Reproductive Sciences (2023) 30:2481–2488
https://doi.org/10.1007/s43032-023-01196-x

INFERTILITY: ORIGINAL ARTICLE

Effectiveness of GnRH Agonist Short Protocol Versus GnRH Antagonist Protocol in POSEIDON Groups 3 and 4: a Retrospective Cohort Study

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Received: 4 October 2022 / Accepted: 5 February 2023 / Published online: 17 February 2023

Abstract

The aim of this study is to compare the ART (assisted reproductive technology) outcomes and cancellation rates between GnRH antagonist protocol and GnRH agonist short protocol in POSEIDON (Patient-Oriented Strategy Encompassing IndividualizeD Oocyte Number) groups 3 and 4. It is a retrospective cohort study conducted in the Department of Reproductive Medicine and Surgery of a tertiary-level hospital. Women who underwent ART treatment with either GnRH antagonist or GnRH agonist short protocol with fresh embryo transfer, between January 2012 and December 2019 belonging to POSEIDON 3 and 4 groups, were included. Among the 295 women who belonged to the POSEIDON groups 3 or 4, 138 women received GnRH antagonist and 157 women received GnRH agonist short protocol. The median total dose of gonadotropin in the GnRH antagonist protocol was not significantly different from GnRH agonist short protocol [3000, IQR (2481-3675) vs. 3175, IQR (2643-3993), $p = 0.370$]. There was a significant difference in the duration of stimulation between the GnRH antagonist and GnRH agonist short protocol [10, IQR (9-12) vs. 10, IQR (8-11), $p = 0.002$]. The median number of mature oocytes retrieved was significantly different in the cohort of women receiving GnRH antagonist protocol compared to GnRH agonist short protocol [3, IQR (2-5) vs. 3, IQR (2-4), $p = 0.029$]. There was no significant difference in the clinical pregnancy rate (24% vs. 20%, $p = 0.503$) and cycle cancellation rate (29.7% vs. 36.3%, $p = 0.290$) between the GnRH antagonist and agonist short protocols respectively. Live birth rate was not significantly different between the GnRH antagonist protocol (16.7%) and GnRH agonist short protocol (14.0%) [OR 1.23, 95% CI (0.56-2.68), $p = 0.604$]. After adjusting for the significant confounding factors, the live birth rate was not significantly associated with the antagonist protocol compared with the short protocol [aOR 1.08, 95% CI (0.44-2.63), $p = 0.870$]. Though GnRH antagonist protocol results in higher mature oocyte yield when compared with GnRH agonist short protocol, it does not translate into an increase in live birth in POSEIDON groups 3 and 4.

Keywords Diminished ovarian reserve · GnRH antagonist protocol · GnRH agonist short protocol · POSEIDON group 3 · POSEIDON group 4

Introduction

Worldwide, there is an increasing trend toward postponement of parenthood which has translated into a higher number of women of advanced age seeking fertility treatment [1, 2].

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Earlier studies have reported that approximately one in ten women experiences an accelerated loss of ovarian reserve after the age of 30 years. This accelerated loss of ovarian reserve frequently leads to the diagnosis of diminished ovarian reserve (DOR) which in turn is associated with a significant reduction in fecundity [3–5]. Once a diagnosis of DOR is made, many women are fast-tracked toward assisted reproductive technology (ART) due to unpredictability around the rate of decline of the ovarian reserve which is an important prognostic factor for ART [6, 7]. Commonly, women with DOR have a poor response to standard controlled ovarian hyperstimulation (COH) regimes during ART.

