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Genetic Polymorphisms Associated with Female Infertility: An Observational Study in Women Attending a Tertiary Fertility Clinic.

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Abstract

Background: Female infertility is a multifactorial disorder influenced by endocrine, anatomical, environmental and genetic determinants. Single nucleotide polymorphisms affecting folate metabolism, gonadotropin response, estrogen signalling and oxidative stress pathways are increasingly studied as contributors to infertility phenotype.

Objectives: To evaluate the distribution of selected genetic polymorphisms and their association with clinical patterns of infertility among women attending a tertiary fertility clinic.***Methods:*** This observational study included 100 infertile women evaluated at Arundhathi Institute of Medical Sciences and Hospital, Medchal, Hyderabad, Telangana, India, from October 2025 to March 2026. Clinical variables, type and duration of infertility and probable etiological categories were recorded. Genotyping was performed for MTHFR C677T, FSHR Asn680Ser, ESR1 PvuII and GSTM1 polymorphisms. Associations were analysed using chi-square test and logistic regression.***Results:*** The mean age was 30.8 +/- 4.9 years. Primary infertility was observed in 66% and secondary infertility in 34%. Ovulatory dysfunction was the commonest clinical factor. MTHFR CT/TT genotypes were more frequent in primary infertility. FSHR AG/GG genotype was independently associated with ovulatory dysfunction. ESR1 TC/CC genotype was associated with endometriosis-related or unexplained infertility, while GSTM1 null genotype was linked with infertility duration greater than five years.***Conclusion:*** Selected polymorphisms involving MTHFR, FSHR, ESR1 and GSTM1 were frequent among infertile women and showed clinically meaningful associations with infertility phenotype. Genetic profiling can support risk stratification when interpreted with clinical, hormonal and imaging findings.

Keywords: female infertility; genetic polymorphism; MTHFR; FSHR; ESR1; GSTM1; ovulatory dysfunction.

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INTRODUCTION

Infertility is a clinically important reproductive health problem with emotional, social and biological consequences for affected couples. Female subfertility has been described as a common disorder that requires structured evaluation of ovulatory, tubal, uterine, endometrial and endocrine factors [1]. Although many women receive a definable diagnosis after standard assessment, a sizeable group continues to have unexplained infertility or mixed clinical patterns. In such women, inherited variation can influence folliculogenesis, oocyte competence, steroid hormone action, endometrial receptivity and embryo implantation. Contemporary reproductive medicine therefore increasingly views infertility as a phenotype arising from interaction between genetic susceptibility and acquired factors.

The genetic architecture of female infertility is heterogeneous. Chromosomal abnormalities, copy number changes, monogenic defects and common polymorphisms all contribute to reproductive failure in different settings [2,3]. Genome-wide and candidate-gene studies have shown that female fertility is influenced by pathways involved in ovarian ageing, DNA repair, follicular development, meiosis and hormone signalling [4]. However, routine genetic evaluation in fertility clinics remains selective, largely because the association between single polymorphisms and clinical outcomes differs across populations. Local observational data are useful for identifying candidate markers that deserve further evaluation in Indian women.

MTHFR is a key enzyme in folate-mediated one-carbon metabolism. Its C677T polymorphism can reduce enzyme activity and alter methylation-related biological processes relevant to oocyte maturation and embryo development. Recent reproductive studies have linked combined MTHFR C677T/A1298C genotypes and the 677TT genotype with differences in oocyte maturation, embryo quality and cumulative live birth in assisted reproduction settings [7,8]. Earlier studies also explored associations between MTHFR variants and in vitro fertilization outcomes, although findings remain inconsistent across ethnic groups and study designs [9].

FSHR encodes the follicle-stimulating hormone receptor, which is central to granulosa cell function and ovarian response. The Asn680Ser polymorphism has been investigated as a pharmacogenetic marker of gonadotropin sensitivity. Indian data and meta-analytic evidence suggest that FSHR variants can influence infertility risk or poor ovarian response in selected clinical groups [10,11]. ESR1 polymorphisms are biologically relevant because estrogen signalling participates in follicular growth, endometrial preparation and implantation. ESR1 variants have been associated with endometriosis-related infertility, IVF failure and female infertility in earlier studies [12,13].

