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Review

Descriptive overview of gene variants potentially affecting female infertility treatments: A systematic review

Asunta Martinez-Martinez [1], Francisco José Sanz [1], Pablo Garcia-Acero [1], Patricia Sebastian-Leon, Patricia Diaz-Gimeno [*]

IVIRMA Global Research Alliance, IVI Foundation, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia, Spain

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ABSTRACT

Pharmacogenetics is an emerging discipline that explores how genetic variants affect drug response, potentially leading to side effects or treatment failure. Although widely applied in other medical specialties, its use in female reproductive medicine remains limited. The objective of this systematic review is to investigate and summarize the current state of knowledge in pharmacogenetics as it applies to female reproductive diseases or conditions, aiming to support clinical application. A comprehensive systematic search was conducted using PubMed up to September 2025, following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines. Keywords related to female infertility and pharmacogenetics/pharmacogenomics were used. The search yielded 603 articles, of which 75 were ultimately included. Evaluation of the studies identified 46 genetic variants affecting drug response in the field of female infertility. Pharmacogenetic research in this field remains limited, with notable gaps for conditions such as endometriosis and uterine fibroids that influence reproductive outcomes. The variants associated with responses during infertility therapies could contribute to preventive medicine aimed at avoiding reduced drug efficacy, excessive responses, or the development of adverse effects. Additionally, greater dissemination of these findings within clinical settings is essential to improve awareness and understanding in this field and to facilitate the study of these variants and their potential translation into clinical practice. This review summarizes the current state of pharmacogenetics in the context of female infertility and aims to serve as a reference and to encourage further research in this area.

1. Introduction

Women's reproductive health covers a broad spectrum of diseases and life stages, ranging from menarche to menopause. Some conditions within this therapeutic area include uterine and ovarian diseases, as well as contraception, infertility, and pregnancy [1–4]. Specifically, female infertility remains a significant global health challenge affecting 10–15 % of couples. Advances in assisted reproductive technologies (ARTs) have improved pregnancy outcomes, but variability in treatment response among women still persists, complicating clinical management [5].

Drug effectiveness and toxicity are commonly assessed through a trial-and-error process, which may not always achieve optimal clinical outcomes for women's health [6,7]. Inter-individual variation influenced by age, sex, pregnancy, body weight, or genetic factors has been described as a source of drug response variability across populations [8–10]. Emerging evidence suggests that genetic factors are one of the main causes of this variability, accounting for 20–40 % of drug response differences, and they may also influence follicular development and response to ovarian stimulation protocols [11].

Although it is estimated that approximately 97 % of patients carry at least one genetic variant affecting drug response [12], this knowledge has not yet been fully translated into clinical practice to improve current treatments [13]. Pharmacogenomics is an emerging discipline that aims to study how genetic variants influence drug response, potentially leading to side effects or reduced treatment effectiveness [14]. This discipline offers a promising approach to developing personalized therapies, improving drug efficacy and safety, and reducing costs in many medical fields [15]. However, there are currently no specific guidelines for pharmacogenomics in reproductive disorders affecting

* Correspondence to: IVIRMA Global Research Alliance, IVI Foundation, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Av. Fernando Abril Martorell 106, Valencia 46026, Spain.
E-mail address: patricia.diaz@ivirma.com (P. Diaz-Gimeno).
[1] A.M.M., F.J.-S and P.G.-A contributed equally to this work and should be regarded as joint first authors

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women and so it has not yet been implemented in routine clinical practice [16]. This systematic review aimed to comprehensively evaluate the current evidence on gene variants affecting female infertility treatment response, with a particular focus on reproductive outcomes.

2. Materials and methods

2.1. Search strategy

A comprehensive systematic review was conducted using PubMed to identify relevant studies published up to September 2025, following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines [17]. A manual search of the reference lists of all the articles assessed for eligibility was also performed to identify additional studies. Search terms included all potential keywords relating to women's reproductive health and pharmacogenetics/pharmacogenomics (MeSH terms were used where applicable): ("Pharmacogenetics"[MeSH] OR "Pharmacogenomic variants"[MesH]) AND ("Fertility agents, female"[MeSH] OR "Reproductive techniques"[MeSH] OR "Fertilization in vitro"[MeSH] OR "Pregnancy"[MeSH] OR "Menopause"[MeSH] OR "Contraceptive agents, female"[MeSH] OR "Uterus"[MeSH] OR "Ovary"[MeSH] OR "Gynecology"[MeSH] OR "Endometriosis"[MeSH] OR "Polycystic ovary syndrome"[MeSH] OR "Primary ovarian insufficiency"[MeSH] OR "Pre-eclampsia"[MeSH] OR "Ovulation induction"[MeSH] OR "Female reproduction" OR "Recurrent implantation failure").

This systematic review was prospectively registered in the PROSPERO database (registration number CRD42023431012).

2.2. Study selection

Eligible studies were those with a full-text published in English and conducted in women (*Homo sapiens*) with genotype data, drug outcomes related to different genotypes, and associated reproductive outcomes. Exclusion criteria was the involvement of cancer-related diseases, case reports, editorials, opinion pieces, commentaries, and in vitro or in silico research.

2.3. Screening and quality assessment

Three team members (P.G-A., F.J.S., and A.M-M.) independently screened the titles, abstracts, and full texts of all the retrieved studies. Potential discrepancies in article quality or selection were resolved by consultation with a senior investigator (P.D-G.).

2.4. Data extraction

All the investigators jointly developed a structured data extraction spreadsheet. The extracted data included the following information: year of publication; authors; study design; genes analyzed; specific gene variants; reproductive condition (and related conditions, where applicable); sample size and mean age; ethnicity; drug name and dosage; and main drug outcome or effect. Eligible studies were thoroughly read and examined by the reviewers (P.G-A., F.J.S., and A.M-M.) to extract relevant data, which were compiled in a spreadsheet and cross-checked by the other investigators. Disagreements concerning the extracted data were resolved through discussion with the senior investigator (P.D-G.).

2.5. Risk of bias assessment

The methodological quality of the included studies was assessed by four reviewers (P.G-A., F.J.S., A.M-M., and P.S-L.) using the Newcastle–Ottawa Scale [18], which is recommended by the Cochrane Collaboration for assessing observational studies, including case-controlled and cohort designs. The reviewers assessed study quality independently and any discrepancies were resolved by consensus among the whole team.

