ORIGINAL ARTICLE

Evaluation of FSH Receptor Gene Polymorphisms among infertile women and its correlation with Ovarian Reserve Markers and fertility outcomes: A Prospective Observational Study from Northern India

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ABSTRACT

Background: Genetic polymorphisms in the Follicle-Stimulating Hormone *Receptor* (FSHR) gene may influence ovarian response in women undergoing controlled ovarian stimulation, but their relevance in infertile women undergoing ovulation induction remains uncertain. **Aims & Objectives:** To assess the association of FSHR polymorphisms Thr307Ala (rs6165) and Asn680Ser (rs6166) with ovarian reserve markers and fertility outcomes in infertile women undergoing ovulation induction. **Methodology:** This prospective observational study, conducted from August 2021 to May 2025, included 82 infertile women and 25 fertile controls. All participants underwent Day 2–5 (AMH, FSH, LH, E2), Antral Follicle Count (AFC), and FSHR genotyping using PCR-RFLP. Letrozole was used for ovulation induction for up to four cycles. **Results:** Genotype and allele distributions for both polymorphisms did not differ significantly between infertile and fertile women. All genotype frequencies conformed to Hardy–Weinberg equilibrium except *Asn680Ser* (rs6166) in controls. Ovarian reserve markers were comparable across genotypes, except for higher AMH in fertile controls with the AA genotype of *Thr307Ala* ($p = 0.017$) and significantly higher AFC among infertile women ($p = 0.0001$). Letrozole-induced ovulation and pregnancy rates (12%). **Conclusion:** FSHR polymorphisms Thr307Ala and Asn680Ser do not significantly affect ovarian reserve parameters or clinical outcomes in infertile women undergoing ovulation induction, indicating limited predictive value in this setting.

KEYWORDS

FSHR Gene Polymorphism; Thr307Ala; Asn680Ser; Ovarian Reserve; Infertility; Letrozole; Ovulation Induction.

INTRODUCTION

Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, affects 10–15% of reproductive-age couples globally, with a rising burden in low- and middle-income countries such as India (1,2). Ovarian reserve is commonly assessed using serum Anti-Müllerian Hormone (AMH), day 2–5 Follicle-Stimulating Hormone (FSH), and Antral Follicle Count (AFC). However, these markers do not fully explain the wide inter-individual variation in ovarian response

observed during Controlled Ovarian Hyperstimulation (COH), even among women with similar baseline profiles (3,4).

FSH, a glycoprotein hormone secreted by the anterior pituitary, regulates folliculogenesis, estrogen production, and granulosa cell proliferation. Its actions are mediated through the FSH receptor (FSHR), a G protein–coupled receptor expressed on granulosa cells (5). Among the identified genetic variants, two exon 10 single nucleotide polymorphisms—Thr307Ala (rs6165) and Asn680Ser (rs6166)—have gained attention for their potential impact on receptor sensitivity and signaling (6). The AA genotype is associated with better ovarian response, AG with intermediate response, and GG with reduced sensitivity and poorer outcomes.The functional significance of these polymorphisms has been demonstrated in studies showing altered FSH thresholds, gonadotropin requirements, and ovarian response patterns (7–14). Evidence from India remains limited and inconsistent (15–17).

This study evaluates the association of these FSHR polymorphisms with ovarian reserve markers and fertility outcomes in infertile women from Northern India

Figure 1: Interpretation of FSHR polymorphisms Thr307Ala (rs6165) and Asn680Ser (rs6166)

Codon	Common Genotypes	Genotype Band Patterns
307	Thr/Thr, Thr/Ala, Ala/Ala	AA (Thr/Thr),AG (Thr/Ala),GG(Ala,Ala)
680	Asn/Asn, Asn/Ser, Ser/Ser	AA(ASN/ASN),AG(Asn /Ser),GG(Ser/Ser)

Primary Objective: To determine FSHR gene polymorphisms (680 & 307) in infertile patients & parameters of ovarian reserve markers.

Secondary Objectives: To determine association of FSHR gene polymorphism with ovarian reserve markers-Age, FSH, AMH, AFC and to determine association of FSHR gene polymorphisms with Fertility outcome.

MATERIAL & METHODS

Study design & duration: This was a prospective observational study conducted from August 2021 – May 2025.