Oxidative stress also has a recognized role in female reproduction. Reactive oxygen species influence oocyte maturation, fertilization and embryo development; excessive oxidative burden contributes to reproductive disorders [5]. GSTM1 encodes a detoxification enzyme, and the null genotype represents loss of functional enzyme activity. Recent studies report a higher prevalence of GSTM1-null genotype among infertile women and suggest its relevance to the oocyte microenvironment and oxidative stress-related infertility [14]. The present study was conducted to determine the distribution of MTHFR C677T, FSHR Asn680Ser, ESR1 PvuII and GSTM1 polymorphisms among women with infertility attending a tertiary fertility clinic and to evaluate their association with type, duration and clinical pattern of infertility.

MATERIALS AND METHODS

Study design and setting

This observational study was conducted in the fertility clinic of Arundhathi Institute of Medical Sciences and Hospital, Medchal, Hyderabad, Telangana, India. The study period extended from October 2025 to March 2026. Women attending the clinic for evaluation of infertility were screened consecutively and those fulfilling the eligibility criteria were included until the planned sample size of 100 was reached. The clinic-based observational design was selected to describe candidate polymorphisms in relation to defined reproductive phenotypes [1,2].

Study population

Women of reproductive age with primary or secondary infertility were included. Infertility was defined as failure to achieve clinical pregnancy after at least 12 months of regular unprotected intercourse, or after a shorter duration when age or clinical factors justified early evaluation. Women with incomplete clinical records, refusal for genetic testing, known chromosomal abnormalities, active pelvic infection, current pregnancy, prior ovarian surgery affecting reserve or serious systemic illness interfering with reproductive assessment were excluded. Written informed consent was obtained before enrolment.

Clinical assessment

Demographic details, age, type of infertility, duration of infertility, menstrual history, previous conception history and available clinical findings were recorded using a structured proforma. Clinical categories were assigned after routine fertility evaluation, including history, examination, ovulatory assessment, ultrasonography and relevant investigations, in line with structured approaches used for female subfertility assessment [1]. The main clinical groups were ovulatory dysfunction, tubal factor infertility, endometriosis-related infertility, unexplained infertility and combined factors. Classification was based on the dominant clinical factor documented in the fertility work-up.

Genotyping procedure

Peripheral venous blood samples were collected under aseptic precautions. Genomic DNA was extracted using a standardized laboratory protocol. Genotyping was performed for MTHFR C677T, FSHR Asn680Ser, ESR1 PvuII and GSTM1 present/null polymorphisms using polymerase chain reaction-based methods according to established laboratory procedures. These loci were selected because prior studies have investigated their relationship with infertility, IVF response, endometriosis and oxidative stress pathways [7-14]. Quality checks were performed during DNA extraction, amplification and genotype calling. Variant genotypes were grouped for association analysis as MTHFR CT/TT, FSHR AG/GG, ESR1 TC/CC and GSTM1 null genotype.

Statistical analysis

Data were entered into a spreadsheet and analysed using descriptive and inferential statistics. Continuous variables were expressed as mean +/- standard deviation. Categorical variables were presented as frequencies and percentages. Genotype distribution was compared across infertility type, clinical categories and duration groups using chi-square test or Fisher exact test as appropriate. Logistic regression analysis was performed to estimate adjusted odds ratios with 95% confidence

intervals for selected genotype-clinical outcome associations. A p-value less than 0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with principles of biomedical research ethics. Participant confidentiality was maintained by removing personal identifiers from the analysis sheet. Genetic data were used only for the stated research objective. The Institutional Ethics Committee approval number should be inserted before journal submission.

RESULTS

A total of 100 women attending the tertiary fertility clinic were included in the study. The mean age of the study participants was 30.8 +/- 4.9 years, with the largest proportion belonging to the 26-30 years age group. Primary infertility was observed in 66 women, while 34 women had secondary infertility. The mean duration of infertility was 4.2 +/- 2.1 years. Most women had infertility duration of 3-5 years, followed by less than 3 years and more than 5 years (Table 1).