3. Results

3.1. Search results

The results of our systematic search are summarized in Fig. 1. We identified 603 articles. After screening the titles and abstracts, 218 full-text articles were retrieved for detailed assessment. Finally, after including articles manually identified from selected papers, 75 studies were included in the systematic review. Details of the risk-of-bias assessment are provided in Supplementary Table. 1.

3.2. Pharmacogenetic variants affecting female infertility drug response: systematic results from the literature

3.2.1. Ovarian response in controlled ovarian stimulation

Controlled ovarian stimulation (COS) is an essential component of assisted reproductive technologies aimed at increasing the retrieval of mature oocytes [19,20]. Several therapeutic strategies have been developed to achieve COS. Most protocols are based on the exogenous administration of follicle-stimulating hormone (FSH) to promote the development of multiple oocytes, followed by administration of human chorionic gonadotrophin (hCG) to trigger ovulation [21].

In this context, 67 studies evaluated the effect of gene variants in drugs used in COS treatments, considering metabolic effects (i.e., hormone levels), treatment strategy (medication dose and duration), and treatment outcomes (the number of oocytes retrieved or maturation). The results are summarized in Table 1 for studies reporting significant findings, while all of the results, including those without significant findings, are provided in Supplementary Tables 2–4.

Variants in the *Follicle Stimulating Hormone Receptor* (*FSHR)* gene, mentioned in 37 reports, were the most consistently studied [22–57]. Although some of the findings were controversial, the majority of studies indicate that Ser/Ser, Ala/Ala, and AA genotypes in the Asn680Ser, Ala307Thr, and −29 G>A variants are associated with a poorer response to COS treatment [22,24–28,31–34,36,37,44,45,51–55,58]. Additionally, combinations of these three genetic variants were associated with differential responses to COS treatments [57].

Other important genes evaluated during COS treatment include *Estrogen Receptor 1 (ESR1)* and *Estrogen Receptor 2 (ESR2)*, addressed in 11 studies [35,36,41,44,57,59–64]. The variants in *ESR1* studied to date have shown contradictory results regarding the number of oocytes retrieved and drug response [35,60,61,63]. For *ESR2*, the *Rsa*I G/A, Alu G/A, and 39 A>G variants appear to influence COS treatment response [44,55,63]. Additionally, several studies evaluated combinations of variants in the *FSHR*, *ESR1*, and *ESR2* genes, finding that the combined presence of multiple variants can influence COS response [36,41,44,65].

Anti-Müllerian hormone is a well-known biomarker of ovarian function [66]; therefore, variants of this gene and its receptors (*Anti-Müllerian hormone (AMH)* and *Anti-Müllerian hormone receptor type 2 (AMHR2)*) have also been studied [67–70]. Regarding *AMH*, no association between gene variants and COS treatment response has been reported [67–70]; however, for *AMHRH2*, five variants have shown altered responses after COS treatment [67,69]. Four variants of luteinizing hormone/choriogonadotropin receptor (*LHCGR*) have also been evaluated and two of them (rs2293275 and rs12470652) were found to exhibit variations in the number of oocytes retrieved, oocyte maturation, and estradiol (E_2) serum levels on the day of hCG administration [71,72]. Regarding *Methylenetetrahydrofolate Reductase (MTHFR)*, two studies reported that the 677 C>T variant affects COS treatment outcomes [54,71]; however, no differences in these parameters for rs2293275 have been found in other studies [52–54,73]. In addition, the Ala222Val variant of *MTHFR* also influences oocyte retrieval and basal FSH serum levels [11,20].

Among the remaining genes identified in our systematic search,

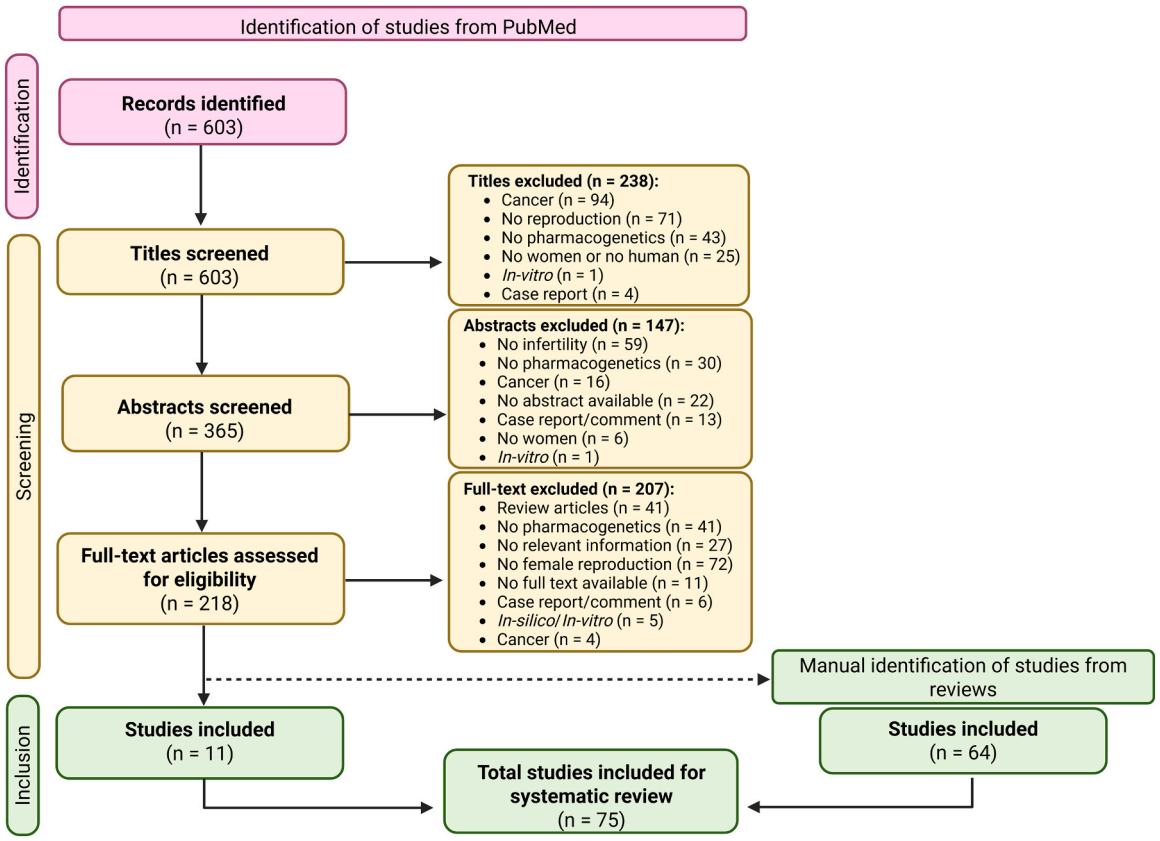


Fig. 1.