Study Setting & population: The case group included 82 infertile women consulting the Gynaecology OPD for infertility services with patent tubes on Hysterosalpingography (HSG) or Laparoscopy. The control group consisted of 25 fertile controls who were attending the OPD for other gynaecological ailments and were explained about the study. They were requested to provide blood to study FSH receptor polymorphisms. The study was started after Institute Ethical Committee approval (AIIMS/IEC/21/547) and recruitment was done after informed consent.

Sample size calculation: Sample Size calculated consisted of 82 infertile women (% women with mutation & poor responders as 33%,

estimated total sample size is 74 at significance level of 95% and power of80%. Assuming a loss to follow-up rate of 5%, final sample size required will be ~ 82) and control group consisted of 25 fertile controls

Inclusion criteria: Infertile cases were women aged 22 and 38 years with unexplained infertility or Polycystic ovarian syndrome (PCOS); BMI 19–30 kg/m² with normal tubal patency and normal semen parameters.

Exclusion criteria: Endometriosis**,** previous ovarian surgery**,** single ovary**,** endocrine disorders (uncontrolled thyroid or prolactin disorders)**,** FSH >12 IU/L and AMH < 1 ng/ml.

Strategy for data collection: After ethical approval and informed consent detailed history of participants including age, demographics, duration and type of infertility was documented. Clinical examination findings included weight, height and BMI. Baseline hormone assays such as FSH, LH, E2, AMH were taken by chemiluminescence based immunoassay. Transvaginal scan for Antral Follicle Count (AFC) was performed between day 2 to 5 of menstrual cycle. Five ml of blood sample were taken from the study participants and stored in sterile EDTA vacutainers and stored at −80°C for later use. Peripheral blood mononuclear cell (PBMC) isolation was done followed by DNA isolation (Figure 2) .

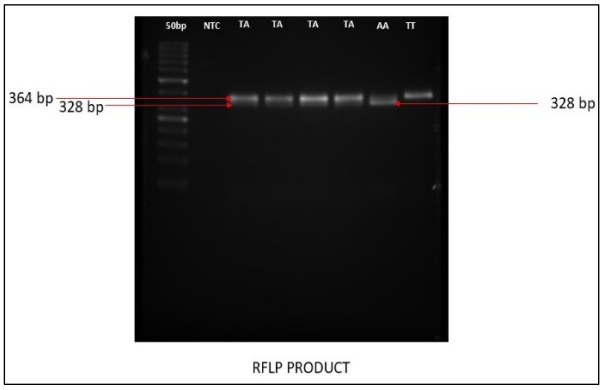
In our study 5 subjects (2 cases and 3 controls) were excluded from molecular analysis as DNA quantification was ≤ 5 ng/µl (Figure 3). A laboratory-based molecular analysis was conducted to identify the Thr307Ala (rs6165) polymorphism in the FSHR gene using the Nested polymerase chain reaction-restriction fragment length polymorphism (Nested-PCR-RFLP) method. Genotypes were interpreted based on band patterns: Thr/Thr (TT) yielded a single 364 bp band; Thr/Ala (TA) showed bands at 364 bp and 328 bp; and Ala/Ala (AA) showed bands at 328 bp (Figure 4). Asn680Ser (rs6166) polymorphism in the follicle-stimulating hormone receptor (FSHR) gene was identified using

the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

Figure 2: showing DNA bands after DNA isolation

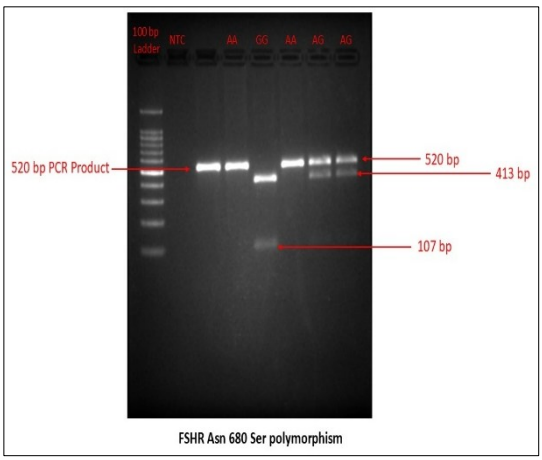
Figure 3: DNA quantification

Figure 4: RFLP DNA bands for 307 mutation



After gel electrophoresis Asn/Asn (homozygous A allele) a single band was visualised at 520 bp, Asn/Ser (heterozygous A/G) had three bands at 520 bp, 413 bp, and 107 bp, and Ser/Ser (homozygous G allele) had two bands at 413 bp and 107 bp, based on the genotype interpretation (Figure 4).

