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ORIGINAL ARTICLE ***Infertility***

Towards an optimal luteal support modality in agonist triggered cycles: a randomized clinical trial

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STUDY QUESTION: In ICSI patients with high risk of ovarian hyperstimulation syndrome (OHSS), are antagonist cycles triggered by gonadotropin releasing hormone (GNRH) agonist with a specialized luteal support regimen associated with comparable ongoing pregnancy rate (OPR) and less OHSS than those triggered by hCG?

SUMMARY ANSWER: In antagonist ICSI cycles, GnRH agonist triggering with a specialized luteal support regimen is associated with comparable OPR to those triggered by hCG but may be less likely to be associated with OHSS.

WHAT IS KNOWN ALREADY: In IVF/ICSI protocols, exogenous hCG was used for years as a substitute of the endogenous LH surge. However, because of its longer half life, hCG is associated with more risk of OHSS, especially in high risk women. For this reason, GnRH agonist triggering was introduced. There is, however, no consensus on the best protocol for luteal support on agonist triggered cycles.

STUDY DESIGN, SIZE, DURATION: Randomized controlled open label trial including 190 participants recruited from June 2015 to March 2016 in a private fertility center. Participants were divided into 2 equal groups; GnRH agonist trigger and hCG trigger. Randomization was done using identical sealed envelope technique.

PARTICIPANTS/MATERIALS, SETTING, METHODS: One hundred ninety women, predicted to have high response, were randomized on the day of final oocyte maturation into two equal groups: group (A), GnRH agonist trigger followed by specialized regimen (1500 IU hCG) at time of oocyte retrieval plus oral estradiol and intramuscular progesterone during luteal phase; and group (B), 5000 IU of hCG with luteal support (oral estradiol and vaginal progesterone).

MAIN RESULTS AND THE ROLE OF CHANCE: The 2 groups were comparable in baseline characteristics. OPR per randomized patient was comparable in the 2 groups {49/95 (51.6%) in group A, and 50/95 (52.6%) in group B (($P = 0.88$); RR = 0.980, 95% CI: 0.75–1.29)}. Considerable (moderate + severe) OHSS was higher in group B (13/95 [14%] versus 5/95 [5%] $P = 0.047$; uncorrected Chi-square test). Upon performing multivariate regression analysis for predicting OHSS, number of follicles ≥11 mm on trigger day was the only independent predictor ($P = 0.0004$).

LIMITATIONS, REASONS FOR CAUTION: Strict selection criteria limit generalization of results. The study was powered for pregnancy rate not OHSS, so that the strength of evidence on OHSS prediction is weak.

WIDER IMPLICATIONS OF THE FINDINGS: We recommend the use of GnRH agonist plus the specialized luteal phase support in high responders with high risk of OHSS undergoing IVF/ICSI cycles. This protocol achieved a similar ongoing pregnancy to hCG triggering and may be less likely to result in moderate to severe OHSS.

STUDY FUNDING/COMPETING INTEREST(S): None.

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Key words: agonist triggering / ICSI / pregnancy rate / OHSS / luteal support / antagonist cycles

Introduction

In ART, we aim to achieve high pregnancy rates with the safest and most convenient protocols of controlled ovarian stimulation (COS) and luteal phase support. An essential step in the IVF/ICSI protocols is final oocyte maturation. For this purpose, exogenous hCG was used for years as a substitute of the endogenous LH surge. Although both can bind to and stimulate the same receptors (Kessler *et al.*, 1979), the longer half life of hCG produces a prolonged luteotrophic effect, multiple corpora lutea and supraphysiologic steroids levels securing good reproductive outcomes (Itskovitz *et al.*, 1991). This prolonged luteotrophic effect however has been implicated in the occurrence of ovarian hyperstimulation syndrome (OHSS) after hCG triggering (Haning *et al.*, 1985). OHSS is a serious complication of ART treatment. It may occur in donor and non-donor cycles. It affects 1–14% of all IVF or ICSI cycles (Garcia-Velasco and Pellicer, 2003). Early severe OHSS was reported in 11.3% of 353 high responder women (Lainas *et al.*, 2012) and in 1.3% of oocyte donors (Bodri *et al.*, 2009). There is worldwide emphasis on the need to eliminate the occurrence of OHSS. The last report from HEFA has shown a decline in the total number of reported cases of severe OHSS in UK (HEFA, 2017)