variants in *Bone Morphogenetic Protein 15* (*BMP15*) [43,74], *Growth Differentiation Factor 9* (*GDF-9*) [75,76], *Androgen Receptor* (*AR*) [77], *Histidine Rich Glycoprotein* (*HRG*) [78], *Methionyl Aminopeptidase Type 1D Mitochondrial* (*METAP1D*), *NLR Family Pyrin Domain Containing 11* (*NLRP11*), *Rhomboid Like* (*RHBDL*), *Synaptonemal Complex Protein 2 Like* (*SYCP2L*), *Tudor Domain Containing 3* (*TDRD3*), and *Transmembrane Protein 150B* (*TMEM150B*) [11] have been reported to affect COS treatment. Heterogeneous results have been described for the v-betaLH variant of *Luteinizing Hormone Subunit Beta* (*LHB*) regarding FSH dose [79,80], although the T/T genotype has been associated with reduced oocyte retrieval and maturation [54]. No effect has been described in variants in *Sex Hormone Binding Globulin* (*SHBG*), *Cytochrome P450 Family 19* (*CYP19*), *Minichromosome Maintenance 8 Homologous Recombination Repair Factor* (*MCM8*), *DNA Primase Subunit 1* (*PRIM1*), *Ring Finger Protein 44* (*RNF44*), *Tousled Like Kinase 1* (*TLK1*), *Ubiquitin Interaction Motif Containing 1* (*UIMC1*), *ASH2 Like* (*ASH2L*), or *Fibronectin Type III Domain Containing 4* (*FNDC4*) [11,36,81,82]. Finally, one study evaluated 454,102 different single-nucleotide polymorphisms (SNPs), none of which showed any correlation with ovarian response [83].

It is worth to mention that one of the most severe side effects of COS is ovarian hyperstimulation syndrome (OHSS), which can be life-threatening in its most severe forms [84,85]. Although age, body weight, and the presence of polycystic ovarian syndrome (PCOS) are the most important risk factors [85], several studies have evaluated the effect of gene variants in OHSS. Table 1 summarises the results for studies reporting significant findings, and the results of all the studies considered, regardless of significance, are provided in Supplementary Table 3.

Regarding *FSHR*, three studies found no association between the Asn680Ser variant and OHSS [28,38,45], while one reported an increased risk of OHSS among Asn carriers [42]. Two studies found no relationship between the Ala307Thr variant and OHSS [28,38], whereas one associated the AA genotype with a higher prevalence of OHSS [45]. In addition, the −29 G>A variant and combination of 2039 A>G and −29 G>A have been associated with the onset of OHSS [47].

Furthermore, the Alu G/A variant in *ESR2*, the C677T variant in *MTHFR* and associations of variants in gene *BMP15* have been reported to affect the likelihood of OHSS [63,86]. Finally, no significant differences in OHSS risk have been observed for the rs4073366 and insLQ variants in *LHCGR*, although an increased risk has been reported when both variants were combined in the non-insLQ/C haplotype [72].

To sum up, COS relies mainly on exogenous FSH followed by hCG administration to increase the number of oocytes obtained. Sixty-seven studies have evaluated genetic variants influencing COS response, focusing on hormonal effects and clinical outcomes. *FSHR* variants were the most studied and were generally associated with poorer COS response, including genotypes combinations. Variants in *ESR1* showed inconsistent associations, whereas *ESR2* variants showed more consistently influenced response. Combined variants in *FSHR*, *ESR1*, and *ESR2* also modulated COS outcomes. Additionally, several *AMHR2*, *LHCGR* and *MTHFR* variants, among others, were linked to differences in oocyte number, maturation, and hormone levels, although findings were sometimes inconsistent. On the other hand, many variants and a large genome-wide analysing different SNPs revealed no significant effects on ovarian response. Several studies have also evaluated genetic susceptibility to OHSS, the most serious complication of COS, beyond established clinical risk factors. Findings for *FSHR* variants are inconsistent, some variants, including −29 G>A, and specific *FSHR* haplotypes, have been linked to increased OHSS risk, although most studies reported no association with specific variants. Variants in *ESR2* (Alu G/A) and *MTHFR* (C677T) have been also associated with altered OHSS susceptibility. *LHCGR* variants alone showed no effect, but specific combined haplotypes were associated with increased OHSS risk.

Table 1
Pharmacogenetic variants that affect drug response significantly in controlled ovarian stimulation protocols. Gene symbol, pharmacogenetic variant, number of patients included in the study (N), treatment, outcome, and the reference of the study are presented. The alleles, genotypes, or haplotypes that account for drug response variability are shown in parentheses.