Figure 5: Native PCR gel electrophoresis Band visualisation



Cases enrolled in the study were started on oral letrozole 5 mg for 5 days from day 2-5 of cycle. Follicle monitoring was done from day 9/10 onwards till the dominant follicle reached 17-18 mm in size and endometrial thickness showed trilaminar pattern. Injection Human Chorionic Gonadotropin (HCG) 5000 IU IM was administered for inducing ovulation and patients advised timed coitus and to review after 2 weeks later if missed periods or on day 2 of next menstrual cycle. Clinical pregnancy was defined as viable gestation at 6-7 weeks scan and ongoing pregnancy as viable gestation beyond 12 weeks.

Data analysis: Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0. Presentation of the categorical variables was done in the form of number and percentage (%). Quantitative data with normal distribution was presented as means ± SD & data with non-normal distribution as median with 25th and 75th percentiles (interquartile range). Data normality was checked by using Shapiro-Wilk test. The association of the variables which were quantitative and not normally distributed were analysed using Mann-Whitney Test (for two groups) and Kruskal Wallis test (for more than two groups) and variables which were quantitative and normally distributed in nature were analysed using Independent t test (for two groups) and ANOVA test (for more than two groups). The association of the variables which were qualitative in nature were analysed using Fisher's exact. Hardy-Weinberg equilibrium was assessed separately for cases and

controls using Chi-square goodness-of-fit test. Odds ratio with 95% CI was calculated for genotype and alleles. For statistical significance, p value of less than 0.05 was considered statistically significant.

RESULTS

The mean age, BMI, and hormonal parameters were comparable as shown in Table 1. However, statistically significant difference was observed in AFC, which was higher in cases (17.91 ± 3.94) compared to controls (8.23 ± 1.63) (p value < 0.0001).The frequency of primary and secondary infertility were 44 (53.6%) and 38 (46.3%) respectively among cases with mean duration of infertility being 5.7 years. DNA quantification between cases and controls showed no statistically significant difference with a median of 44.2 (21-79.5) and 48 (32.2-68.7) amongst cases and controls respectively (p=0.646)

Table 1:-Comparison of baseline characteristics between cases and controls.

Baseline characteristics	Cases (N=80)	Controls (N=22)	P value
Age (years)	29.79 ± 4.52	29.32 ± 5.11	0.676†
Body mass index (kg/m²)	25.75 ± 4.35	25.44 ± 1.09	0.558†
AFC (n)	17.91 ± 3.94	8.23 ± 1.63	<.0001†
FSH (mIU/mL)	6.15 (5.55-7)	6.35 (6-7)	0.906‡
AMH (ng/mL)	5.8 (4.8-7.6)	6.75 (5-8)	0.544‡

*† Independent t test, ‡ Mann Whitney test, * Fisher's exact test*

Compared to controls, cases had comparable distribution of Asn680Ser (rs6166) mutation: normal AA type (43.75% in cases vs. 45.45% in controls), heterozygous AG type (45% vs. 54.55%) and homozygous mutant GG type (11.25% vs 0%) (p value = 0.301). Similarly, distribution of Thr307Ala (rs6165) mutation was comparable between cases vs controls: normal AA type (48.75% vs. 63.64%), heterozygous AG type (41.25% vs. 36.36%) and homozygous mutant GG type (10% vs. 0%) (p value = 0.262) (Table 2).

Table 2:-Comparison of mutation type between cases and controls.

Mutation type	Cases (N=80)	Controls (N=22)	P value
680 mutation			
AA	35 (43.75%)	10 (45.45%)	0.301*
AG	36 (45%)	12 (54.55%)	
GG	9 (11.25%)	0 (0%)	
307 mutation			
AA	39 (48.75%)	14 (63.64%)	0.262*
AG	33 (41.25%)	8 (36.36%)	
GG	8 (10%)	0 (0%)	

** Fisher's exact test*

As shown in Table 3, for genotype frequency at Asn680Ser (rs6166), majority had AG genotype 45% vs. 54.55% (OR = 0.857, 95% CI: 0.3283 to 2.2376) among cases and controls showing no statistically significant difference. For genotype frequency at Thr307Ala (rs6165), majority had AA genotype among cases and controls 48.75% vs. 63.64% (OR = 0.160, 95% CI: 0.008686 to 2.9564), showing no significant difference.