For this reason, other alternatives were studied to substitute hCG, specially in women at high risk for OHSS. GnRHa was revived as a triggering agent after the introduction of antagonist protocols 1990s (Itskovitz-Eldor *et al.*, 2000). It provided a good and safe alternative in oocyte donors (Hernandez *et al.*, 2009). However, owing to the difference in the hormonal milieu of the luteal phase in the GnRHa and hCG triggered cycles, the pregnancy rate was disappointing in autologous cycles triggered by GnRHa (Kolibianakis *et al.*, 2005). The agonist binds to the pituitary GnRH receptors and replaces the antagonist, flaring up both LH and FSH, leading to oocyte maturation in a manner similar to that of natural cycles. Variations, however, exist between the natural surge and the agonist induced surge of gonadotrophins. The natural LH surge consists of three phases and lasts 48 h (Hoff *et al.*, 1983), while the surge produced after agonist triggering has two phases lasting 24–36 h (Itskovitz *et al.*, 1991). Therefore, there is a lower amount of gonadotrophins in the luteal phase of agonist triggered cycles, thus a subsequent rapid luteolysis and deficient luteal phase occur (Itskovitz *et al.*, 1991).

Several regimens were suggested to overcome this problem (Engmann *et al.*, 2006, 2008; Humaidan *et al.*, 2010; Griffin *et al.*, 2012; Papanikolaou *et al.*, 2011).

The addition of a bolus of 1500 IU hCG on the day of retrieval was suggested to rescue the luteal phase, increase the ongoing pregnancy rate (OPR) as well as eliminating the occurrence of OHSS in agonist triggered cycles. Humaidan and colleagues in a randomized controlled trial, upon 302 antagonist cycles, compared the use of 10 000 IU hCG for triggering ovulation versus using 0.5 mg GnRHa (buserelin) supplemented with 1500 IU hCG on retrieval day. Vaginal progesterone and oral estradiol were used for luteal support in both groups. None of the agonist triggered cycles developed OHSS, whereas three cases developed in the hCG group (one severe and two moderate). However, high risk patients were not included and a difference of 7% in OPR in favor of the HCG trigger group was reported (Humaidan *et al.*, 2010).

Another modality of rescuing luteal phase was giving intense luteal support and hormone replacement regimens, similar to the ones used for a gonadal oocyte donor recipient. The investigators recommended the use of intramuscular progesterone and high dose of estradiol during the luteal phase and early pregnancy and reported favorable outcome (Engmann *et al.*, 2006, 2008). Others did not find evidence to support this modality and reported lower pregnancy and implantation rate upon using the aforementioned intense support approach (Orvieto, 2012).

There is a need to explore for a more optimal luteal support mode in these cases. It might worth trying to combine the two aforementioned modalities and give a specialized luteal support mode in form of a bolus of 1500 IU hCG on the day of oocyte retrieval as well as giving intense hormonal support. The number of follicles, measuring ≥11 mm and/or estradiol level on the day of final oocyte maturation are among the most effective predictors for high response. In a study upon 2524 antagonist cycles, the presence ≥18 follicles, measuring ≥11 mm on trigger day was reported to have high prediction for OHSS (Papanikolaou *et al.*, 2006). Additionally, estradiol level ≥4000 pg/ml (14684 pmol/l) was elicited as the cutoff for high responders (percentile > 90%) among 1196 cycles (Chen *et al.*, 2007).

The aim of the present RCT is to compare the outcomes of antagonist cycles triggered by agonist with a specialized luteal support regimen to that triggered by hCG in ICSI patients with a high risk of OHSS. Further, to study whether the former regimen can decrease the occurrence of moderate/severe OHSS.