Gene	Variant	N	Treatment	Outcome	Reference
AMHR2	-482A>G (rs2002555)	108	BSN + hMG + hCG	(wild type): ↑oocytes ↑pregnancy rate	(67)
		124	FSH + CLX + TPN	(A/A): ↓gonadotropin dose and duration of stimulation	(64)
	ISV 5–6 C>T	108	BSN + hMG + hCG	(wild type): ↑pregnancy rate	(67)
	1749 C>G (rs2071558)	186	rFSH + hCG	(G/G): ↑follicles ↑mature oocytes	(69)
		485	GnRH antagonist protocol + GnRH agonist	(T genotype): ↑high response	(55)
	4952 G>A (rs3741664)	186	rFSH + hCG	(G/G): ↑FSH serum levels (basal)	(69)
	10 A>G (rs11170555)	186	rFSH + hCG	(G/G): ↑E2 and ↓AMH serum levels (basal)	(69)
BMP15	-9C>G (rs3810682)	191	NFN + rFSH or HMG + hCG	(C/G and C/G + GG): ↓good response group	(43)
		307	rFSH + hCG	(G allele): ↑good response group	(74)
	IVS1 + 905 A>G	307	rFSH + hCG	(G allele): ↑good response group	(74)
	-673C>T / -9C>G / IVS1 + 905 A>G/ N103S	307	rFSH + hCG	(TGGA): ↑OHSS risk (CCAA): ↓OHSS risk	(74)
ESR1	Pvull (rs2234693)	200	BSN + rFSH + hCG + P4	(C/C):↓follicles ↓oocytes ↓pregnancy rate	(60)
		159	CLX or OGN + rFSH + hCG	(C/C): ↑follicles ↑oocytes	(61)
		104	TPN + NFN + rFSH + hCH	(T/T): ↓mature oocytes ↓fertilization rate	(62)
		280	LEU + rFSH + hCG	(T/C): ↑poor response group	(35)
		136	rFSH + hCG	(T/T): ↑dose and duration of FSH	(63)
		124	FSH + CLX + TPN	(T/T): ↑ oocytes retrieved	(64)
	Xbal (rs4986938)	136	rFSH + hCG	(A/A): ↑follicles ↑mature oocytes	(63)
		104	TPN + NFN + rFSH + hCH	(A/A): ↓mature oocytes ↓fertilization rate	(62)
		159	CLX or OGN + rFSH + hCG	(G/G): ↑serum estradiol levels	(61)
	(TA)n repeat	104	TPN + NFN + rFSH + hCH	(LL): ↓fertilization rate	(62)
		124	FSH + CLX + TPN	(<17 repeats): ↑ oocytes retrieved	(64)
ESR1/FSHR	*Pvu*II / Asn680Ser	109	BSN + rFSH + hCG	(CC/AA): ↓follicles ↓oocytes ↓E2 serum levels (hCG day) ↑FSH dose ↓pregnancy rate	(41)
ESR2	Rsal (rs4986938)	136	rFSH + hCG	(G/G): ↑dose and duration of FSH ↑E2 serum levels (basal)	(63)
	Alul (rs1256049)	216	HMG + CLX + hCG	(G/G): ↑good response group	(44)
		136	rFSH + hCG	(G/G): ↑OHSS risk	(63)
	39 A>G	495	GnRH antagonist protocol + GnRH agonist	(A genotype): ↑ poor response	(55)
FMR1	CGGn	531	LEU + DHEA + FSH + hCG	(low FMR1 allele): ↓embryo quality ↓pregnancy rate	(88)
FOLR1	1816C/delC / 1841G>A	439	CLX or OGN + rFSH + hCG	(CdelC/GA): ↑pregnancy loss	(94)
FSHB	rs611246	471	GnRH | rFSH + P4	(A/A): ↓ Pregnancy rate	(11)
FSHR	2039 A>G	368	TPN + FSH + hCG	(Asn/Asn): ↑oocytes	(37)
	Asn680Ser (rs6166)	1421	N/A	(Ser/Ser): ↑FSH dose (Asian population) (Ser/Ser) ↑FSH serum levels (basal)	(22)
		178	rFSH + hCG	(Ser/Ser): ↑FSH serum levels (basal)	(23)
		161	FSH + hCG	(Ser/Ser): ↑FSH serum levels (basal) ↑FSH dose	(24)
		586	GNX, NFN, or BSN + rFSH or MNS + hCG	(Asn): ↑OHSS risk	(42)
		170	TPN + rFSH + hCG	(Ser/Ser): ↑poor response group (Asn/Ser): ↑good response group	(36)
		125	BSN + FSH + hCG	(Asn/Ser): ↑E2 serum levels (hcG day) ↑good response group ↑follicles ↑oocytes (Ser/Ser): ↑LH and FSH serum levels (basal)	(25)
		263	TPN or CLX + rFSH or FSH + hCG	(Ser/Ser): ↓oocytes (long protocol) ↑ FSH serum levels (basal) and reduced E2 serum levels (hcG day) (Asn/Asn): ↑pregnancy rate	(26)
		102	rFSH + hCG	(Ser/Ser): ↑poor response group	(31)
		240	CC + FSH	(Ser/Ser): ↑FSH dose	(27)
		450	rFSH + hCG	(Ser/Ser): ↑FSH serum levels (basal) ↑duration of stimulation ↑poor response group	(28)

(*continued on next page*)

Table 1 (*continued*)

Gene	Variant	N	Treatment	Outcome	Reference
		105	LEU + rFSH + hCG	(Ser/Ser): ↑implantation rate ↑pregnancy rate	(40)
		108	BSN + FSH + hCG	(Asn/Asn): ↑oocytes	(32)
		145	CLX + FSH	(Asn/Asn): ↑follicles ↑oocytes (Ser/Ser): ↑dose of gonadotropins ↑duration of stimulation	(33)
		42	DPL + FSH + hCG	(Ser/Ser): ↑poor response group	(34)
		93	FSH + hCG	(Ser/Ser): ↑E2 serum levels (hcG day)	(29)
		109	BSN + rFSH + hCG	(Asn/Asn): ↑dose of gonadotropins	(41)
		427	rFSH + hCG	(Ser/Ser): ↑mature oocytes (Asn/Asn): ↓ LH and FSH serum levels (basal)	(30)
		280	LEU + rFSH + hCG	(Asn/Ser): ↑poor responder group	(35)
		495	GnRH antagonist protocol + GnRH agonist	(Ser): ↑poor response group	(55)
		210	TPN or OGN + Follitropin alpha or Follitropin beta or Urofollitropin + hCG	(Ser): ↑poor response group (Asn/Asn): ↑oocytes retrieved	(51)
	Ala307Thr (rs6165)	150	FSH + hCG	(Ala/Ala): ↑E2 serum levels (hcG day) ↑OHSS (Thr/Thr): ↑dose of FSH	(46)
		450	rFSH + hCG	(Ala/Ala): ↑FSH serum levels (basal) ↑duration of stimulation ↑poor response group	(28)
		216	HMG + CLX + hCG	(Ala/Ala): ↑poor response group	(44)
	-29G>A (rs139420)	150	FSH	(A/A): ↓E2 serum levels (hCG day) ↓follicles ↓oocytes ↑FSH dose	(45)
		100	FSH + hCG	(A/A): ↓ follicles ↓oocytes ↑FSH dose ↓mature oocytes ↑poor response group	(58)
		559	OGN or BSN + FSH	(G/G): ↑OHSS ↓pregnancy rate ↓live birth rate	(47)
		368	TPN + rFSH + hCG	(G/G): ↑oocytes	(37)
	Ala307Thr / Asn680Ser	552	GnRH + hCG	(AS/AS): ↑FSH serum levels (basal) ↑hMG dose	(48)
		374	FSH + hCG	(AS/AS): ↑poor response group	(49)
		368	GnRH antagonist + rFSH + hCG or GnRH agonist	(AG/AG): ↑poor response group (GG/AA): ↓poor response group	(57)
	Asn680Ser / -29G>A	559	OGN or BSN + FSH	(GA): ↓OHSS ↑pregnancy rate ↑live birth rate	(47)
		150	FSH + hCG	(Asn/Asn – A/A): ↑poor response group ↓follicles ↓oocytes ↑FSH dose (Asn/Asn - G/G): ↑mature oocyte	(50)
		368	GnRH antagonist + rFSH + hCG or GnRH agonist	(AA/GG): ↓poor response ↑oocytes retrieved (AG/AA): ↑poor response	(57)
	rs2268363	471	GnRH | rFSH + P4	(T/T): ↑ Number of follicles	(11)
	Ala307Thr / -29G>A	368	GnRH antagonist + rFSH + hCG or GnRH agonist	(AA/AG): ↓oocytes retrieved	(57)
FSHR/ESR2	Ala307Thr / Rsal	216	HMG + CLX + hCG	(AG/AA): ↑poor response group (AG/GA): ↑good response group	(44)
FSHR/SHBG/ CYP19A1	FSHR Gly307Ala / FSHR Asn680Ser / SHBG (TAAAA)n / CYP19A1 (TTTA)n	600	LEU + FSH + hCG	(Ala/Ser/short allele/short allele): ↑follicles ↑oocytes	(65)
FSHR/LHCGR	Asn680Ser / N312S	665	Gonarelin or NFN or BSN + Follitropin alpha or Follitropin beta or Urofollitropin or Menotropin + hCG	(SS): ↑pregnancy rate	(56)
FSHR1 / ESR1 / ESR2	Asn680Ser / *Pvu*II / *Alu*I	170	TPN + rFSH + hCG	(Ser/Ser, T/T, G/G): ↑poor response group	(36)
GDF9	546 G>A (rs10491279)	226	TPN + rFSH + hCG	(G/G in diminished ovarian reserve group): ↓FSH dose ↑mature oocytes ↓poor response group ↑embryo quality ↑fertilization rate ↑pregnancy rate	(75)
		290	TPN + FSH + hCG	(G/G): ↑good response group ↑fertilization rate	(76)
	447 C>T (rs254286)	290	TPN + FSH + hCG	(T/C): ↑poor response group ↓fertilization rate	(76)
		495	GnRH antagonist protocol + GnRH agonist	(G allele): ↑progesterone levels	(55)
		495	GnRH antagonist protocol + GnRH agonist	(C allele): ↑progesterone levels	(55)

