Does serum follicle-stimulating hormone during controlled ovarian hyperstimulation predict to ovarian response and reproduction potential in IVF/ICSI clinical practice?

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Research

Keywords: serum follicle stimulating hormone level, ovarian response, controlled ovarian hyperstimulation, IVF, ICSI

Posted Date: February 13th, 2020

DOI: https://doi.org/10.21203/rs.2.23440/v1

Abstract

Background: Although serum basal follicle stimulating hormone (FSH) is widely used to evaluate the ovarian response, the necessity of levels of serum FSH during the controlled ovarian hyperstimulation (COH) is controversy. When the ovarian response to COH is suboptimal due to the insufficient dose of FSH, which is often adjusted in subsequent treatment accordingly, we could detect serum FSH levels and considering that exogenous FSH is inadequate to optimal FSH threshold. We, therefore, aim to evaluate the association between the ovarian response and the difference value of serum FSH concentration in the first five days of ovarian stimulation.

Methods: In this retrospective single-center study, patients were enrolled for first IVF/ICSI during the period from August 2015 to December 2017. The COH only included gonadotrophin-releasing hormone agonist (GnRH-a) protocols in which endogenous serum FSH values were suppressed, and stimulated with 150IU fixed-dose recombinant FSH (rFSH) during the first five days. Patients met all inclusion criteria were selected: age ≤ 40 years, body mass index (BMI) ≤ 32 kg/m^2, regular menstruation cycle of 21-35 days and non-ovarian factor infertility. Groups were divided by the amount of oocytes collection as follows: (A) poor responders (n=27), (B) normal responders (n=638), (C) hyper responders (n=205). A multivariable logistic regression model was performed to evaluate the relationship between the ovarian response and difference value of serum FSH levels during the first five days of ovarian stimulation.

Result(s): The difference value of serum FSH level (ΔFSH) between the sixth day and the first day during ovarian stimulation was measured as the primary outcome. Mean serum ΔFSH levels between groups B and C were 7.45 and 6.87, which had significant differences (*p*=0.0259). ΔFSH was stratified in quartiles as below: (a) ΔFSH≤5.16, (b) ΔFSH 5.16-7.11, (c) 7.11-9.09, (d) ΔFSH 9.09. After adjusted by potential confounding factors, there was no relationship exists between ΔFSH levels and ovarian response.

Conclusion(s): There is no relevance between the ovarian response and ΔFSH in the 150 IU fixed dose rFSH treatment protocol during COH. Serum FSH might not be used as an effective predictor for ovarian response and reproduction potential in IVF/ICSI clinical practice.

Introduction

Both during natural conception and assisted reproductive technology (ART), ovarian reserve is one of the important factors determining female fertility. In in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment, obtaining a certain number of mature oocytes by controlled ovarian hyperstimulation (COH) is the key to achieving a satisfactory pregnancy outcome. The ovarian response can be predicted by assessing ovarian reserve prior to ovulation induction[1].

Ovarian response refers to the reaction of the follicle to the exogenous gonadotropin (Gn) during the COH, which is mainly determined by the quality and quantity of ovarian reserve[2]. Depended on the number of oocytes retrieved, the ovarian response is generally defined as poor, normal or hyper[3, 4]. Only the normal response is considered appropriate. In contrast, the poor one is closely associated with lower pregnancy

rates and the hyper one is related to an incidence rate of developing the ovarian hyperstimulation syndrome (OHSS), which both of two are leading to higher rates of cycle cancellation[5, 6]. To forecast different patient's ovarian response to medication for COH and to individualize the initial dose of exogenous Gn or the necessity for exogenous luteinizing hormone (LH), various physical examination, endocrine, transvaginal ultrasonography, and genetic characteristics have been explored[2]. Those are including age, BMI, serum basal follicle stimulating hormone (bFSH), bFSH/basal LH, anti-Müllerian hormone, Inhibin B, and antral follicle count (AFC), which is combined to help clinicians to evaluate and select the initial FSH dose for ovarian stimulation[7].

