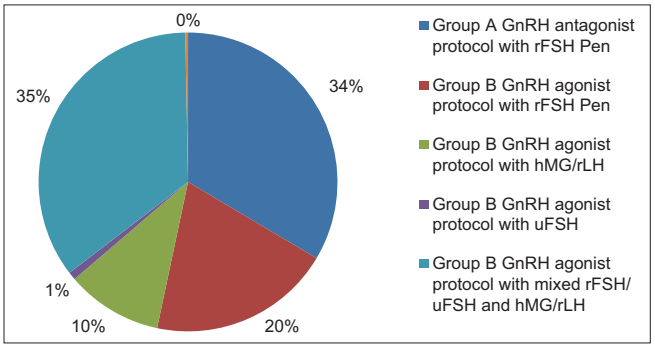

Figure 2: Subject enrolment according to treatment assigned

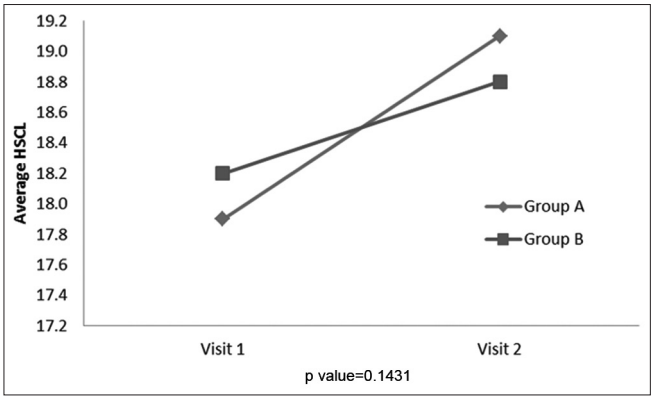

Figure 3: Change in Physical Burden (HSCL Score)

Assessment of safety endpoints

No AEs were reported for the subjects in Group A. In Group B, the overall AE rate was 0.2% (1/460). This event was SAE

of Grade I OHSS which was of mild grade and resolved without any sequelae.

DISCUSSION

This study was designed to explore the impact of different COS protocols on physical and psychological burden of women undergoing IVF/ICSI. The statistical analysis of the primary and secondary endpoints included all subjects allocated to any of the treatment arm in the study and also comprised the safety population. The analysis demonstrated that there were statistically significant changes in physical and psychological burden [Tables 2 and 3] in women undergoing IVF/ICSI. However, when compared between two protocols (GnRH antagonist vs. GnRH agonist), the change was not statistically significant [Tables 2 and 3].

There was a significant increase in physical burden (HSCL score) for both treatment protocols compared to baseline, although when compared between groups it was not statistically significant. This is consistent with the results of the previous study, where no significant differences between the groups (mild protocol with GnRH Antagonist vs. conventional protocol with GnRH Agonist) in the anxiety, depression, physical discomfort, or sleep quality were observed.[15] In the present study, the mean change of score from Visit 1 to Visit 2 for neither anxiety nor depression was significant [Table 2]. The level of anxiety and depression varied between the treatment groups. The percentage of subjects that experienced anxiety and depression was numerically higher in the Group B (GnRH agonist) than Group A (GnRH antagonist), though not statistically significant. In this study, subjects undergoing a GnRH antagonist treatment protocol (Group A) scored slight higher on COSI questionnaire than the subjects undergoing a GnRH agonist (Group B) treatment protocol (although the difference was not statistically significant). A higher score reflects a lower treatment impact on the women's' daily life and well-being.

Table 1: Summary of demographic and baseline characteristics

Characteristics	Statistics	Group A (*N*=232)	Group B (*N*=460)
Age (years)	*N*	232	460
	Mean (SD)	30.6 (3.83)	30.7 (4.21)
	Median	30.0	30.0
	Min, max	23, 42	19, 44
Height (cm)	*N*	232	460
	Mean (SD)	156.8 (7.24)	156.4 (7.37)
	Median	157.0	157.0
	Min, max	127, 177	108, 177
Weight (kg)	*N*	232	460
	Mean (SD)	60.7 (10.14)	59.7 (9.10)
	Median	60.0	60.0
	Min, max	38, 98	32, 93
BMI (kg/m2)	*N*	232	460
	Mean (SD)	24.76 (4.33)	24.51 (4.24)
	Median	24.20	24.22
	Min, max	15.6, 40.3	10.6, 56.6
Subject came from the same city as the site			
Yes	*n* (%)	129 (55.6)	254 (55.2)
No	*n* (%)	103 (44.4)	206 (44.8)

An interventional, noninferiority study conducted with the primary outcome measure of pregnancy and term live birth within 1-year of randomization, total cost per couple and patient discomfort compared the two protocols similar to the present study that is, the mild treatment strategy (GnRH Antagonist protocol and single embryo transfer [ET]) and conventional treatment (GnRH Agonist protocol) for IVF.[15] It was also noted that depression and anxiety scores showed an increasing trend over IVF cycle one to cycle four. However, the present study was an observational study and analyzed only one cycle as compared to the cumulative effect of three to four cycles as done in the study by Heijnen *et al*.;[15] yet both studies demonstrated that there were no significant differences in anxiety, depression and physical discomfort between the 2 protocols. It was also noted that the mean scores for depression and anxiety were <7 in both the studies.