(*continued on next page*)

Table 1 (*continued*)

Gene	Variant	N	Treatment	Outcome	Reference
	C398G	67	rFSH + OGN + rhCG	(C allele): ↑number follicles, oocytes retrieved and oocyte maturation	(73)
	-39 G>C (rs254285)	495	GnRH antagonist protocol + GnRH agonist	(C allele): ↑progesterone levels)	(55)
HRG	633 C>T (rs9898)	67	BSN or NFN or GNX or rFSH + hCG	(T/T): ↑FSH serum levels (basal) ↑FSH dose ↓oocytes ↓mature oocytes ↓fertilization rate	(78)
KPNA3	rs3736830	471	GnRH | rFSH + P4	(C/C & C/G): ↑ Number of follicles	(11)
LHB	v-bLH	220	BSN + rFSH + hCG + P4	(v-bLH carrier): ↑FSH dose	(79)
		60	TPN + rFSH + hCG	(v-bLH carrier): ↑FSH dose	(80)
		94	BSN + rhFSH + hCG	(T/T): ↓oocytes retrieved and matured oocytes	(54)
	Trp8Arg	591	GnRH agonist or antagonist protocol	(non-carrier): ↑pregnancy rate (carrier): ↑E2 serum levels (hCG day)	(93)
LHCGR	935 G>A Ser312Asn (rs2293275)	553	TPN + rFSH + rLH	(N/N): ↑oocytes ↑mature oocytes	(71)
		210	TPN or OGN + Follitropin alpha or Follitropin beta or Urofollitropin + hCG	(S): ↑ pregnancy rate (fresh embryo transfers)	(51)
		94	BSN + rhFSH + hCG	(TT): ↓estradiol levels (hCG day)	(54)
	rs12470652	94	BSN + rhFSH + hCG	(TT): ↓estradiol levels (hCG day) ↓oocytes retrieved and mature oocytes	(54)
	28 G>C (rs4073366) / insLQ (rs4539842)	172	LEU + rFSH + hCG	(C/no-insLQ): ↑OHSS risk	(72)
METAP1D	rs7606918	471	GnRH | rFSH + P4	(A/G & G/G): ↑ Number of follicles & oocytes retrieved	(11)
MTHFR	677 C>T (rs1801133)	105	NFN + rFSH	(C/C): ↓FSH dose ↑oocytes ↑E2 serum levels (hCG day)	(90)
		61	hMG or FSH + hCG	(T/T): ↑ OHSS risk	(86)
		82	OGN + FSH + hCG	(C/C): ↓mature oocytes	(91)
	1298 C>T	82	OGN + FSH + hCG	(A/A): ↑oocytes	(91)
	Ala222Val (rs1801133)	223	FSH + hCG	(A/C): ↑ FSH serum levels (basal)	(20)
NLRP11	rs12461110	471	GnRH | rFSH + P4	(A/A): ↑ FSH dose needed	(11)
RHBDL2	rs4246511	471	GnRH | rFSH + P4	(C/C & T/C): ↑ FSH dose needed (T/T & T/C): ↓ Pregnancy rate	(11)
SOD2	Ala16Val	148	TRP + rFSH + hCG	(Ala/Ala): ↑pregnancy rate	(92)
SYCP2L	rs2153157:G>A	471	GnRH | rFSH + P4	(C/C & C/T): ↑ FSH dose needed (C/C): ↓ Pregnancy rate	(11)
TDRD3	rs4886238:G>A	471	GnRH | rFSH + P4	(G/G & G/A): ↑ Number of follicles & oocytes retrieved	(11)
TMEM150B	rs11668344	471	GnRH | rFSH + P4	(G/G): ↑ FSH dose needed	(11)

BSN, buserelin; CC, clomiphene citrate; CLX, cetrorelix; DHEA, dehydroepiandrosterone; DPL, decapeptyl; E2, estradiol; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; HMG, human menopausal gonadotropin; N/A, not available; NFN, nafarelin; GNX, galinerlix; LEU, leuprolide; MNS, menotropins; NFN, nafarelin; OGN, orgalutran; OHSS, ovarian hyperstimulation síndrome; P4, progesterone; rFSH, recombinant follicle-stimulating hormone; r-hLH, recombinant human luteinizing hormone; TPN, triptorelin.