During the COH for IVF or ICSI, administration of Gn, gonadotrophin-releasing hormone (GnRH) analogs or other adjuvants will be used. Exogenous FSH as the major component requires daily injections are administered to maintain steady-state serum FSH concentration and prolongs the period above the threshold level, which is necessary to attain multiple follicular growths[8, 9]. Extrinsic FSH dose is always adapt to a subsequent treatment if the ovarian response to stimulation is suboptimal after four or five days, thereby we could detect serum FSH levels and assuming that were inadequate for optimal stimulation[10].

The randomized controlled trial by Oudshoorn et al. assessed the association between the serum FSH values and a number of retrieved oocytes when the second day of menstruation and triggering, during the GnRH antagonist cotreatment with a fixed dose of 150 IU Gn protocol for COH, revealed that is no consistent correlation between two on day of trigger[10]. The newest meta-analysis has compared individualizing FSH dose based on ovarian markers, including lots of dose-response studies, revealed the same as a policy of giving all women 150IU[11]. Further, the FSH dose probably is reduced in hyper responders based on ovarian reserve tests[11]. Therefore, we assume that serum FSH levels be likely to predict ovarian response during COH.

To our knowledge, no published studies have shown that the difference in serum FSH concentration during ovarian stimulation might forecast the ovarian response. The objective of this research was to examine the role of serum FSH difference levels (ΔFSH) between the sixth day (Day 6) and the first day (Day1) during COH in predicting the ovarian response of patients.

Materials And Methods

Patients population

This was a retrospective cohort study in a single reproduction center. A total of 23667 patients had experienced a whole series of maternity evaluation and were performed on firstly IVF or ICSI cycle from August 2015 to December 2017. The inclusion criteria of this study were: age of women less than or equal to 40 years; body mass index (BMI) less than or equal to 32 kg/m^2; regular menstrual cycle (average length of the cycle between 21 and 35 days). Exclusion criteria were: diagnosed as ovarian

factor infertility; starting dose of recombinant FSH (rFSH) unequal to of 150 IU/L; absence of the serum sample on the sixth day or the first day during COH; pituitary down-regulation with GnRH antagonists.

Stimulation protocol

Gonadotrophin-releasing hormone agonist (GnRH-a) was used in COH. The triptorelin depot (Diphereline, 3.75 mg; IPSEN, France) is administered to down-regulation pituitary with a dose of 3.75 mg. After 30–42 days, the standard of down-regulation was reached (LH < 1mIU/mL, E2 < 30 pg/mL, FSH < 5mIU/mL, P4 < 1 ng/mL; ovarian cysts between 3–5 mm), and Gn was used for ovarian stimulation. No further GnRH analog was given during the ovarian stimulation.

rFSH (Gonal F or Puregon; Merck Serono, Netherlands) was used for ovarian stimulation with a daily fixed dose of 150 IU subcutaneously (s.c.) during the first five days. During the stimulation, the ovarian response was evaluated by the growth of follicular via transvaginal ultrasound measurements and serum hormones including FSH E2 LH P concentrations each 1 to 3 days.

When at least one follicle of ≥ 20 mm and three follicles of ≥ 17 mm or two third follicles of ≥ 16 mm in mean diameter were monitored, 250 μg of r-hCG (Ovidrel, 250 μg; Merck Serono, Italy) and 2000 IU of human chorionic gonadotropin (hCG, 2000 IU; Lizhu Pharma, China) were injected. The oocyte was collected 36–37 h after HCG administration with a transvaginal ultrasound approach. Insemination was carried out 4 to 5 hours after oocytes retrieval, pronuclei were recognized 16 to 18 hours after insemination and ET was carried out at 68 to 70 hours later. Progesterone supplementation was sustained everyday with vaginal gel preparation (Crinone 8%; Merck Serono, Netherlands) from the day of oocyte collection.