Women with a poor response or "poor ovarian responders" (POR) are a heterogeneous population with an estimated prevalence of 5-24% in couples undergoing ART [8, 9]. Women with DOR, age > 35 years, and those with certain FSH (follicle-stimulating hormone)/LH (luteinizing hormone) receptor polymorphisms are at a higher predisposition to respond poorly to COH during an ART treatment [10, 11]. In spite of various improvements in ART treatment protocols, the live birth rate (LBR) in POR ranges between 2 and 8% [12]. For many years, it was a challenge to evaluate the effectiveness of various interventions being advocated in routine clinical practice for POR due to the lack of standardized definition which captures the heterogeneity and varying levels of the prognosis within the population [9]. To address this problem, the Bologna criteria were introduced to bring uniformity to the definition [12]. However, the Bologna criteria had its own shortcomings [13]. Subsequently, a more pragmatic classification system, Patient-Oriented Strategy Encompassing IndividualizeD Oocyte Number (POSEIDON) criteria, was introduced for identification and better stratification of the women with a low prognosis on the basis of qualitative and quantitative parameters [13]. In POSEIDON classification, the poor ovarian responders were stratified into four groups. Women having adequate ovarian reserve but had a suboptimal or poor response in previous IVF cycle were classified into group 1 (women < 35 years of age) and group 2 (women ≥ 35 years of age). Groups 3 (women < 35 years of age) and group 4 (women ≥ 35 years of age) included women with diminished ovarian reserve. While the advocated strategy during ART for the POSEIDON group is to maximize the yield of oocytes in order to improve the LBR, it is a challenge for women with compromised ovarian reserve [14]. The POSEIDON 3 and 4 groups mainly include women with DOR.

The ultimate rationale of any protocol is to optimize the oocyte yield and subsequently the reproductive outcomes. The gonadotropin-releasing hormone (GnRH) agonist short protocol (or the "flare protocol") and the gonadotropin-releasing hormone (GnRH) antagonist protocol have been commonly employed during ART in women with POR [15]. However, studies comparing these two protocols are scarce and have reported conflicting results regarding the superiority of one protocol over the other [16]. While one study reported a higher clinical pregnancy rate with GnRH agonist short protocol, other studies demonstrated significantly higher pregnancy rates in the antagonist group or no significant difference in clinical pregnancy rate between the two protocols in patients with poor ovarian response [17–19]. However, none of these studies used POSEIDON criteria to define women with DOR. With the broader acceptance of POSEIDON classification in current practice, it is important to study the effectiveness of various proposed treatment strategies.

In view of the dearth of studies comparing GnRH agonist short protocol versus GnRH antagonist protocol in women with DOR as defined by POSEIDON criteria, we planned the current study to evaluate the effectiveness of GnRH agonist short protocol versus GnRH antagonist protocol in POSEIDON groups 3 and 4.

Materials and Methods

Study Population

The retrospective cohort study was conducted in the Department of Reproductive Medicine and Surgery, Christian Medical College, Vellore, India which is a tertiary-level hospital. Women who underwent ART treatment between January 2012 and December 2019 were screened for eligibility. Women belonging to the POSEIDON 3 and 4 groups who underwent ART with either (GnRH) agonist short protocol or GnRH antagonist were included in the study. Women aged < 35 and ≥35 years with DOR (defined by anti-Müllerian hormone level (AMH) <1.2 ng/ml and/or antral follicle count (AFC) <5) were categorized as POSEIDON 3 and 4, respectively [20]. Women undergoing a fresh ART treatment cycle for various indications like male factor, endometriosis, tubal, unexplained and combined factors were included, while the frozen embryo transfer cycles were excluded. Women with recurrent implantation failure and corrected uterine anomalies (septate uterus) were included. If a couple had undergone more than one cycle in this time period, only the first cycle was included while the subsequent cycles were excluded from the analysis. Data of those women who had given written consent for the use of anonymous data in retrospective studies were included in the current study. Ethics committee approval was obtained from the institutional review board (IRB Min No 14080, dated 30.06.2021) for use of anonymous data.

Assessment of ovarian reserve was done by measuring antral follicle count (AFC) and/or serum levels of AMH. Measurement of serum AMH levels was performed using an electrochemiluminescence assay (Cobas e602 analyzer,

Roche, Germany). The AFC was measured by calculating the total number of follicles which are 2–9 mm in diameter in both ovaries, using a transvaginal ultrasound (Voluson e series, GE Healthcare, Chicago, IL, USA, probe frequency of 7.5 MHz) by an experienced reproductive medicine consultant. In case of discrepancy between AMH and AFC, AMH was given precedence over AFC for final categorization.