3.2.2. Assisted reproductive technology: embryo quality and reproductive outcomes

Many attempts have been made to optimize hormone replacement therapy (HRT) protocols with the aim of improving reproductive outcomes in assisted reproductive technology (ART) [87]. However, gene variants might also play a key role in the response to these treatments and their impact on ART outcomes. In this regard, Table 1 summarizes the main significant results, while the findings from all the studies are shared in Supplementary Table 4. Variants in *GDF-9* and *Fragile X Messenger Ribonucleoprotein 1* (*FMR1)* have been associated with embryo quality [75,88]. In addition, the fertilization rate has been reported to be affected by variants in *ESR1*, *GDF-9*, and *HRG* [62,75,78], while no significant differences have been reported in variants of *FSHR*, *ESR2*, *AMH*, *AMHR*, *MTHFR*, *LHB*, or *LHCGR*, or for the C447T variant of *GDF-9* [25,26,29,40,67,76,79,89–91].

In ART using HRT protocols, the implantation rate is affected by the Asn680Ser variant of *FSHR* [40], while no significant effect has been found for variants in *MTHFR* or *LHB* [79,90]. Regarding the influence of gene variants on the pregnancy rate, the Asn680Ser variant in *FSHR* showed no effect in four studies [22,25,29,32], while contradictory results were found in two others, with an increased pregnancy rate reported in two opposite genotypes [26,40]. The −29 G>A variant, and its combination with 2039 A>G in *FSHR* [47], as well as the rs611246 variant in *Follicle Stimulating Hormone Subunit Beta* (*FSHB)*, have also been found to influence the pregnancy rate [11].

The *Pvu*II variant in *ESR1* showed heterogeneous results, with one study reporting an association with the pregnancy rate [60], while two others found no effect [61,62]. However, the combination of the *Pvu*II variant and the Asn680Ser variant of *FSHR* does affect the pregnancy rate [41]. No differences were found for any of the other variants studied in the *ESR1* and *ESR2* genes [61,62].

As for *AMH*, no significant differences in pregnancy rate were detected when studying the 146 G>T variant [67,68,70]. Regarding *AMHRH2*, the ISV 5–6 C>T and −482 A>G variants affect the pregnancy rate, while no significant differences were found for the other variants evaluated [67,68,70]. Additionally, the 546 G>A variant of *GDF-9* in women with a diminished ovarian reserve, Ala16Val variant of *Superoxide Dismutase 2* (*SOD2)*, Ser312Asn variant of *LHCGR* in women without PCOS or endometriosis, and low FMR1 allele in the CGG_n variant also affect pregnancy rate [51,71,75,88,92]. Other genes with variants influencing pregnancy rate include *Rhomboid Like 2* (*RHBDL2), LHB* and *SYCP2L* [11,93].

No significant differences were found for variants studied in *MTHFR*, *GDF-9*, *Folate Receptor Alpha* (*FOLR1)*, *Transcobalamin 2* (*TCN2)*,

Cystathionine Gamma-Lyase (*CTH*), *Solute Carrier Family 19 Member 1* (*SLC19A1*), *MCM8*, *METAP1D*, *NLR Family Pyrin Domain Containing 1* (*NLRP1*), *PRIM1*, *RNF44*, *TDRD3*, *TLK1*, *TMEM1508*, or *UIMC1* [11,68,76,80,82,91,94]. Pregnancy loss has been associated with the combination of the 1816C/delC and 1841 G>A variants of *FOLR1* [94], while no effect on the rate of pregnancy loss was found for other *FOLR1* variants, or for those in *MTHFR*, *LHB*, *TCN2*, *CTH*, *SLC19A1*, or *LHCGR* [71,80,94]. Finally, the live birth rate is affected by the −29 G>A variant and the combination of the 2039 A>G and −29 G>A variants of *FSHR* [47], while no effect has been reported for variants studied in *AMH*, *AMHR2,* or *LHCGR* [70,71].

In summary, variants in *GDF-9* and *FMR1* have been associated with embryo quality, while fertilization rate may be affected by variants in *ESR1*, *GDF-9*, and *HRG*; most other commonly studied genes show no effect. Implantation and pregnancy rates are mainly influenced by *FSHR* variants, particularly Asn680Ser and −29 G>A, as well as specific *FSHR* haplotypes, as well as by *FSHB* variants, although results are sometimes inconsistent. Combined variants across *FSHR* and *ESR1* also modulate pregnancy outcomes. *AMH* variants show no effect, whereas some *AMHR2* variants are associated with pregnancy rate. Additional associations have been reported for variants in *GDF-9*, *LHCGR*, *FMR1*, *SOD2*, *LHB*, *SYCP2L*, and a few other genes. Pregnancy loss has been linked only to specific *FOLR1* variant combinations, and live birth rate appears to be influenced by *FSHR* variants, with no consistent effects observed for *AMH*, *AMHR*, or *LHCGR*.

3.2.3. Polycystic ovary syndrome

PCOS is a multifactorial endocrine disorder characterized by oligo-anovulation, hyperandrogenism, and the presence of polycystic ovaries. In addition, PCOS is often associated with other reproductive disorders [95]; therefore, most articles related to pharmacogenomics in this disease address the effect of drugs on ovarian function. Significant results related to PCOS are summarized in Table 2, whereas the results of all the studies considered are included in Supplementary Table 5.

Regarding COS treatments in women with PCOS, follicle development, oocyte number, and basal E_2 levels are affected in $(TTTA)_7$ carriers of *CYP19* and responsiveness to recombinant FSH (rFSH) is affected by the Ala307Thr variant in *FSHR* when using the gonadotropin-releasing hormone (GnRH) agonist protocol [96,97]. In turn, the Asn307Ser variant in *FSHR* has been related to a reduced odds of ovulation after clomiphene treatment and resistance to such drug—a drug administered to induce ovulation treatment [98]. Finally, no effect on ovulation per cycle and per patient, free androgen index, or sex hormone-binding globulin (SHBG) levels has been found for variants in *Serine/Threonine Kinase 11* (*STK11*), *ESR1*, *Cytochrome P450 Family 2 Subfamily C Member 9* (*CYP2C9*), *Cytochrome P450 Family 2 Subfamily D Member 6* (*CYP2D6),* or *D19S884,* a microsatellite repeat in intron 55 of the *Fibrillin-3* (*FBN3*) gene [99].