For allele frequency at Asn680Ser (rs6166), majority had A allele which was found in 66.25% of cases vs. 72.73% of controls showing no significant difference. For allele frequency at Thr307Ala (rs6165), majority had G allele found in 69.38% vs. 81.82% (OR = 0.503, 95% CI: 0.2181 to 1.1621), also indicating no significant difference.

Table 3:- Comparison of allele and genotype frequency at SNP 680 and SNP 307 between cases and controls.

Allele & genotype frequency at SNP 680 and SNP 307	Cases N = 80	Controls N = 22	Odds ratio (95% CI)
Genotype frequency {680 mutation}			
AA	35 (43.75%)	10 (45.45%)	1
AG	36 (45%)	12 (54.55%)	0.857(0.3283 to 2.2376)
GG	9 (11.25%)	0 (0%)	5.620(0.3013 to 104.8272)
Genotype frequency {307 mutation}			
AA	39 (48.75%)	14 (63.64%)	0.160(0.008686 to 2.9564)
AG	33 (41.25%)	8 (36.36%)	0.232(0.01214 to 4.4289)
GG	8 (10%)	0 (0%)	1
Allele frequency {680 mutation}			
A	106 (66.25%)	32 (72.73%)	1
G	54 (33.75%)	12 (27.27%)	1.358(0.6482 to 2.8472)
Allele frequency {307 mutation}			
A	49 (30.63%)	8 (18.18%)	1
G	111 (69.38%)	36 (81.82%)	0.503(0.2181 to 1.1621)

§Chi-square goodness-of-fit test, P value – for assessing Hardy–Weinberg equilibrium.

No significant association was seen in ovarian reserve characteristics such as age, AFC, FSH and AMH with Asn680Ser (rs6166) and Thr307Ala (rs6165) in both cases and controls (Table 4). Significant association was seen in AMH levels with Thr307Ala (rs6165) in control group: AMH was significantly higher in AA genotype (8 (6.9–8.4) ng/mL) compared to GG genotype (5.2 (4.15–6.95) ng/mL) (p value = 0.017)

Table 4:-Association of ovarian reserve characteristics with Asn680Ser (rs6166) and Thr307Ala (rs6165)

Ovarian reserve characteristics	AA	AG	GG	P value
680 mutation Mean +/- SD				
Age (years)				
Cases N=80	29.97 ± 4.66	29.97 ± 4.23	28.33 ± 5.36	0.598¶
Control N=22	29.5 ± 4.84	29.17 ± 5.54	-	0.883†
AFC (n)				
Cases N=80	18.54 ± 3.85	17.11 ± 3.86	18.67 ± 4.44	0.26¶
Control N=20	8.4 ± 1.58	8.08 ± 1.73	-	0.661†
FSH (mIU/mL)				
Cases N=80	6 (5-6.9)	6.6 (5.95-7)	6 (5.8-6.6)	0.346**
Control N=22	6.4 (6-6.775)	6.25 (4.873-7.33)	-	0.974‡
AMH (ng/mL)				
Cases N=80	6 (4.9-8)	5.15 (4.645-7.025)	6.2 (5.5-8)	0.327**
Control N=22	5.5 (4.25-6.95)	7.1 (5.775-8.25)	-	0.155‡
307 mutation	**AA**	**AG**	**GG**	**P value**
Age (years)				
Cases N=80	30.25 ± 5.78	30.03 ± 4.4	29.49 ± 4.46	0.843¶
Control N=22	29.12 ± 6.27	29.43 ± 4.59	-	0.897†
AFC (n)				
Cases N=80	16.88 ± 2.3	18.24 ± 4.11	17.85 ± 4.09	0.676¶
Control N=22	7.75 ± 1.28	8.5 ± 1.79	-	0.311†
FSH (mIU/mL)				
Cases N=80	6.7(6-7.475)	6(5.3-7)	6(5.2-6.9)	0.269**
Control N=22	6.9(6.375-7.7)	6(5.25-6.675)	-	0.092‡
AMH (ng/mL)				
Cases N=80	5.75(5.175-7)	5.8(5-8)	5.3(4.75-7)	0.484**
Control N=22	8(6.9-8.4)	5.2(4.15-6.95)	-	0.017‡

*¶ ANOVA, **Kruskal Wallis test, † Independent t test, ‡ Mann Whitney test*

In our study ten patients (12%) conceived, one had an abortion, 7 delivered uneventfully and two patients have ongoing pregnancies. Pregnancy outcomes showed no statistically significant difference with Asn680Ser (rs6166) and Thr307Ala (rs6165) mutations (Table 5).