Statistical Analysis

Statistical analyses were done on all completed IVF/ICSI cycles. Data management and analysis were accomplished using the SPSS software (version 21.0) for Windows. When dealing with continuous variables, t-test (independent samples) was carried out if subject to a normal distribution, otherwise, Wilcoxon test was used. The dichotomous variables were subjected to Fisher's exact test or Chi-square test, as appropriate. The association between ΔFSH and ovarian reserve were evaluated by the multivariable logistic regression model. In our analysis, $P < 0.05$ was considered statistically significant.

Results

Baseline parameters

From the 23667 patients undergoing the first IVF/ICSI assisted reproduction in our center, 870 women were included (Fig. 1). Of these patients, diagnosed as poor responders were 27, as hyper responders were 205 and as normal responders were 638. Due to the insufficient sample size of the poor response, we just analyze normal and hyper response patients here. Baseline characteristics of patients are listed in Table 1. Age was significant diversity between normal and hyper responders which were 31.37 ±

4.21 years versus 30.56 ± 4.58 years in female (P = 0.0135); in the meanwhile, there were 32.59 ± 5.4 years versus 31.76 ± 5.69 years in male (P = 0.0277). No statistically significant distinction was indicated in the infertile period (4.38 ± 3.35 versus 4.11 ± 3.72, P = 0.1185), BMI (22.88 ± 3.19 versus 23.36 ± 3.42, P = 0.0847), type of infertility (P = 0.4146, number of primary infertility were 309 versus 106; number of secondary infertility were 329 versus 99) and treatment (P = 0.25342, number of ICSI were 117 versus 45; number of IVF were 521 versus 160) in comparing the two group. Obviously, the number of AFC in the hyper group was larger than the normal group (10.69 ± 4.38 versus 12.33 ± 4.58, P < 0.0001). Except for the bFSH level, the basic serum hormone values were also similar in the two groups. Patients with normal response showed a statistically conspicuously higher bFSH level than hyper responders (6.96 ± 1.99 versus 6.28 ± 1.57 mIU/mL, P < 0.0001). As expected, age, AFC and bFSH have a statistically significant difference between two responders, which confirmed all three are important index predicting the ovarian response[12].

Serum hormone levels of patients during ovarian stimulation

On the first day of ovarian stimulation, there was no statistically significant difference on serum E2 (7.86 ± 7.07 versus 7.43 ± 5.41 pg/mL, P = 0.6201), P_4 (0.46 ± 0.23 versus 0.48 ± 0.24 ng/mL, P = 0.3636) and LH (0.57 ± 0.37 versus 0.56 ± 0.36 mIU/mL, P = 0.7623) level between two groups (Table 2), and that all of them much lower than basal level, which suggested an almost suppression on pituitary and ovary. After five days of stimulation with the same dose of Gn, serum LH and P4 level still sustained lower levels and were similar between two groups (0.51 ± 0.57 versus 0.44 ± 0.43 mIU/mL, P = 0.2243 & 0.12 ± 0.15 versus 0.14 ± 0.16 ng/mL, P = 0.3255). Nevertheless, in terms of the serum value of E2 increased up more than ten times, particularly in hyper responders (110.20 ± 133.30 versus 135.76 ± 137.12 pg/mL, P < 0.0001). Suppression of LH until 8 weeks after injection GnRH-a and secretion of serum E2 began to be restored in the duration of 7–8 weeks[13]. No matter on Day 1 or Day 6 during ovarian stimulation, serum FSH value in the normal group were higher than the hyper one (3.27 ± 1.36 versus 3.01 ± 1.21 mIU/mL, P = 0.0395 & 10.72 ± 2.86 versus 9.88 ± 2.34 mIU/mL, P = 0.0001, respectively), and what we focus on the difference value between two (ΔFSH) also have a statistical difference (7.45 ± 3.26 versus 6.87 ± 2.61, P = 0.0259).