ART Protocol

Pre-treatment oral contraceptives were given for cycle scheduling purposes for all the women. The controlled ovarian hyperstimulation (COH) was achieved with recombinant gonadotropins (Gonal-F, Merck Serono, Switzerland or Recagon, Merck Sharp & Dohme, NJ, USA) and the starting dose was between 300 and 450 IU. The GnRH antagonist (Cetrorelix, Merck Serono, Netherlands or Ganirelix, Ferring Pharmaceuticals, USA) was initiated from the day when lead follicle reached the diameter of 12–13 mm, at a dose of 0.25 mg, subcutaneously and was continued until the day of trigger (flexible protocol) for those women receiving GnRH antagonist protocol. In the GnRH agonist short protocol, a daily injection of GnRH agonist (Lupride acetate, Sun Pharmaceuticals, India) at a dose of 1 mg subcutaneously was started on the first day of the menstrual cycle and reduced to 0.5 mg daily after 3 days. The recombinant gonadotropin was started from the third day of the menstrual cycle and continued along with the GnRH agonist until at least two-three follicles reached a diameter of 17 mm when the ovulatory trigger was administered. Recombinant hCG injection (Ovitrelle, Merck Serono, Middlesex) trigger at a dose of 250 mcg was administered subcutaneously for final oocyte maturation. Transvaginal oocyte pickup was planned 35 h after the trigger. Fresh embryo transfer was performed if the endometrial pattern was ≥7 mm and <15 mm at the cleavage stage or blastocyst stage (day 2, day 3, or day 5). Embryo grading was done according to the existing lab protocol and depending upon the grade of embryos, and between one and three embryos was transferred. Luteal support was started on the day of oocyte retrieval with vaginal micronized progesterone at a dose of 400 mg (Naturogest SR 400, Zydus Healthcare Ltd.) twice daily. In addition, either parental progesterone (Gestone, Ferring Pharmaceuticals) at a dose of 100 mg intramuscular twice weekly or oral dydrogesterone (Duphaston, Abbott Pharmaceuticals) 10 mg thrice daily was also continued until the day 18 post retrieval, based on clinician's preference. If the pregnancy test was positive, the luteal support was continued with vaginal progesterone alone until 12-week gestation. The pregnancy outcomes were followed by hospital medical records or telephonically as well as via email communication.

Outcomes

The primary outcome measure was the live birth rate (LBR) per woman. Live birth was defined as a fetus showing evidence of life beyond 22 completed weeks of gestational age [21].

Secondary outcomes were cycle cancellation rate (percentage of initiated ART cycles canceled before oocyte pickup due to no response or mono follicular response), number of mature oocytes retrieved (number of oocytes retrieved that were in metaphase II stage), and clinical pregnancy rate per women (pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs).

Statistical Analysis

Continuous variables were expressed as either means ± SD or median with interquartile range (IQR) and were compared with Student's *t*-test or Mann–Whitney *U* test respectively. Categorical variables were expressed as frequency and percentage and compared using the Chi-square test or Fisher's exact test. Logistic regression analysis was done to check the association between the variable and outcome and expressed as an odd's ratio with 95% CI (confidence interval). Multivariable analysis was conducted by logistic regression by entering clinically important covariates associated with live births and the results were expressed as adjusted odds ratio (OR) with 95% CI. SPSS (Ver. 21.0, IBM, Chicago, IL, USA) and STATA IC version 16 (StataCorp, College Station, TX, USA) were used for statistical analysis. A p value of less than 0.05 was statistically significant.

Results

A total of 2570 ART cycles were conducted between January 2012 and December 2019. Out of these, 295 women belonged to the POSEIDON groups 3 or 4 and received treatment with either GnRH agonist short protocol ($n = 157$) or GnRH antagonist protocol ($n = 138$) and were included in the final analysis as shown in Fig. 1.