Patients and Methods

Study design

This randomized controlled trial was conducted during the period from June 2015 to March 2016 in a private fertility center. Women undergoing ICSI, who fulfilled the following inclusion criteria, were considered eligible for enrollment: (i) female age 18–35 years; (ii) women at high risk for OHSS, defined as having ≥18 follicles, measuring ≥11 mm and/or estradiol level ≥14684 pmol/l on the day of final oocyte maturation; and (iii) either regular cycles or oligomenorrhea/amenorrhea.

The study was approved by the institutional review board of the center and its PACTR trial registration number is PACTR 201506001132105.

Written informed consent was obtained form all participants.

Stimulation regimen

A dose between (150–225 IU) of recombinant FSH (Gonal F, Merck Serono) was commenced on the second or third day of the cycle and continued for the first 5 days. Then the dose was adjusted according to the response (monitored by ultrasound assessment and estradiol level). The

GnRH antagonist was started on Day 6 of stimulation (Cetrotide, 0.25 mg, Merck Serono). When three or more follicles reached ≥17 mm, our study participants were randomized into two groups. In group A, triggering was achieved by a subcutaneous administration of 0.3 mg of triptorelin (Decapeptyl, Ferring) followed by a dose of 1500 IU of hCG (pregnyl, Organon), 35 h after triggering. In group B, triggering was achieved by an intramuscular injection of 5000 IU of hCG (pregnyl, Organon).

Randomization

The recruited women were randomly assigned to either group in a ratio of 1:1. Overall, 190 identical sealed envelops were prepared; 95 contain 'HCG group' with all instruction details and the other 95 envelops contain 'GnRH agonist group' with all instruction details. Every recruited woman was allowed to choose one envelop once to determine to which group she was assigned.

Luteal phase support

Participants in group A received daily IM injections of progesterone, 100 mg (prontogest, Ibsa) starting from the day of retrieval and lasting for the entire luteal phase. Along with P supplementation, 2 mg E_2 valerate (cycloprogenova, Schering) was given three times daily starting from the day of retrieval and lasting for the entire luteal phase.

Participants in group B received daily vaginal progesterone, 100 mg (endometrin, Ferring), three times daily starting from the day of retrieval and lasting for the entire luteal phase. E_2 valerate, 6 mg daily, was started on the day of embryo transfer (ET) and lasting for the entire luteal phase (our routine luteal support regimen) (Elgindy *et al.*, 2010).

In both groups, when pregnancy test was positive, the progesterone was taken vaginally in a dose of 100 mg three times daily throughout the first 8 weeks of gestation. E_2 valerate, 6 mg daily was continued up to 8 weeks of pregnancy in group A and was stopped once pregnancy was positive in group B.

Patient evaluation for OHSS

Each woman was assessed for the risk of development of OHSS on the day of oocyte retrieval and on the day of ET (according to Navot *et al.*, 1992). Criteria for diagnosis of mild OHSS were abdominal distension and discomfort, nausea with or without vomiting and/or diarrhea and enlarged ovaries 5–12 cm. Moderate OHSS was diagnosed by the same criteria of mild OHSS plus ultrasound evidence of ascites. Severe OHSS was diagnosed in presence of variable sized ovaries, massive ascites with or without hydrothorax, hematocrit >45%, WBC > 15000, oliguria, creatinine clearance >50 ml/min, creatinine 1.0–1.5 mg/dl, liver dysfunction and/or anasarca. If criteria of considerable (moderate or severe) OHSS were encountered, the couples were counseled about freeze all strategy. Another evaluation for OHSS development was performed after 1 week after ET.

Outcome variables

The primary outcome was the OPR. The occurrence of OHSS, clinical pregnancy rates, number of mature oocytes were the secondary outcome measures.

Clinical pregnancy was defined as positive pregnancy test and ultrasound evidence of intrauterine gestational sac 4 weeks after ET. Ongoing pregnancy was defined as clinical pregnancy continuing beyond 20 weeks of gestation.