The characteristics of ovarian stimulation and outcome

The characteristics of ovarian stimulation and outcome of embryos transferred are described in Table 3. Although the length of stimulation was comparable between two groups (13.42 ± 1.90 versus 13.61 ± 1.50 days, P = 0.0721), the use of the total amount of Gn (2814.88 ± 683.97 versus 2562.07 ± 590.78 IU, P < 0.0001) and the number of ET (556 (87.28%) versus 148 (72.2%), P < 0.0001) in normal responders was more than another. Clearly, high responders using less Gn were able to achieve the desired number of follicles and were more likely to develop OHSS resulting in a lower transplantation rate. More amount of oocytes retrieved, qualified oocytes, MII oocytes, 2PN embryos, cleavage embryos were obtained in the hyper responders, and the freeze all embryo rate was larger (40 (6.28%) versus 53 (25.85%), P < 0.0001) at the same time. The above results showed that the hyper responders not only had more oocytes but also had a better quality of oocytes and embryos.

Correlation

To evaluate the association between ΔFSH and ovarian response, multivariate logistic regression was utilized and the results were presented in Table 4. ΔFSH was divided according to the interquartile range because there was no standard to classify it in previous studies. The variables that were different between the normal and hyper groups (female age, basal FSH levels, AFC) were selected as potential confounding factors. Another factor (infertility year) was also selected based on clinical experiences, although it was comparable between both groups. Greater ΔFSH was associated with a significantly lower risk of hyper ovarian response when adjusting for female age (OR = 0.57; 95% CI: 0.36, 0.91; p = 0.018) in the highest difference compared with the lowest. Adjusted by the previously noted potential confounding factors, this association was attenuated (OR = 0.79; 95% CI: 0.47, 1.32; p = 0.3228). It indicated that ΔFSH was not a significant predictor for the ovarian response.

Discussion

Ovarian reserve can be evaluated by many indicators, of which serum FSH on the second, third or fourth day of a menstrual cycle is widely used[14]. At the beginning of ovarian reserve reduction, bFSH have low sensitivity and with estradiol is a portion of an endocrine axis feedback system, which both serum values are dependent on each other. Moreover, varies in these two hormones arise comparatively belatedly in the reproductive aging progress, while the ovarian reserve has gone as far as the crisis level and possibilities of pregnancy have considerably declined[15]. We will discuss if the serum FSH levels during ovarian stimulation could give us more information.

Pituitary suppression and ovarian function appear to be carried on until 8 weeks after the injection of GnRH-a[16]. After pituitary downregulation, there is the bare contribution of endogenous FSH to serum values until day 6 of stimulation, which makes it possible to reassess and predict ovarian response using serum FSH. Factors other than the daily dose of FSH may impact of the serum level of FSH. The majority of clinical evidence suggests comparable clinical efficacy and safety of uFSH and rFSH products[17]. rFSH be used in our study due to having a shorter elimination half-life and more rapid metabolic clearance[18]. The capacity of FSH to advance folliculogenesis depend on the plasma concentration of FSH developing after administration. With successive daily administration of rFSH, steady-state levels are deemed to be attained after 3–5 days of treatment[19]. During stimulation, the standard dose of 150 IU rFSH was used in the first five days[11]. The serum FSH level be detected on Day 6 is appropriate, the elevated part compared serum FSH from the Day 1 can be considered as an ovarian response to stimulation.

In the present research, we demonstrate that a considerably higher serum FSH levels on Day 6 in the same response. It is clear that the difference to serum FSH level on first six days (no matter the sixth day, the first day or the difference between both) during ovarian stimulation is different between the normal and hyper ovarian responders, despite the lack of significant correlation between ΔFSH difference and ovarian response. A similar study, what missing in our study, assessed the correlate serum FSH levels in

the early phase of ovarian stimulation with the COH outcome, revealed that Day 7 FSH level during stimulation could guide FSH dosing in poor responders[20]. As poor ovarian response includes opposition to the effect of FSH, one method to ameliorate response is to augment the daily dose of FSH that is administrated. Follicles are allowed by this way possibly with demanding a higher FSH threshold and fewer FSH receptors, to react to the stimulation[20]. On the other hand, hyper response to decreasing the dose of FSH[11]. To sum up, serum FSH concentration during ovarian stimulation could partly respond ovarian reaction of the follicle to the exogenous Gn during the COH.