The baseline characteristics of the two cohorts are summarized in Table 1. There was a significant difference in the distribution of mean age of the women belonging to the GnRH antagonist protocol (33.96 ± 4.40 years) compared to the GnRH agonist short protocol (35.98 ± 4.32 years). There were significant differences in the type of infertility between the two groups.

The median total dose of gonadotropin in the GnRH antagonist protocol (3000 IU, IQR 2481-3675) was not significantly different from GnRH agonist short protocol (3175 IU, IQR 2643-3993) ($p = 0.370$) (Table 2). However, the median duration of stimulation in the GnRH antagonist protocol, 10 days (IQR 9-12) was significantly

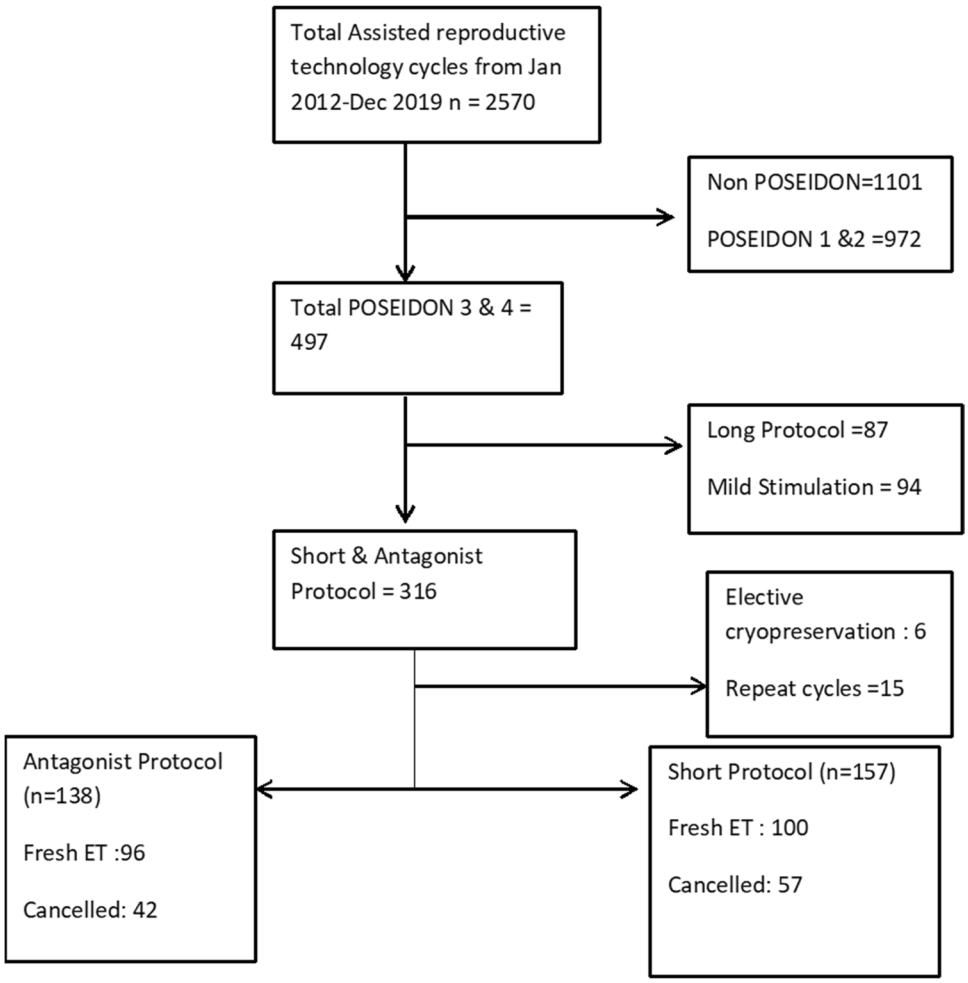

Fig. 1 Data selection flowchart of the women

Table 1 Baseline characteristics of the women

		Antagonist ($n = 96$)	Short ($n = 100$)	P value
Age†		33.96 ± 4.40	35.98 ± 4.32	0.001
BMI†		26.72 ± 4.25	26.53 ± 4.18	0.746
Type of infertility *n* (%)	Primary (%)	70 (72.9)	46 (46.0)	0.001
	Secondary (%)	26 (27.1)	54 (54.0)	
Indication *n* (%)	Male	21 (21.9)	9 (9.0)	0.062
	Anovulation	2 (2.1)	1 (1.0)	
	Tubal	12 (12.5)	19 (19.0)	
	Unexplained	17 (17.7)	27 (27.0)	
	Endometriosis	8 (8.3)	4 (4.0)	
	Combined	36 (37.5)	40 (40.0)	
POSEIDON *n* (%)	3	50 (52.1)	34 (34.0)	0.011
	4	46 (47.9)	66 (66.0)	

† Mean ± standard deviation

n (%) data expressed as number of women (percentage) for categorical variables

longer compared to 10 days (IQR 8-11) in the GnRH agonist short protocol ($p = 0.002$). The median number of mature oocytes retrieved was significantly higher in the cohort of women receiving GnRH antagonist protocol compared to GnRH agonist short protocol (3, IQR 2-5 vs. 3, IQR 2-4, $p = 0.029$).

The live birth rate per woman was not significantly different between the GnRH antagonist protocol (11.6%) and the

Table 2 Assisted reproductive technology treatment characteristics

		Antagonist ($n = 96$)	Short ($n = 100$)	p value
Total dose (IU) ‡		3000 (2481-3675)	3175 (2643-3993)	0.370
Days of stimulation‡		10 (9-12)	10 (8-11)	0.002