Nonrandomization remains one of the limitations of the study. In another study conducted by Boivin *et al*., it was suggested that causes of burden can originate from the patient, clinic or treatment.[16] This psychological and physical burden can be addressed by comprehensive

Table 2: Comparison of change in psychological burden using Hospital Anxiety and Depression Score (HADS)

Visit	HADS	Statistics	Group A	Group B	*P* value*
Change from visit 1	Anxiety	*N*	231	444	0.9552
		Mean (SD)	−0.5(3.67)	−0.4 (3.66)	
		Median	0.0	0.0	
		Min, Max	−17, 11	−16, 16	
	Depression	*N*	231	444	0.3582
		Mean (SD)	−0.1(3.57)	0.1 (3.67)	
		Median	0.0	0.0	
		Min, Max	−13, 13	−12, 15	

*Mann-Whitney U test was used to calculate the significant difference between treatment groups

Table 3: Analysis of change in physical burden using Hopkins Symptom Check List (HSCL) score by treatment group

Treatment	Statistics	Visit 1	Visit 2	Change from visit 1	*P* value*
Group A	*N*	232	231		<0.0001
	Mean (SD)	17.9 (5.17)	19.1 (5.45)	1.1 (3.87)	
	Median	17.0	18.0	0.0	
	Min, Max	12, 37	12, 35	-17, 14	
	Missing	0	1		
Group B	*N*	460	444		0.0014
	Mean (SD)	18.2 (5.19)	18.8 (5.23)	0.6 (4.24)	
	Median	17.0	18.0	0.0	
	Min, Max	12, 36	12, 37	-16, 22	
	Missing	0	16		

*Mann-Whitney U test was used to calculate the significant difference between treatment groups

Table 4: Analysis of psychological burden, interference with daily life, and handling of medication using Controlled Ovarian Stimulation Impact (COSI) questionnaire

Visit 2	Categories†	Statistics	Group A	Group B	*P* value*
	Psychological burden	*N*	231	444	0.2033
		Mean (SD)	19.8 (6.35)	19.2 (6.12)	
		Median	20.0	18.0	
		Min, Max	9, 40	9, 41	
		Missing	1	16	
	Interference with daily life	*N*	231	444	0.1682
		Mean (SD)	25.0 (9.64)	23.8 (8.98)	
		Median	20.0	18.0	
		Min, Max	9, 40	9, 41	
		Missing	1	16	
	Handling of medication	*N*	231	444	0.4964
		Mean (SD)	14.8 (5.37)	14.4 (5.62)	
		Median	15.0	14.0	
		Min, Max	5, 25	5, 25	
		Missing	1	16	

*Mann-Whitney U test was used to calculate the significant difference between treatment groups. †: 3 categories and their respective calculations are: 1) Psychological Burden domain (based on the total calculated score of Q1), 2) the combined domains of Interference with Daily Life (based on the total calculated score of Q4+Q6) and Injection Burden (based on the total calculated score of Q5) and 3) Handling of Medication (based on the total calculated score of Q5) for compliance worry domain

educational materials, screening to identify highly distressed patients, the provision of tailored coping tools and improvements in the clinic environment and medical interventions. Some researchers have proposed that the frequent treatment visits, daily injections, scans and invasive procedures, such as oocyte retrieval, may be responsible for the high psychological and physical burden.[17] However, in this study, the psychological burden was not statistically significant compared to baseline score, though the physical burden increased post GnRH Agonist treatment protocols similar to the previous study.[17] These results may be due to the fact that all the participants were first cycle IVF treatment women and were comparatively well adjusted psychologically in comparison of subjects who had experienced unsuccessful IVF treatment previously.

In 85 Indian women undergoing first cycle of IVF, it has been observed that the positive affect (PA) scores before ovum pick up (OPU) and ET were significantly lower than those at baseline. The mean negative affect (NA) and state anxiety (St ANX) scores before OPU and ET were significantly higher than baseline scores. The PA and St ANX scores were statistically insignificant within cycle variations. However, the present study did not differentiate on PA, NA and St ANX scores, which are important tools for measuring psychological burden. It may be speculated that such an in depth analysis could perhaps explain the difference observed between the two studies. Large sample size and multi-center design are the major strength of this study.[18]

A systematic review has concluded that use of GnRH antagonist protocols as compared with longer GnRH agonist protocols, were associated with a lower incidence of OHSS with no evidence of a difference in live-birth rates.[4] In our study, there was one case of OHSS reported in the GnRH agonist group (Group B) and no cases of OHSS reported in the GnRH antagonist group (Group A).

The role of physical and psychological burden in infertility and infertility treatment outcome is not very clear. Both men and women experience anxiety during

an IVF–treatment, independent of the stage of the procedure (1st time or repeated cycle).[19] However, Domar and Prince suggested that psychological and physical burden may have some impact on the outcome of the IVF treatment.[20]

CONCLUSION

To the best of our knowledge, this is the first study conducted in an Indian population comparing different protocols to evaluate psychological and physical burden in women undergoing IVF/ICSI treatment. The study demonstrated significant physical burden with both treatment protocols. However, a statistically significant difference between the protocols was not demonstrated in either psychological or physical burden. This reiterates importance of comprehensive education and counseling to reduce physical burden as well as safety aspects of different stimulation protocol which can improve quality of life and IVF treatment outcomes.

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