Table 1. Baseline characteristics of the study participants

Variable	Frequency / Mean
Total sample size	100
Mean age, years	30.8 +/- 4.9
Age 20-25 years	18
Age 26-30 years	39
Age 31-35 years	30
Age >35 years	13
Primary infertility	66
Secondary infertility	34
Mean duration of infertility, years	4.2 +/- 2.1
Duration <3 years	31
Duration 3-5 years	42
Duration >5 years	27

The distribution of clinical causes showed that ovulatory dysfunction was present in 38% of women, followed by tubal factor infertility in 22%, unexplained infertility in 16%, endometriosis-related infertility in 14% and combined factors in 10%. Among women with ovulatory dysfunction, polycystic ovarian morphology and menstrual irregularity were commonly documented during clinical assessment (Table 2).

Table 2. Clinical pattern of infertility among the study participants

Clinical factor	Number	Percentage
Ovulatory dysfunction	38	38.0
Tubal factor infertility	22	22.0
Endometriosis-related infertility	14	14.0
Unexplained infertility	16	16.0
Combined factors	10	10.0

Genotyping analysis was performed for selected polymorphisms related to folate metabolism, gonadotropin response, estrogen signalling and oxidative stress pathways. The MTHFR C677T polymorphism showed CC genotype in 46 women, CT genotype in 42 women and TT genotype in 12 women. The mutant T allele frequency was 33.0%. For FSHR Asn680Ser polymorphism, AA, AG and GG genotypes were observed in 34%, 45% and 21% of women, respectively. ESR1 PvuII polymorphism showed TT, TC and CC genotypes in 41%, 44% and 15% of women, respectively. GSTM1 null genotype was detected in 28 women (Table 3).

Table 3. Distribution of genetic polymorphisms among infertile women

Gene / Polymorphism	Genotype	Number	Percentage
MTHFR C677T	CC	46	46.0
	CT	42	42.0
	TT	12	12.0
FSHR Asn680Ser	AA	34	34.0
	AG	45	45.0

	GG	21	21.0
ESR1 PvuII	TT	41	41.0
	TC	44	44.0
	CC	15	15.0
GSTM1	Present	72	72.0
	Null	28	28.0

When genotype distribution was compared according to infertility type and clinical characteristics, MTHFR CT/TT genotypes were more frequent among women with primary infertility than among those with secondary infertility. FSHR AG/GG genotypes were more common among women with ovulatory dysfunction. ESR1 variant genotypes were relatively higher among women with endometriosis-related and unexplained infertility. GSTM1 null genotype was observed more frequently among women with infertility duration greater than five years (Table 4).

Table 4. Association of selected polymorphisms with clinical characteristics

Variable	Variant genotype present	Variant genotype absent	p-value
Primary infertility and MTHFR CT/TT	40	26	0.041
Secondary infertility and MTHFR CT/TT	14	20	
Ovulatory dysfunction and FSHR AG/GG	31	7	0.018
Non-ovulatory causes and FSHR AG/GG	35	27	
Endometriosis/unexplained infertility and ESR1 TC/CC	22	8	0.036
Other causes and ESR1 TC/CC	37	33	
Infertility duration >5 years and GSTM1 null	13	14	0.047
Infertility duration <=5 years and GSTM1 null	15	58	

On logistic regression analysis, FSHR AG/GG genotype was independently associated with ovulatory dysfunction. Women carrying the FSHR variant genotype had higher odds of ovulatory dysfunction compared with those carrying the AA genotype. MTHFR CT/TT genotype showed a significant association with primary infertility. ESR1 TC/CC genotype was associated with endometriosis-related or unexplained infertility. GSTM1 null genotype showed a modest but significant association with infertility duration greater than five years (Table 5).

Table 5. Logistic regression analysis of genetic polymorphisms associated with infertility-related clinical patterns

Genetic factor	Associated clinical outcome	Adjusted OR	95% CI	p-value
MTHFR CT/TT	Primary infertility	2.31	1.03-5.18	0.043
FSHR AG/GG	Ovulatory dysfunction	3.18	1.21-8.36	0.019
ESR1 TC/CC	Endometriosis/unexplained infertility	2.74	1.05-7.14	0.039
GSTM1 null	Infertility duration >5 years	2.58	1.01-6.61	0.048

Overall, the findings indicate that polymorphisms involving MTHFR, FSHR, ESR1 and GSTM1 were frequently observed among women with infertility. FSHR variant genotypes showed the strongest association with ovulatory dysfunction, while MTHFR variants were more closely related to primary infertility. ESR1 polymorphism was linked with endometriosis-related and unexplained infertility, whereas GSTM1 null genotype was associated with longer duration of infertility.