Although metformin is used in patients with PCOS to address metabolic dysfunction, its effect on ovarian function according to gene variants has also been evaluated. Reproductive hormone levels are affected by the Gly972Arg variant in *Insulin Receptor Substrate 1* (*IRS-1*), ovulation per cycle by the rs8111699 variant in *STK11*, and free androgen index changes by the rs741765 variant in *STK11* and rs1934963 variants in *CYP2C9* [99,100]. In addition, no association between menstrual characteristics, ovulation outcomes, and/or SHBG levels have been reported for *Organic Cation Transporter 1* (*OCT1*), *ESR1*, *CYP2D6,* or *D195S884* variants in women treated with metformin [99,101]. Finally, the effect of several variants on the combined use of clomiphene and metformin has been investigated, showing that the *Pvu*II variant in *ESR1* affects ovulation per cycle and the A8/X;XX variant in *D19S884* influences changes in SHBG [99].

In closing, in women with PCOS undergoing COS, variants in *CYP19* and *FSHR* influence follicular development, oocyte number, hormone levels, and responsiveness to rFSH, while the Asn680Ser variant in *FSHR* is associated with reduced ovulation and clomiphene resistance. No significant effects have been reported for several other genes involved in steroid metabolism and hormone regulation. For metformin treatment, variants in *IRS-1*, *STK11*, and *CYP2C9* affect reproductive hormones, ovulation rates, and androgen levels, whereas no associations have been found for multiple other variants. Combined clomiphene–metformin therapy is also modulated by specific *ESR1* and D19S884 variants affecting ovulation and SHBG levels.

4. Discussion

The results presented in this review demonstrate that genetic variants have a strong influence on the efficacy, drug dosage, and side effects of drugs used in the field of female infertility. These findings support the implementation of personalized (precision) medicine based on the genetic profile of women in clinical practice. They also highlight the need for further clinical studies to translate this knowledge into customary use.

Pharmacogenetics is an emerging discipline that allows personalized treatment strategies based on genetic variability [102]. A lot of effort has been put into the translation of pharmacogenetic information into routine clinical practice. An example is the publication of genotype-based drug guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIP) or incorporation of pharmacogenetic information on approved drug labels by several drug regulatory agencies [103,104]. Moreover, pharmacogenetic testing is becoming increasingly accessible due to the growing affordability of sequencing technologies [105].

However, its implementation in female reproductive health and infertility is limited, except in medical fields such as oncology or psychiatry where it has already shown significant benefits [106,107]. For example, a recent study demonstrated that pharmacogenetic-guided treatment in psychiatry resulted in a significant reduction in side effects, number of hospitalised days, and costs [108]. Another example shows that dose adjustments of fluoropyrimidines —drugs employed to

Table 2
Pharmacogenetic variants that significantly affect drug response in polycystic ovarian syndrome for controlled ovarian stimulation. The treatment, gene symbol, pharmacogenetic variant, number of patients included in the study, outcome, and the reference of the study are presented. The alleles or genotypes that account for drug response variability are shown in parentheses.

Treatment	Gene	Variant	N	Outcome	Reference
Leuprolide + rFSH + hCG	CYP19	(TTTA)n	132	((TTTA) 7 carriers): ↓E2 basal. (Homozygous (TTTA)7): ↓ large folicles and oocyte number	(96)
Buserelin + FSH + hCG	FSHR	Ala307Thr (rs6165)	40	(Ala307Thr):↑ responsiveness to rFSH.	(97)
Clomiphene		Asn680Ser	193	(Ser/Ser): ↑ Clomiphene resistant and ↓ odds ratio of ovulation.	(98)
Metformin	IRS-1	Gly972Arg	60	(G972A-negative): ↓ LH, DHEAS, total testosterone and FTI after treatment.	(100)
	STK11	rs8111699	98	(C allele): ↓ ovulation per cycle.	(99)
		rs741765	98	(C/T): ↑ FAI change.	(99)
	CYP2C9	rs1934963	98	(C/C): ↑ FAI change.	(99)
Clomiphene + Metformin	ESR1	*Pvu*II (rs2234693)	112	(C/C): ↑ ovulation per cycle.	(99)
Clomiphene + Metformin	D19S884	A8/X; XX	112	(X/X): ↑ SHBG change.	(99)

treat several types of tumours—based on DPYD genotype, resulted in reduced drug toxicity when implemented in routine clinical practice [109,110].

Nevertheless, pharmacogenetics has not yet been applied in routine clinical practice in the context of female reproductive health, likely because infertility has historically not been considered a disease and other life-threatening illnesses were prioritized [111]. However, the WHO does recognize infertility as a disease [112]. Moreover, infertility is associated with high levels of stress and anxiety and ART is a mentally, physically, and economically challenging process. Therefore, addressing pharmacogenetics in the context of infertility should be a priority for the scientific community [113]. Fortunately, current studies are highlighting the potential for implementing pharmacogenetics in ART clinics. For example, a recent work demonstrated that personalized FSH prescriptions increased cumulative pregnancy and live birth rates compared with standard FSH prescription based solely on clinical parameters [114].

COS protocols are usually designed based on several predictive markers of ovarian response such as body mass index, age, ovarian reserve, or hormonal levels [115,116]. However, this approach often fails to accurately predict COS treatment outcomes [117] and it has been proposed that genetic variants may play a key role in ovarian response to such treatments [118]. The results obtained in this review suggest that the translation of pharmacogenetics into clinical practice in the field of female infertility could lead to relevant improvements in treatment outcomes and patient quality of life. For instance, early prediction of ovarian response to COS treatment based on genetic variants could improve treatment management, which is especially important since modifying the COS protocol after day 7–8 might lead to development of a heterogeneous cohort of follicles [118].

Therefore, tailoring COS protocols to individual genetic profiles could potentially increase both the number and quality of oocytes retrieved per cycle. Additionally, early identification of genetic variants influencing COS treatment response, especially in women suffering PCOS, a disorder related with hyper-response, could reduce the occurrence of OHSS [45].