Attaining approving outcomes in assisted reproductive technology demand heedful appraisal of the patient and examination of her ovarian reserve. A suitable ovarian reserve test ought to be capable to forecast pregnancy's odds and the birth of live babies in an infertile population referring to fertility treatment and decide the optimal dose of the hormone that is chosen for ovarian stimulation.

However, the relationship between the stimulation response and probability of pregnancy is poorly understood, so the use of surrogate outcomes such as the number of eggs retrieved does not necessarily reveal the effects on pregnancy and live birth. Therefore, the pregnancy rate and live birth rate were not included in our study. In addition, limitations of this study also include small sample size, single-center study, retrospective study and so on. Additional prospective trials or Meta-analysis are required to confirm these observations.

Conclusion

In our study, we demonstrated for the first time the serum FSH level on first six days (no matter the sixth day, the first day or the difference between both) during ovarian stimulation are different between the normal and hyper ovarian responders, but it could not be used as a potential predictor of ovarian response and reproduction potential in IVF/ICSI clinical practice. However, poor responders were not be analyzed in our study, further large-scale and prospective investigation are required to validate the use of serum FSH in the prediction and guidance of COH.

Abbreviations

AFC: antral follicle count; bFSH: basal follicle stimulating hormone; BMI: body mass index; COH: controlled ovarian hyperstimulation; E2: estradiol; ET: embryos transferred; FSH: follicle stimulating hormone; Gn: gonadotropin; GnRH: Gonadotrophin-releasing hormone; GnRH-a: gonadotrophin-releasing hormone agonist; ICSI: intracytoplasmic sperm injection; IVF: in-vitro fertilization; LH: luteinizing hormone; MII: metaphase II oocyte (mature); OR: Odds ratio; OHSS: Ovarian hyperstimulation syndrome; P4: progesterone; PN: pronucleus; PRL: pituitary prolactin; rFSH: recombinant follicle stimulating hormone; SD: standard deviation.

Declarations

Acknowledgments

This study was supported by the Reproductive Medicine Center at the First Affiliated Hospital of Zhengzhou University. We thank the people for their participation in this project.

Authors' contribution

YM collected the samples and wrote the initial draft. BS edited the initial draft and supported in the statistical sense. LH and FW critically reviewed the paper for important intellectual content. YS participated in the design of the study and revised the final version of the manuscript. All authors read and approved the final manuscript.

Funding

This work was funded by Chinese Medical Association Clinical Medical Research Special Fund Project (FDN-17020190688), Medical Science and Technology Research Project Joint Co-construction Project of Henan Province (FDN-2018020116), and Henan Provincial Higher Education Key Research Project Plan (FDN-19A320056).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Study protocols were approved by the Zhengzhou University Research Ethics Board and all participants provided informed consent prior to enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Tables

Table 1. Basic characteristics of 843 patients from August 2015 to December 2017			
Variable	Normal(N=638)	Hyper(N=205)	P value
Female Age(y)	31.37±4.21	30.56±4.58	0.0135
Male Age(y)	32.59±5.49	31.76±5.69	0.0277
Duration of infertility(y)	4.38±3.35	4.11±3.72	0.1185
Body mass index(kg/m^2)	22.88±3.19	23.36±3.42	0.0847
Antral follicular count	10.69±4.38	12.33±4.58	<0.0001
Baseline hormone levels			
FSH (mIU/mL)	6.96±1.99	6.28±1.57	<0.0001
E2 (pg/mL)	42.52±31.88	41.29±41.17	0.1382
P4 (ng/mL)	0.66±0.62	0.68±0.49	0.2702
LH (mIU/mL)	4.97±4.06	4.61±2.04	0.4366
PRL (ng/mL)	19.40±28.56	19.88±22.66	0.3847
Type of infertility			0.4146
Primary infertility	309 (48.43)	106 (51.71)	
Secondary infertility	329 (51.57)	99 (48.29)	
Treatment			0.25342
ICSI	117 (18.34)	45 (21.95)	
IVF	521 (81.66)	160 (78.05)	

Note: Data are mean + standard deviation or N (% of response group). FSH = follicle-stimulating hormone; E2 = estradiol; P4 = progesterone; LH = luteinizing hormone; PRL = pituitary prolactin.