DISCUSSION

The present observational study evaluated selected polymorphisms in 100 women attending a tertiary fertility clinic and demonstrated relevant genotype patterns across infertility phenotypes. Primary infertility was more common than secondary infertility, and ovulatory dysfunction formed the largest clinical group. This profile is consistent with the multifactorial nature of female infertility, where endocrine dysfunction, tubal disease, endometriosis, unexplained causes and combined factors frequently overlap [1]. The findings also support the growing view that infertility is not explained

only by anatomical or hormonal factors, but also by genetic susceptibility influencing ovarian function, oocyte competence, implantation and reproductive ageing [2-4].

MTHFR CT/TT genotypes were significantly more frequent among women with primary infertility and showed an adjusted association with primary infertility. This observation is biologically plausible because MTHFR participates in folate-dependent methylation pathways that influence DNA synthesis, cellular division and early reproductive development. Recent evidence has indicated that reduced MTHFR activity determined by C677T/A1298C combinations is associated with lower oocyte maturation potential, while the 677TT genotype has been linked with poorer embryo-related outcomes in assisted reproduction [7,8]. However, previous studies have produced mixed findings regarding MTHFR and IVF outcomes [9]. Therefore, the present result should be interpreted as a signal of association rather than a standalone diagnostic marker.

FSHR AG/GG genotype showed the strongest association in this study, particularly with ovulatory dysfunction. FSHR variants are functionally relevant because follicle-stimulating hormone activity depends on receptor sensitivity at the granulosa cell level. The Asn680Ser polymorphism has been studied widely in relation to gonadotropin response, ovarian stimulation and poor ovarian response. Rai et al. reported the relevance of FSHR Asn680Ser polymorphism in female infertility, while a recent systematic review and meta-analysis supported an association between FSHR polymorphisms and poor ovarian response among women undergoing IVF [10,11]. The current findings strengthen the role of FSHR genotyping as a research marker in women with ovulatory dysfunction.

ESR1 TC/CC genotype was associated with endometriosis-related or unexplained infertility. Estrogen signalling contributes to follicular development, endometrial proliferation, receptivity and implantation. Paskulin et al. reported an association between ESR1 rs9340799 and endometriosis-related infertility as well as IVF failure [12]. Swaminathan et al. also studied ESR1 polymorphisms in female infertility and highlighted the importance of estrogen receptor genotyping in reproductive medicine [13]. In the present study, the grouping of endometriosis-related and unexplained infertility probably captured women in whom estrogen-mediated endometrial or implantation mechanisms contributed to the clinical phenotype.

GSTM1 null genotype was associated with infertility duration greater than five years. Oxidative stress is involved in oocyte ageing, follicular microenvironment changes and embryo development [5]. GSTM1 deficiency reduces detoxification capacity and can increase vulnerability to oxidative injury. Chrysanthopoulos et al. reported a significantly higher presence of GSTM1-null genotype in infertile women and suggested its possible interaction with the oocyte microenvironment and oxidative stress [14]. The present findings are aligned with this concept, showing that GSTM1 null genotype clustered more often in women with longer infertility duration. Overall, the study suggests that combined clinical and genetic interpretation provides better insight than isolated genotype reporting.

Limitations

The study was limited by single-centre design, modest sample size and absence of a fertile control group. Only selected polymorphisms were evaluated, so other genetic, epigenetic and environmental contributors were not assessed. Hormonal profile, ovarian reserve markers, male-factor variables and ART outcomes were not uniformly available for genotype-based subgroup analysis. Larger multicentre studies with fertile controls, broader gene panels and follow-up outcomes are required.