Statistical methods

Data were described in terms of mean ± SD, median and range, or frequencies (number of cases) and percentages as appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing normally distributed data and/or groups >30 records, otherwise, Mann Whitney *U* test for independent samples was used. For comparing categorical data, Chi-squared (χ^2) test was performed.

Univariate and multivariate regression analysis models were used to test effect of important variable(s) on occurrence of considerable OHSS. Accuracy was represented using terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cutoffs for studied markers in predicting considerable OHSS. Two sided *P* values <0.05 was considered significant. All calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Sample-size calculation

Ongoing pregnancy was used as the primary outcome. Chi-squared test for independent samples was used for performing the calculation. OPR was 30 and 50% in the agonist and hCG triggered cycles, respectively, in our preliminary pilot study. For an α-error of 0.05, and a power of 80% the calculated size of each group was 93 cases, and after adding a dropout rate of 2%, the final size of each group was determined to be 95.

Results

A total of 430 patients were potentially eligible for recruitment. Thirty women refused to participate, 200 did not meet the inclusion criteria, and 10 participants were excluded for other reasons (Fig. 1). Therefore, 190 women were randomized on the day of final oocyte maturation into group A (Agonist triggering, $n = 95$) and group B (HCG triggering, $n = 95$). The two groups were balanced in respect of the demographic, clinical and ICSI cycles characteristics (Table I). The number of participants having PCOS, according to Rotterdam criteria, was comparable between the two groups (Table I).

Per started cycle, clinical and OPR were comparable between the two groups. The 'freeze all' policy was adopted in five women in group A and in seven women in group B. OPR per ET were 54% (49/90) in group A and 57% (50/88) in group B (Table I). Twin pregnancy occurred in 25% (12/49) of group A and in 28% (14/50) of group B.

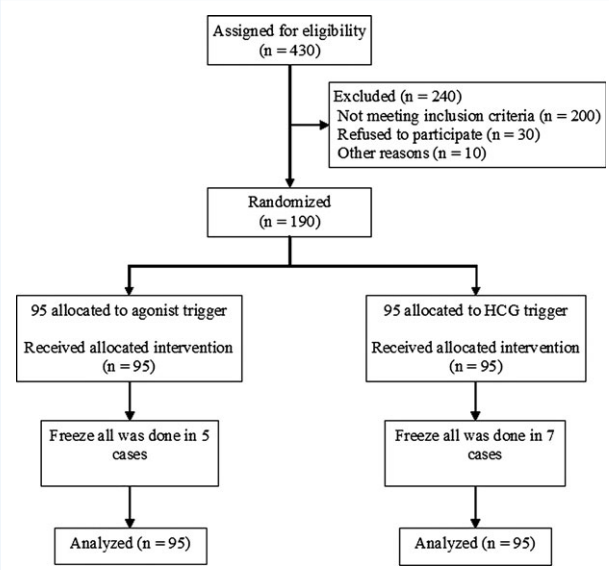

Figure 1 Flow diagram of the study population showing the total illegible, excluded and finally allocated participants.

Table I Demographic, clinical, ICSI cycle characteristics and outcome of the studied groups. Data are mean ± SD or *n* (%).

	Agonist trigger (*n* = 95)	HCG trigger (*n* = 95)	*P* value
Age (years)	27.8 ± 4.2	28 ± 4.3	0.125
Type of infertility			
Primary	78 (82)	74 (80)	0.770
Secondary	17 (18)	18 (20)	
Duration of infertility (years)	5.2 ± 2.6	4.8 ± 2.6	0.360
Cause of infertility			
Male	31 (33)	40 (42)	
Female	44 (46)	39 (41)	0.512
Both	13 (14)	12 (13)	
Unexplained	7 (7)	4 (4)	
PCO	57 (60)	56(59)	0.883
AMH (pmol/l)	48.6 ± 33.6	40 ± 22.1	0.076
AFC	18.6 ± 3.9	18.7 ± 3.8	0.818
Estradiol level (pmol/l)	15678.8 ± 4353.8	15590.7 ± 3964.7	0.886
Number of mature oocytes	14.9 ± 5.2	15.6 ± 5.2	0.379
Number of embryos	11.3 ± 5.2	11.1 ± 4.5	0.824
Number of good and fair quality embryos	10.2 ± 5.3	9.1 ± 4.4	0.121
Number of frozen embryos	4.96 ± 3.4	5.1 ± 3.0	0.802
Day of ET			
D3 ETs	8 (9)	5(6)	
D5 ETs	82 (91)	83(94)	0.41
Number of embryo transferred	1.93 ± 0.5	1.9 ± 1.6	0.600
Clinical pregnancy/cycle	51 (54)	53(56)	0.745
Ongoing pregnancy/cycle	49 (52)	50(53)	0.885
Ongoing pregnancy/ET	49 (54)	50(57)	0.750
Mild OHSS	3 (3)	3 (3)	0.678
Moderate OHSS	5 (5)	10(11)	0.18
Considerable OHSS[†]	5 (5)	13(14)	0.047