Table 2. Serum hormone levels of patients during ovarian stimulation			
Variable	Normal(N=638)	Hyper(N=205)	P value
Hormone levels on Day 1			
FSH (mIU/mL)	3.27±1.36	3.01±1.21	0.0395
E2 (pg/mL)	7.86±7.07	7.43±5.41	0.6201
P4 (ng/mL)	0.46±0.23	0.48±0.24	0.3636
LH (mIU/mL)	0.57±0.37	0.56±0.36	0.7623
Hormone levels on Day 6			
FSH (mIU/mL)	10.72±2.86	9.88±2.34	0.0001
E2 (pg/mL)	110.20±133.30	135.76±137.12	<0.0001
P4 (ng/mL)	0.12±0.15	0.14±0.16	0.3255
LH (mIU/mL)	0.51±0.57	0.44±0.43	0.2243
ΔFSH	7.45±3.26	6.87±2.61	0.0259

Note: Numbers are mean + standard deviation. FSH = follicle-stimulating hormone; E2 = estradiol; P4 = progesterone; LH = luteinizing hormone; PRL = pituitary prolactin. ΔFSH: The difference value of serum FSH level between the sixth day (Day 6) and the first day (Day 1) during ovarian stimulation.

Table 3. The stimulation characteristics and outcome of patients			
Variable	Normal(N=638)	Hyper(N=205)	P value
Total amount of Gn (IU)	2814.88±683.97	2562.07±590.78	<0.0001
Length of stimulation(d)	13.42±1.90	13.61±1.50	0.0721
Total oocytes retrieved	10.00±3.04	20.03±4.22	<0.0001
No. of qualified oocytes	8.07±2.92	16.32±4.25	<0.0001
No. of MII oocytes	7.85±3.16	15.99±4.69	<0.0001
No. of 2PN embryos	5.97±2.86	12.24±4.44	<0.0001
No. of cleavage embryos	7.18±3.21	14.79±4.73	<0.0001
The outcome of ET			<0.0001
Freeze all embryos	40 (6.28)	53 (25.85)	
Non-cleaved embryo	3 (0.47)	0	
Non-PN	4 (0.63)	0	
Non-ET	1 (0.16)	3 (1.46)	
No high-quality embryos	33 (5.18)	1 (0.49)	
No. of ET	556 (87.28)	148 (72.2)	
Missing	1		

Note: Data are mean + standard deviation or N (% of response group). Gn = gonadotropin; MII = metaphase II oocyte (mature); PN = pronucleus; ET = embryos transferred.

Table 4. The multivariate logistic regression for the relationship between ΔFSH and ovarian response					
Groups	Normal/Hyper	OR(95%CI)*	*P*	OR(95%CI)**	*P*
ΔFSH <=5.16	153/58	1.00(reference)	.	1.00(reference)	.
5.16<ΔFSH <=7.11	158/53	0.86(0.56-1.34)	0.6946	0.86(0.54-1.38)	0.6077
7.11<ΔFSH <=9.09	156/55	0.91(0.59-1.40)	0.4662	1.10(0.68-1.78)	0.2624
ΔFSH >9.09	171/39	0.57(0.36-0.91)	0.018	0.79(0.47-1.32)	0.3228

Note: OR = odds ratio; CI = confidence interval; ΔFSH: The difference value of serum FSH level between the sixth day (Day 6) and the first day (Day 1) during ovarian stimulation.

*Adjusted for female age.