Consistently, *FSHR* is the most studied gene in pharmacogenetic evaluations of COS treatment. Moreover, some existing reviews of pharmacogenetics in infertility have focused exclusively on this gene [118–120]. However, this review extends beyond *FSHR*, encompassing variants in other genes related to sex hormone function (*ESR1*, *ESR2*, *AMH*, and *LHB*, etc.) that affect COS response. This is unsurprising given the nature of hormonal changes induced by COS treatment and the administration of sex hormones and their agonists or antagonists in HRT [122]. For example, the presence of the v-betaLH variant in *LHB* gene has been associated with reduced oocyte retrieval and maturation. v-betaLH is caused by a doublet of SNPs resulting in two amino acid substitutions in the LH beta subunit (*LHB* Trp8Arg and *LHB* Ile15Thr). The LHB 15Thr introduces an additional glycosylation site to v-betaLH, which is likely to alter the serum half-life of LH and, consequently, its bioactivity [121]. This altered biological activity may account for the observed negative impact of v-betaLH on COS performance.

Additionally, PCOS and OHSS also show a strong dependence on regulation by sex hormones [123,124]. Therefore, it is expected that genetic variants of these genes, which alter their function, would influence drug responsiveness. As an example, the rs1801133 polymorphism in the *MTHFR* gene, which has been associated with an increased risk of OHSS, encodes a key enzyme involved in folate (vitamin B9) metabolism. This enzyme catalyzes the conversion of folate to its biologically active form, 5-methyltetrahydrofolate (5-MTHF), which is essential for DNA synthesis and amino acid metabolism. The rs1801133 polymorphism results in an alanine-to-valine substitution, leading to reduced enzymatic activity and potentially elevated homocysteine levels. Hyperhomocysteinemia has been linked to vascular dysfunction and thrombotic disorders, which is biologically consistent with the pathophysiology of OHSS, a condition characterized by intravascular fluid depletion, hemoconcentration, and an increased risk of thrombosis [86,125].

Other important groups of genes evaluated in this review include those related to drug metabolism, such as the CYP family, and drug transport, such as the Solute Carrier Organic Anion Transporter (SLCO) family [126]. However, our search identified only one or two gene from each of these families associated with infertility, which highlights the need for additional pharmacogenetic studies in this field—especially since these enzymes, which regulate absorption, distribution, metabolism, and excretion (ADME) processes, strongly influence the pharmacokinetics of the studied drugs [127]. Notably, the $(TTTA)_7$ variant of the aromatase *CYP19* gene, which consists of seven TTTA repeats within an intronic region, has been associated with lower E2 levels in PCOS patients. This observation is biologically plausible, as a lower number of TTTA repeats has been linked to reduced aromatase activity, resulting in decreased conversion of androgens to estrogens. Consequently, reduced E2 levels may contribute to smaller follicular size and a lower number of oocytes retrieved during COS [128].

Some of the variants included in this systematic review were also reported in previous reviews published by Altmäe et al. in 2011 and Lledo et al. in 2014 [116,129]. However, in this work we provide updated information on pharmacogenetics in the field of female infertility. Moreover, we aimed to include pharmacogenetic studies of other relevant disorders related to infertility, but only identified studies addressing pharmacogenetics in PCOS. In this context, we note the absence of pharmacogenetic studies focused on other relevant disorders that have a strong influence on reproductive outcomes such as endometriosis or uterine fibroids, among others, and encourage researchers to explore these areas further.

Endometriosis is a chronic inflammatory disease associated with pelvic pain and infertility. The efficacy and duration of pain relief with current treatments is limited in some women due to a lack of response or poor tolerability [130]. Therefore, the implementation of pharmacogenetics in the management of endometriosis could potentially improve reproductive outcomes. As for uterine fibroids, although hysterectomy is the main procedure used to treat the disease, pharmacological options are often used to preserve fertility, most of which rely on HRT [131]. As shown in this systematic review, genetic variants in hormone receptors affect drug response; hence, it would not be surprising that efficacy of HRT for uterine fibroids is also influenced by genetic variants. However, HRT is also used for endometrial preparation in IVF, and none of the studies we found assessed genetic variant-related drug response in this context of infertility, thereby highlighting significant gaps of pharmacogenomic research within the field of IVF.

To the best of our knowledge, this is the first systematic review to comprehensively examine the role of pharmacogenetics in the field of female infertility, not only covering the response to COS treatments, but also addressing other key infertility treatments such as HRTs and conditions that might affect reproductive outcomes. The works included in this review confirm the lack of pharmacogenetic studies in this field, the key role of genetic variants in drug response, and the existence of specific knowledge gaps. However, we also found heterogeneous results among the included studies, likely because of differences in study design. In fact, variations in design parameters may explain the absence of significant associations in some studies, especially when other studies did find them.

In addition, population-level genetic differences, including allele frequency variation, may influence findings between cohorts and could explain discrepancies across studies. In this regard, additional factors such as departure from the Hardy–Weinberg equilibrium might have affected population comparisons in these studies. This equilibrium reflects the relative allele frequencies within a population according to the evolutionary forces operating. When disequilibrium is observed, it may reflect either technical issues (e.g., genotyping errors) or biological phenomena (e.g., population stratification, inbreeding, or selective pressures). Therefore, the presence of disequilibrium should be

considered and calculated because it introduces bias and limits the interpretability of genetic findings. Other factors contributing to population heterogeneity include variations in treatment protocols, concomitant drug use, and the comparison of study cohorts from different ethnic backgrounds.

5. Conclusions

This is the most comprehensive systematic review to date examining the influence of gene variants on drug response in infertility. The implementation of personalized medicine based on genetic profiles has been shown to produce major benefits such as preventing adverse treatment effects and improving therapeutic efficacy, especially now that sequencing technologies are becoming increasingly accessible due to growing affordability.

On the one hand, this review encourages the scientific community to conduct further research to clarify the precise clinical effects of genetic variants and to design new studies assessing variants that could help improve current treatments in this field. On the other hand, we identified a lack of studies on infertility treatment responses and on conditions influencing ART outcomes such as endometrial preparation response to progesterone and estrogens, or therapies for benign uterine pathologies including endometriosis or uterine fibroids. We also highlighted the paucity of research on genes known to affect drug pharmacokinetics. Therefore, future studies should be carried out to address these gaps.

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CRediT authorship contribution statement

Patricia Sebastian-Leon: Writing – review & editing, Visualization, Data curation. **Patricia Diaz-Gimeno:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Asunta Martinez-Martinez:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Francisco José Sanz:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Pablo Garcia-Acero:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2025.118942.

Data availability

No data was used for the research described in the article.

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