AMH, anti-Mullerian hormone; AFC, antral follicle count; ET, embryo transfer; OHSS, ovarian hyperstimulation syndrome.
[†]Moderate plus severe.

Moderate OHSS occurred in five women in group A and in 10 women in group B with no statistical significant difference. Severe OHSS did not occur in any of the participants in group A, however, it developed in three participants in group B. When both moderate and severe degrees of OHSS were combined (considerable OHSS), a statistically significant difference was evident between both groups (P = 0.047; uncorrected Chi-square test) (Table I).

Univariate analysis was performed for prediction of considerable OHSS. Basal AMH, AFC, number of mature oocytes as well as estradiol level, and number of follicles ≥11 mm on trigger day were significant predictors of considerable OHSS but protocol was not which might be explained by the relatively small number of considerable OHSS cases (Table II). Upon performing multivariate analysis, the number of follicles ≥11 mm on the trigger day was the only independent predictor. AMH and AFC had borderline significance (Table II).

ROC analysis was performed to determine the best cutoffs for predicting considerable OHSS. Cutoff for follicles ≥11 mm was 24 (AUC: 0.846, 95% CI: 0.72–0.967, sensitivity 89% and specificity 66%) (Fig. 2a); AMH had cutoff value 39.3 pmol/l (AUC: 0.62, 95%CI: 0.5–0.74, sensitivity: 55.6% and specificity: 52.3%) (Fig. 2b). Cutoff for AFC was 20 (AUC: 0.835, 95% CI: 0.753–0.917, sensitivity 89% and specificity 67%) (Fig. 2c). For mature oocytes, cutoff was 16 (AUC: 0.84, 95% CI: 0.76–0.91, sensitivity 94.4% and specificity 67%) (Fig. 2d). Cutoff for estradiol was 15326.4 pmol/l (AUC: 0.783, 95% CI: 0.703–0.863, sensitivity 94% and specificity 60%) (Fig. 2e). These results are independent of protocol.

Discussion

Our study observed no difference in OPR, in antagonist cycles triggered by agonist with a specialized luteal support regimen, to that

Table II Univariate and multivariate analysis of predictors of considerable ovarian hyperstimulation syndrome.

	Univariate analysis		Multivariate analysis			
	OR	*P* value	OR	*P* value	95% CI for OR	
					Lower	Upper
Protocol	0.350	0.056	0.539	0.435	0.114	2.549
Number of mature oocytes	1.26	<0.001	1.111	0.275	0.920	1.341
AMH	1.08	0.011	1.284	0.051	0.999	1.651
Estradiol level	1.01	0.001	1.000	0.954	0.999	1.001
AFC	1.45	<0.001	1.238	0.060	0.991	1.547
Number of follicles ≥11 mm	1.39	<0.001	1.324	0.004	1.091	1.607

AMH, anti-Müllerian hormone; AFC, antral follicle count.

triggered by hCG in ICSI patients with a high risk of OHSS. Nevertheless, considerable OHSS was higher in the hCG triggered group.