Table 5:-Association of fertility outcome with Asn680Ser (rs6166) and Thr307Ala (rs6165) in cases

Outcome	AA	AG	GG	P value
680 mutation				
Cases				
Pregnancy achieved				
Not pregnant	30 (85.71%)	32 (88.89%)	8 (88.89%)	0.892*
Pregnant	5 (14.29%)	4 (11.11%)	1 (11.11%)	
Pregnancy outcome				
Aborted	1 (20%)	0 (0%)	0 (0%)	0.333*
Delivered	3 (60%)	4 (100%)	0 (0%)	
Ongoing	1 (20%)	0 (0%)	1 (100%)	
307 mutation	**AA**	**AG**	**GG**	**P value**
Cases				
Pregnancy achieved				
Not pregnant	7 (87.50%)	29 (87.88%)	34 (87.18%)	1*
Pregnant	1 (12.50%)	4 (12.12%)	5 (12.82%)	

Outcome	AA	AG	GG	P value
Pregnancy outcome				
Aborted	0 (0%)	1 (25%)	0 (0%)	0.333*
Delivered	0 (0%)	3 (75%)	4 (80%)	
Ongoing	1 (100%)	0 (0%)	1 (20%)	

** Fisher's exact test*

DISCUSSION

This prospective observational study investigated the association between two common single nucleotide polymorphisms (SNPs) in the follicle-stimulating hormone receptor (FSHR) gene—Thr307Ala (rs6165) and Asn680Ser (rs6166)—and ovarian reserve markers and fertility outcome in infertile women undergoing ovulation induction. Our study revealed no statistically significant differences in genotype or allele frequencies between infertile cases and fertile controls, nor any significant associations of these genotypes with ovarian reserve markers or pregnancy outcomes.

The distribution of genotypes for both SNPs was comparable between infertile cases and fertile controls, though GG at Asn680Ser (rs6166) was observed only in the infertile group. This trend, while not statistically significant, aligns with prior studies suggesting a potential association of these genotypes with altered FSHR function or ovarian responsiveness. Sundaram et al. in a large Indian cohort undergoing IVF, found no association of FSHR polymorphisms with live birth or ovarian response, although genotype frequencies varied by clinical phenotype (18). A meta-analysis involving 24 studies indicated only a modest increased risk of poor ovarian response (POR) with the Ser680 allele (OR ≈1.29), primarily in women undergoing high-dose gonadotropin stimulation (19).

Our study showed no significant correlation between FSHR genotypes and ovarian reserve markers such as age, antral follicle count (AFC), anti-Müllerian hormone (AMH), and baseline FSH in either infertile or fertile women, except for a statistically significant higher AMH among in controls with the AA genotype at rs6165 (p = 0.017) as well as AFC count amongst cases. This can be explained as the cases included PCOS patients. These findings are consistent with reports by Codina-Pascual et al. and Silva et al. which found no impact of rs6165 and rs6166 on AMH or AFC, suggesting these polymorphisms may not be reliable predictors of baseline ovarian reserve in normo-ovulatory women (20,21).

Although several studies suggest that the Ser680 (G) allele is associated with higher basal FSH and reduced sensitivity to FSH, we observed no such pattern in this cohort. This discrepancy could stem from differences in population ethnicity, treatment protocols, or inclusion criteria. Notably, our cohort excluded women with diminished ovarian reserve, potentially minimizing the observable effect size.

Letrozole-based ovulation induction showed no significant difference in ovulation or pregnancy outcomes across genotypes. The clinical pregnancy rate in our study was 12 % and did not differ by genotype. This supports earlier findings that FSHR polymorphisms may not significantly influence outcomes in low-stimulation protocols. In contrast, their effect may be more pronounced under controlled ovarian hyperstimulation with exogenous FSH, as highlighted in studies from East Asia and Europe showing genotype-dependent variation in gonadotropin dose requirement and follicular response.