Number of mature oocytes‡		3 (2-5)	3 (2-4)	0.029
Number of embryos transferred‡		2 (1-3)	2 (1-2)	0.705
Stage of embryo transferred n (%)	Cleavage	92 (95.8%)	96 (96.0%)	0.953
	Blastocyst	4 (4.2%)	4 (4.0%)	1.000

‡Median (25th centile-75th centile)

GnRH agonist short protocol (8.9%) ($p = 0.45$) (Table 3). There was no significant difference in the clinical pregnancy rate per woman (16.7% vs. 12.7%) ($p = 0.34$) in the GnRH antagonist vs. GnRH agonist short protocol, respectively.

The live birth rate per embryo transfer was not significantly different between the GnRH antagonist protocol (16.7%) and GnRH agonist short protocol (14.0%) (Table 4). There was no significant difference in the clinical pregnancy rate (24.0% vs. 20.0%) and miscarriage rate (30.4 % vs. 30.0%) in the GnRH antagonist vs. GnRH agonist short protocol respectively. The cycle cancellation rate was 30.4% in GnRH antagonist protocol and 36.3% in GnRH agonist short protocol; however, the difference was not statistically significant ($p = 0.29$) (Table 3).

Logistic regression analysis with clinical pregnancy as outcome showed no significant association with the GnRH antagonist protocol in comparison to GnRH short protocol [odd's ratio (OR) 1.26, 95% CI (0.64-2.48)]. After adjusting for the significant confounding factors (age, type of infertility, BMI, indication of infertility, number of mature oocytes retrieved), the clinical pregnancy rate did not show any significant association with the antagonist protocol compared with GnRH agonist short protocol [aOR 0.92, 95% CI (0.43-1.93)] (Table 5).

For the live birth, no significant difference was observed with the GnRH antagonist protocol in comparison to GnRH short protocol [OR 1.23, 95% CI (0.56-2.68), p value 0.61]. After adjusting for the significant confounding factors (age, type of infertility, BMI, indication of infertility, number of mature oocytes retrieved), the live birth rate per embryo transfer was not significantly associated with the antagonist protocol compared with the short protocol [aOR 1.08, 95% CI (0.44-2.63), p value 0.87] (Table 6).