The administration of agonist for final oocyte maturation can produce a gonadotrophin surge which is sufficient for yielding a satisfactory number of mature oocytes. In current study, the number of mature oocytes was comparable between both groups. However, after agonist triggering the luteal phase is defective due to the reduced duration and concentration of the gonadotrophin surge (Itskovitz *et al.*, 1991) with a subsequent adverse effect on corpus luteum and the endometrial function (Rao, 2001). The addition of 1500 IU of hCG on retrieval day has been reported to rescue the luteal phase and to achieve satisfactory mid-luteal LH and progesterone levels (Humaidan *et al.*, 2010)

However, the CPR was lower with this protocol compared to hCG triggered cycles. To further improve the pregnancy rate, Humaidan *et al.* (2013) evaluated the addition of a second bolus of 1500 IU hCG, 5 days after oocyte retrieval in women with low risk of OHSS. Although this regimen provided better reproductive outcomes, a higher incidence of OHSS was observed in these low risk patients. On the other hand, the ability of intensive luteal support (Engmann *et al.*, 2008) to rescue the luteal phase specially in women with estradiol level of <4000 pg/ml on trigger day was questioned later (Engmann *et al.*, 2016).

In current study, we combined the addition of a bolus of 1500 IU hCG on retrieval day with intramuscular progesterone and high dose of estradiol, to test whether this package could rescue the luteal phase and provide adequate steroid levels for the endometrium. Progesterone is rapidly absorbed in the circulation when injected intramuscularly or administrated in the vagina. However, the blood levels after intramuscular administration was found to drop more slowly than after vaginal administration. Therefore, higher and frequent doses are needed to maintain the high plasma level of progesterone needed in luteal phase when using vaginal route compared to the intramuscular one. It has been suggested that the intramuscular site of progesterone administration might lead to progesterone accumulation within fatty tissue and hence working as a reservoir with continuous release that leads to a steady and more sustained concentration of progesterone in plasma compared to the vaginal or rectal rout (Nillius and Johansson, 1971). This is in contrast to the vaginal route of administration where vaginal mucosa might act as a rate-limiting membrane that allows only a limited amount of progesterone to be absorbed, therefore contributing to the less steady blood level of progesterone (Archer *et al.*, 1995). Therefore, the use of intramuscular progesterone appeared as a suitable modality to ensure an adequate steroid support for the endometrium. Additionally, the use of 6 mg of estradiol was also adopted as it was shown to maintain adequate estradiol levels during the luteal phase (Elgindy *et al.*, 2010).

In current study, there was continuation of steroid support during early pregnancy, as earlier reports had shown that the rising hCG during early pregnancy is not sufficient to rescue the early luteolysis occurring after agonist trigger (Nevo *et al.*, 2003). This specialized luteal support mode succeeded in achieving an OPR comparable to the hCG triggered cycles.

Considerable OHSS was lower in the agonist triggered protocol but it was not totally eliminated. It appears that even the addition of a low dose of hCG can trigger moderate OHSS in high responders having our inclusion criteria. Humaidan *et al.* (2013) reported no considerable OHSS in their patients receiving agonist and one bolus of 1500 IU hCG. Patients in their study had different inclusion criteria and should have had from 15 to 25 follicles, measuring ≥11 mm on trigger day. Admittedly, the concept of agonist triggering and freeze all is suggested for high responders. There are however limitations for routine application. An optimal cryopreservation program is not available in all ART units. Larger trials are needed to confirm this concept and its superiority. In our country, it remains more acceptable for our patients to undergo fresh transfer.

Blastocyst embryo transfer (BET) increased the pregnancy rate in women with high estradiol on the day of oocyte triggering, especially for those having E_2 > 15 420 pmol/l (4200 pg/ml) (Elgindy *et al.*, 2011). Delaying ET offers the endometrium time to recover from any negative effects caused by the exposure to peak super-physiological levels of E2. In current study, most of participants in both groups had undergone extended culture.