** Adjusted for female age, infertility year, baseline FSH, and antral follicular count.

Figures

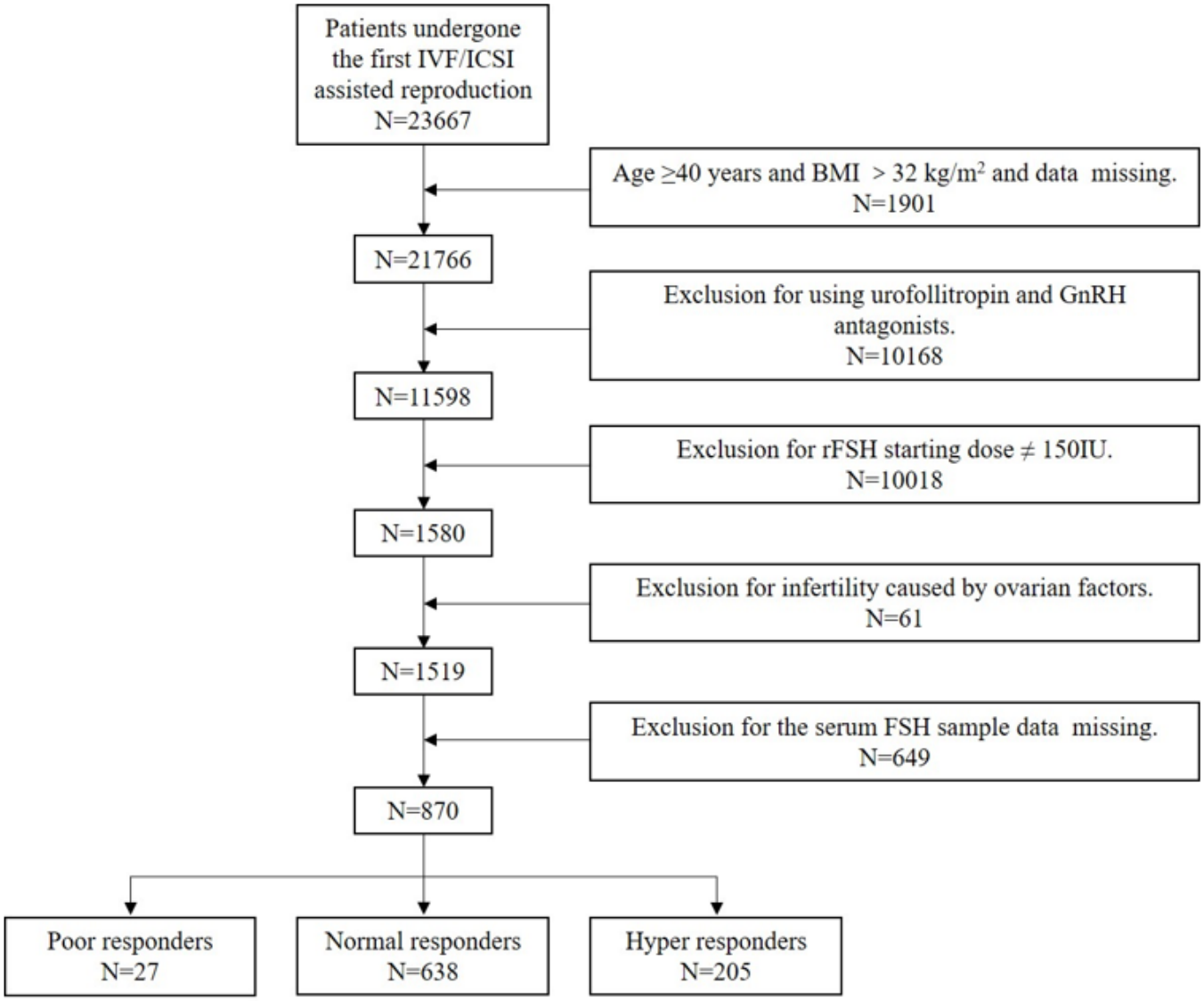

Figure 1. Flowchart describing inclusion and exclusion criteria.

Figure 2

Flowchart describing inclusion and exclusion criteria.