A sub-group analysis was done for POSEIDON 3 and 4 groups for the important reproductive outcomes i.e., clinical pregnancy rates, live birth rates, and miscarriage rates between GnRH antagonist and short protocol (Supplementary Table 1). There was no significant difference in these outcomes between the two protocols in both POSEIDON 3 and 4 groups.

Table 3 Reproductive outcome characteristics per woman recruited

	Antagonist ($n = 138$)	Short ($n = 157$)	P value
Positive pregnancy rate§	26/138 (18.8%)	27/157 (17.1%)	0.71
Clinical pregnancy rate§	23/138 (16.7%)	20/157 (12.7%)	0.34
Live birth rate§	16/138 (11.6%)	14/157 (8.9%)	0.45
Cycle cancellation rate¶	42/138 (30.4%)	57/157 (36.3%)	0.29

§All rates expressed per woman recruited

¶Cycle cancellation rate expressed per cycle initiated

Table 4 Reproductive outcome characteristics per embryo transfer

	Antagonist ($n = 96$)	Short ($n = 100$)	P value
Pregnancy rate†	26/96 (27.1%)	27/100 (27.0%)	0.990
Clinical pregnancy rate†	23/96 (24.0%)	20/100 (20.0%)	0.503
Live birth rate†	16/96 (16.7%)	14/100 (14.0%)	0.604
Miscarriage rate‡	7/23 (30.4%)	6/20 (30.0%)	0.975

†All rates expressed per embryo transfer

‡Miscarriage rate expressed per clinical pregnancy

Table 5 Logistic regression based on occurrence of clinical pregnancy

	Clinical pregnancy Yes ($n = 43$)	Clinical pregnancy No ($n = 153$)	Odds ratio (95% confidence interval)	P value	Adjusted odds ratio* (95% confidence interval)	P value*
Short protocol	20 (20.0%)	80 (80.0%)	Reference			
Antagonist protocol	23 (24.0%)	73 (76.0%)	1.26 (0.64-2.48)	0.50	0.92 (0.43-1.93)	0.82

*Adjusted for confounding factors—age, BMI, number of mature oocytes obtained, indication, type of infertility

Table 6 Logistic regression based on occurrence of live birth

	Live birth ($n = 30$)	No live birth ($n = 166$)	Odds ratio (95% confidence interval)	p value	Adjusted odds ratio* (95% confidence interval)	p value*
Short protocol	14 (46.7)	86 (51.8)	Ref		Ref	
Antagonist protocol	16 (53.3)	80 (48.2)	1.23 (0.56-2.68)	0.61	1.08 (0.44-2.63)	0.87

*Adjusted for confounding factors—age, BMI, number of mature oocytes obtained, indication, type of infertility

Discussion

The current study findings suggest that among the women categorized under POSEIDON 3 and 4 who underwent ART, the LBR and CPR did not differ significantly following the use of the GnRH antagonist protocol versus the GnRH agonist short protocol. While the yield of mature oocytes was significantly higher following the GnRH antagonist protocol, the cycle cancellation rates did not differ significantly between the two groups.

The ideal protocol for poor responders should be the one that results in the yield of a maximum number of mature oocytes with minimum cycle cancellation and subsequently increased live birth rate.

The optimal response for ART in women under POSEIDON groups 3 and 4, who are at a higher risk of poor response, is unclear. To our knowledge, there are no studies evaluating GnRH antagonist protocol versus GnRH agonist short protocol in POSEIDON groups 3 and 4. However, few studies have evaluated the two protocols for women who are at risk of poor response.