Following patients for 5 days after retrieval enabled further evaluation and offering freeze all modality before undergoing BET if any manifestations of OHSS had appeared. Freeze all modality was offered to all the five women who showed OHSS in the agonist trigger group. Meanwhile, 7 of the 13 women who showed OHSS in the hCG trigger group underwent freeze all. Nevertheless, six participants developed considerable OHSS in the hCG trigger group with 4 of them having the late onset type. Two of these four cases of late onset OHSS had twin pregnancy.

OHSS is one of the most distressing complications in assisted reproduction. Nowadays, prevention of this problem is a major goal. In

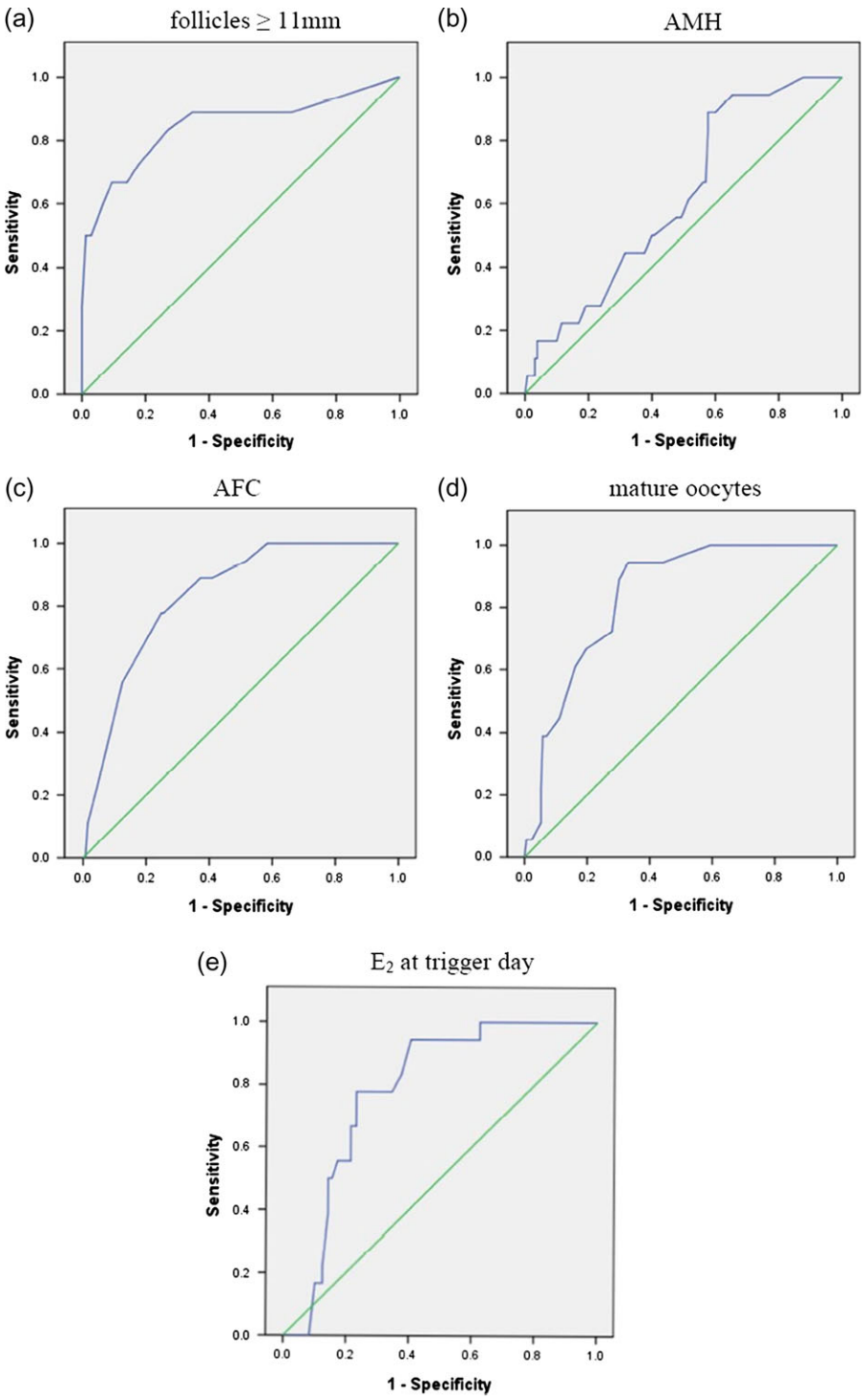

Figure 2 Receiver operator characteristic (ROC) curve for predictors of moderate/severe OHSS: number of follicles ≥11 mm; anti-Mullerian hormone (AMH); antral follicle count (AFC); number of mature oocytes; and estradiol (E_2) on trigger day.