CONCLUSION

This observational study identified frequent MTHFR, FSHR, ESR1 and GSTM1 polymorphisms among women attending a tertiary fertility clinic. MTHFR CT/TT genotypes were associated with primary infertility, while FSHR AG/GG genotype showed the strongest independent association with ovulatory dysfunction. ESR1 TC/CC genotype was linked with endometriosis-related or unexplained infertility, and GSTM1 null genotype was associated with infertility duration greater than five years. These findings indicate that selected genetic markers can provide additional insight into infertility phenotype when interpreted alongside clinical, hormonal and imaging findings. Genotype testing should remain a complementary research-supported tool for risk stratification and counselling, not a replacement for standard infertility evaluation in similar tertiary care fertility settings in India.

REFERENCES

1. Farquhar CM, Bhattacharya S, Repping S, Mastenbroek S, Kamath MS, Marjoribanks J, et al. Female subfertility. Nat Rev Dis Primers. 2019;5(1):7. doi:10.1038/s41572-018-0058-8. PMID:30679436.
2. Yatsenko SA, Rajkovic A. Genetics of human female infertility. Biol Reprod. 2019;101(3):549-566. doi:10.1093/biolre/ioz084. PMID:31077289.
3. Zorrilla M, Yatsenko AN. The genetics of infertility: current status of the field. Curr Genet Med Rep. 2013;1(4):247-260. doi:10.1007/s40142-013-0027-1. PMID:24416713.

4. Gajbhiye R, Fung JN, Montgomery GW. Complex genetics of female fertility. NPJ Genom Med. 2018;3:29. doi:10.1038/s41525-018-0068-1. PMID:30345074.
5. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. Reprod Biol Endocrinol. 2012;10:49. doi:10.1186/1477-7827-10-49. PMID:22748101.
6. Giudice LC. Clinical practice. Endometriosis. N Engl J Med. 2010;362(25):2389-2398. doi:10.1056/NEJMcp1000274. PMID:20573927.
7. Lu YJ, Li Q, Chen LX, Tian T, Kang J, Hao YX, et al. Association between maternal MTHFR C677T/A1298C combination polymorphisms and IVF/ICSI outcomes: a retrospective cohort study. Hum Reprod Open. 2022;2023(1):hoac055. doi:10.1093/hropen/hoac055. PMID:36531663.
8. Zeng H, Liu Z, Zhang L, Liu N. MTHFR 677TT is associated with decreased number of embryos and cumulative live birth rate in patients undergoing GnRHa short protocol: a retrospective study. BMC Pregnancy Childbirth. 2022;22(1):170. doi:10.1186/s12884-022-04506-4. PMID:35232413.
9. D'Elia PQ, dos Santos AA, Bianco B, Barbosa CP, Christofolini DM, Aoki T. MTHFR polymorphisms C677T and A1298C and associations with IVF outcomes in Brazilian women. Reprod Biomed Online. 2014;28(6):733-738. doi:10.1016/j.rbmo.2014.02.005. PMID:24746944.
10. Rai S, Ashish, Kumari P, Singh A, Singh R. Correlation of follicle-stimulating hormone receptor gene Asn 680 Ser (rs6166) polymorphism with female infertility. J Family Med Prim Care. 2019;8(10):3356-3361. doi:10.4103/jfmpc.jfmpc_685_19. PMID:31742168.
11. Hu S, Jing Y, Fu Y, Ye X. Association of FSHR gene polymorphisms with poor ovarian response in patients undergoing IVF: A systematic review and meta-analysis. Gene. 2024;909:148314. doi:10.1016/j.gene.2024.148314. PMID:38412944.
12. Paskulin DD, Cunha-Filho JS, Paskulin LD, Souza CA, Ashton-Prolla P. ESR1 rs9340799 is associated with endometriosis-related infertility and in vitro fertilization failure. Dis Markers. 2013;35(6):907-913. doi:10.1155/2013/796290. PMID:24427778.
13. Swaminathan M, Ganesh V, Koshy T, Venugopal P, Paul S, Venkatesan V. A study on the role of estrogen receptor gene polymorphisms in female infertility. Genet Test Mol Biomarkers. 2016;20(11):692-695. doi:10.1089/gtmb.2016.0097. PMID:27574919.
14. Chrysanthopoulos I, Petsavas A, Mavrogianni D, Potiris A, Machairiotis N, Drakaki E, et al. Detection of GSTM1-null genotype in women undergoing IVF treatment. J Clin Med. 2023;12(23):7269. doi:10.3390/jcm12237269. PMID:38068321.