A retrospective cohort study by Berin et al. compared the effectiveness of GnRH antagonist and the GnRH short protocol in poor responders ($n = 130$ cycles) defined by either < 5 oocytes retrieved in a prior cycle or FSH > 10 mIU/ml on day 3 along with the requirement of 375 IU of gonadotropin per day from the beginning of COH. The investigators reported no significant difference in CPR (40% vs. 45 %) and LBR (27.7% vs. 31.7%) between the two groups [22]. Akman et al. performed a randomized controlled trial (RCT) in 48 poor responders as defined by baseline FSH > 15 mIU/ml or serum estradiol level on day of trigger < 500 pg/ml or < 4 mature oocytes retrieved. They reported no significant differences in CPR (26.31% vs. 22.2%), and ongoing pregnancy rates (21.05% vs. 16.6%) between GnRH agonist short protocol and GnRH antagonist protocol [17]. In an RCT by Devesa et al. ($n = 172$), no significant difference in CPR per cycle (15% vs. 14.1%) and cycle cancellation rate (12.5% vs. 16.3%) was observed between the GnRH agonist short protocol and GnRH antagonist protocol in poor responders defined by either poor response in the previous cycle or diminished ovarian reserve (abnormal clomiphene citrate challenge test or AFC ≤ 7) [19]. Similarly, Merviel et al. included poor responder women as defined by Bologna criteria in an RCT, and reported no significant differences in the CPR (17.9% vs. 15.9%) and implantation rate (8.9% vs. 8.4%, between the GnRH agonist short protocol and GnRH antagonist protocol) [23]. The results of these studies are broadly in agreement with the current study finding even though there were some differences in the study population due to heterogeneity in the definition of poor responders.

Another RCT by Lainas et al. reported a significantly higher ongoing pregnancy rate (12.2% vs. 4.4%, p value = 0.048) following antagonist protocol ($n = 180$) compared to the GnRH agonist short protocol ($n = 90$) in poor responders who had ≤ 5 oocytes retrieved in a previous cycle using ≥ 300 IU gonadotropin dose per day [18].

Contrary to our study, the RCT by Schimberni et al. reported a significantly higher clinical pregnancy rate in poor responder women receiving GnRH agonist short protocol with respect to those receiving GnRH antagonist protocol (29.3% vs. 14.1%, p value = 0.029). Their inclusion criteria for poor responders were age >40 years, elevated baseline serum FSH level, or history of poor ovarian response in the previous cycle [16]. The results of these studies disagree with the current results due to differences in eligibility criteria.

Xiao et al. in a systematic review of 12 RCTs comparing the antagonist protocol with long and short agonist protocols in poor responders reported similar findings in terms of clinical pregnancy rates and cycle cancellation rates with no significant difference but the oocyte numbers retrieved were significantly lower in antagonist protocol compared with short protocol, contrary to the present study result [24]. The limitation of the meta-analysis was that the criteria for defining poor responders in the included trials were not consistent and some of the studies were at risk of selection bias, attrition bias, and measurement bias.

The current study is one of the first to compare the effectiveness of the GnRH antagonist protocol versus the GnRH

agonist short protocol in the POSEIDON 3 and 4 groups. We also reported a live birth rate which is an important patient-centric outcome. We adjusted for important confounders such as age, BMI, and oocyte yield. However, the retrospective design and modest sample size are important limitations of the current study. The study remains underpowered to detect small differences in the effect size between the two protocols. We did not report cumulative LBR which is another limitation of the current study.

Conclusion

The present study suggests that the LBR is not significantly different following the GnRH antagonist protocol compared to the GnRH agonist short protocol for COH in women belonging to POSEIDON groups 3 and 4 who are at risk of poor response. The study findings suggest that even though the use of GnRH antagonist protocol results in higher mature oocyte yield when compared with GnRH agonist short protocol, it does not translate into an increase in live birth in the study population. However, there is a need for RCT to investigate the current study findings in the POSEIDON 3 and 4 groups. It is also important to include cumulative LBR as the main outcome for future studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s43032-023-01196-x.

Acknowledgements We thank the participants of the study.

Code Availability Not applicable.

Data Availability The data supporting the findings of the study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval Ethics approval was obtained from the institutional review board, IRB no 14080, dated 30.06.2021.

Consent to Participate Written consent for the use of anonymized data was obtained from the participants.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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