current study, our secondary objective was to find the most important predictors of considerable OHSS and to determine cutoffs if possible. Upon using multivariate analysis, the number of follicles ≥11 mm on trigger day was the only independent predictor. Both AMH and AFC had borderline significance.

Because we had only 18 cases with moderate/sever OHSS, we decided to perform ROC analysis only for markers that were significant in univariate analysis. Using ROC analysis, the cut off for follicles ≥11 mm was 24. Previously, a cutoff level of >25 follicles were empirically set and there has been some emphasis on the need to validate

this value (Humaidan *et al.*, 2015). AFC cutoff was 20 with fair AUC and accuracy. The OPTIMST trial used AFC cutoff value 15 for predicting hyper response (van Tilborg *et al.*, 2012). Here, we report the value of 20 for predicting considerable OHSS. Basal AMH hardly touched significant level and its cutoff was 39.3 pmol/l with lower accuracy. Although the number of retrieved mature oocytes was not an independent predictor for developing considerable OHSS; yet, getting 16 mature oocytes or more had reasonable accuracy for predicting OHSS. Ji *et al.* (2013) in an analysis of 2455 cycles, suggested that having more than 15 oocytes increased the incidence of moderate-severe OHSS. Cutoff for E_2 was 15326.4 pmol/l on trigger day, with lower accuracy than that for follicles ≥11 mm. In a study upon 2524 antagonist cycles, E_2 levels were less reliable than the number of follicles in predicting OHSS (Papanikolaou *et al.*, 2006). Larger number of patients however are needed to verify current study cutoffs.

The concept of 'individualized luteal support' is emerging (Humaidan *et al.*, 2015). In high responders, it appears preferable to give the agonist for triggering and target either fresh transfer after giving a specialized luteal support mode or freeze all embryos if there is an estimated high OHSS risk. Based on current study findings, 24 follicles ≥11 mm on the trigger day could be an indication for opting to freeze all the embryos. larger trials are needed to confirm current study cutoffs and whether there are any additional high risk factors for predicting considerable OHSS which justify freeze all modality. Admittedly, the strategy of freezing all embryos should be applied in patients who are at high risk for OHSS.

The strength of our study is that it was adequately powered randomized study for the primary objective. Limitations are that conclusions can only apply to women meeting our selection criteria and that whereas the trial was powered adequately to detect a difference in OPR it was underpowered for OHSS. Hence larger trial using considerable OHSS as an endpoint are needed to strengthen the findings obtained from our trial. Further, we do not have access to the live birth outcome, which is important specially in OHSS cases that could have adverse perinatal outcome.

In conclusion, antagonist cycles triggered by agonist with a specialized luteal support regimen have comparable OPR to that triggered by hCG and considerable OHSS may be lower.

Authors' role

E.E. contributed to study design, acquisition, analysis and interpretation of data, article drafting, critical discussion and final approval of the version to be published. S.H. contributed to acquisition, and interpretation of data, article drafting and critical discussion, and final approval of the version to be published. M.M. contributed to study design, acquisition, analysis, and interpretation of data, article drafting, critical discussion and final approval of the version to be published. G.A. contributed to study design, acquisition, analysis and interpretation of data, article drafting, critical discussion, and final approval of the version to be published. D.E. contributed to study design, acquisition, analysis, and interpretation of data, article drafting, critical discussion, and final approval of the version to be published. M.H. contributed to study design, acquisition, analysis, and interpretation of data, article drafting, critical discussion, and final approval of the version to be published.

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Conflict of interest

None.

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