Lee et al and Zhou et al reported that the Ser680 variant was associated with a higher FSH requirement and lower peak estradiol levels during IVF cycles (19,22). However, these differences are context-dependent and may not apply in settings using oral ovulogens like letrozole, as in our study.

The protective role of the Ser680 allele against PCOS has been emphasized in several meta-analyses, including a recent Indian study showing a reduced risk of PCOS with the G allele under a recessive model (23-25). One of the largest Indian study by Mahey et al where FSHR polymorphisms done on 806 infertile patients showed no significant difference in ovarian response parameters, oocyte yield, and cumulative live birth rates amongst the genotype groups which is similar to our study (26). However, this minimizes confounding from the unique hormonal milieu seen in PCOS, allowing clearer interpretation of genotype-phenotype associations in normo-ovulatory women.

Infertility presents a growing public health challenge, especially in geographically underserved areas like the hilly regions of Northern India, where access to specialized reproductive care is limited. The psychosocial burden of infertility is profound in such communities, often exacerbated by cultural stigma, lack of awareness, and poor health-seeking behavior among couples. Integrating infertility management and genetic screening into primary healthcare systems could promote early identification of high-risk individuals and personalize treatment plans through low-cost pharmacogenomic tools like FSHR genotyping (27).

Community-based outreach, mobile diagnostic services, and telemedicine platforms can help bridge the care gap in these terrains. Strengthening reproductive health programs under the Reproductive, Maternal, Newborn, Child, and Adolescent Health (RMNCH+A) framework and training community health workers to counsel couples may improve awareness and acceptance of genetic screening in reproductive care (28).

The strengths of the present study include prospective design with detailed phenotyping and strict inclusion criteria enhanced internal validity. Exclusion of confounders like endometriosis, low ovarian reserve, and endocrine disorders enabled a focused evaluation of gene–ovarian function relationships. Use of nested PCR-RFLP methodology ensured precise genotyping. Focus on letrozole induction cycles, which are more representative of real-world, resource-limited fertility practices in India. The study adds valuable data on FSHR polymorphisms from a northern Indian population, contributing to ethnically diverse evidence.

Conclusion

In summary, our findings indicate that FSHR polymorphisms Thr307Ala (rs6165) and Asn680Ser (rs6166) are not significantly associated with ovarian reserve markers, ovulation induction, or fertility outcomes in infertile Indian women with normal ovarian function undergoing ovulation induction. While some studies have suggested modest associations of these SNPs with gonadotropin dose or PCOS risk, our results support their limited clinical utility as biomarkers for infertility management in non-IVF settings. Large, multi-ethnic, and treatment-specific studies are warranted to delineate the precise role of FSHR gene variants in reproductive outcomes.

Recommendation

This study provides population-specific evidence that FSHR polymorphisms do not significantly influence ovarian reserve or ovulation induction outcomes in Indian women. These findings help prevent unnecessary genetic testing, reduce treatment costs, and support evidence-based infertility management in resource-limited settings, strengthening reproductive healthcare planning and allocation

Limitation of the Study

The sample size of the study, particularly for the fertile control group, may limit the power to detect small differences or rare genotype effects. Single-center design may restrict generalizability to broader populations. Use of oral ovulogens precludes conclusions about genotype-related variations as seen in IVF or gonadotropin-stimulated cycles. No functional or expression studies were conducted to assess the downstream impact of SNPs on FSHR signaling or ovarian response.

Relevance of the Study

This study adds region-specific evidence showing that FSHR Thr307Ala and Asn680Ser polymorphisms do not significantly influence ovarian reserve or ovulation induction outcomes in Indian women. It helps clarify inconsistent findings in existing literature and supports focusing on established clinical markers rather than routine FSHR genotyping in infertility management.

Authors Contribution

Authors AB, MN, SR and JB have contributed for the concept, design, drafting and final approval of the study. SD, PR and GS have contributed for drafting and final approval of the study

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Conflict of Interest

The Authors have no conflict of interest

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Nil

Declaration of Generative AI and AI Assisted Technologies in the Writing Process

The authors haven't used any generative AI/AI assisted technologies in the writing process.

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