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REVIEW PAPER

Role of ESR1 PvuII T/C variant in female reproductive process: A review

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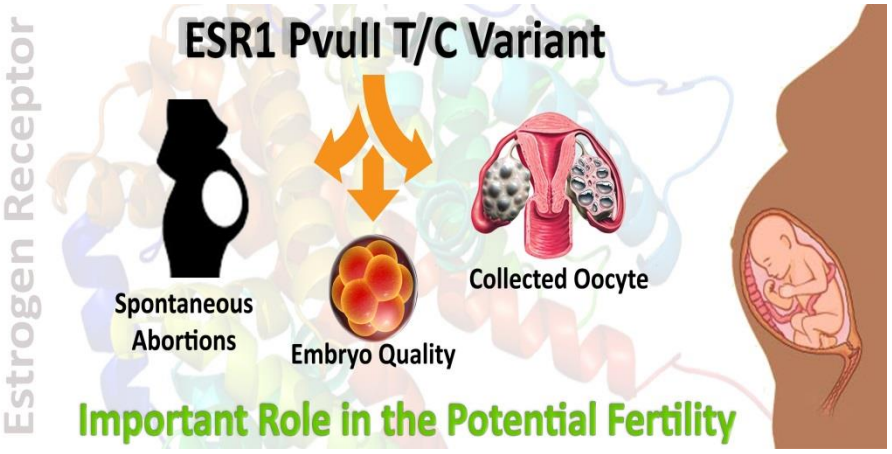
Highlights

- Estrogen hormone via its receptors (ERs) plays an important role in reproductive functions.
- PvuII T/C (rs 2234693) is a common genetic variant in ESR1 gene.
- PvuII T/C (rs 2234693) variant is related to the female reproductive functions.
- This genetic variant might have a significant role in the potential of females fertility.

Graphical Abstract



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Abstract

Estrogen hormone is involved in the process of reproduction by banding to estrogen receptors (ERs). The findings of previous studies showed the association of a common variant, PvuII T/C (rs 2234693), in ESR1 gene with different aspects of reproductive process in women. Thus, the present review focused on effect of this genetic variant on reproductive process in females. The results demonstrated that the variant of ESR1 PvuII T/C (rs 2234693) could be associated with numbers of collected oocyte, maturation and embryo quality, spontaneous abortions, pregnancy rate following in vitro manipulations, preeclampsia, predisposition to endometriosis and infertility. In conclusion, the present study suggested that ESR1 PvuII T/C (rs 2234693) variant might play an important role in potential of females fertility given to the various ethnic backgrounds. Nonetheless, further studies are required in order to determine the more exact role of this variant in the infertility of women.

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Introduction

Infertility, as a vital process in reproduction, affects many couples around the world. Although many genetic causes of infertility in women are known, female infertility's genetic basis is still largely unknown. In a complex disorder, such as female infertility resulting from genetic variations, the evaluation of single nucleotide polymorphism (SNP) as the most common these variations is significant. Sex hormone dysfunction can be one of the causes of female infertility (1, 2). Estrogen is a female sex hormone that plays a vital role in ovulation, oocyte maturation, implantation, pregnancy maintenance, and an essential role in ovulation, oocyte maturation, implantation, pregnancy maintenance, and fertility (3). This hormone is synthesized and secreted in ovarian follicular granulosa cells (4). Estrogen function is through binding to its receptor, the estrogen receptors (ERs). Thus, genetic disorders, including polymorphisms and variations of gene expression levels in the gene encoding ERs, can cause estrogen malfunction and, subsequently infertility (4, 5).

There are two types of ERs, ERα and ERβ, encoded by ESR1 and ESR2. ESR1 gene is located on chromosome 6q25.1 and has eight exons (6). ESR1 gene polymorphisms may effect its activity and are associated with female reproductive processes. PvuII T/C (rs2234693) is a common genetic polymorphism in the ESR1 gene in intron one due to T/C transition (7). This intronic variation may is related to the reproductive functions of females. Thus, the present review aims to evaluate the role of ESR1 PvuII T/C (rs2234693) polymorphism in different aspects of women's reproductive process.

Search Strategy

The present study has evaluated the association of the genetic polymorphism in the ESR1 gene with the female reproductive process. A search was conducted in the scientific journal's Web of Science and PubMed up to November 2020. The keywords of polymorphism, reproduction, infertility, female, SNP, ESR1, PvuII (rs2234693), and variant were used in this search. The relevant articles were selected and reviewed by the author.

Genetic polymorphisms

Today, genetic variations haveve attracted many researchers' attention because they can help to understand better the role of genetic factors in human health and diseases. Genetic polymorphisms are the most common form of genetic diversity and include a high percentage of human genetic variation (8). Polymorphisms can occur in both coding and non-coding sequences of the genome. Since only about 3 to 5 percent of human DNA sequences are coded for protein production, non-coding regions' changes are more common than coding regions. Polymorphisms of coding regions mainly interest researchers because they are more likely to interest researchers because they are more likely to affect a protein's biological function. Sometimes, polymorphism may cause a specific disease and can also evaluate and isolate the disease-causing gene. Many polymorphisms do not affect cell function, but it is believed that they can predispose individuals to disease or affect drug response (9).

Thus, the analysis of polymorphisms in critical genes is one of the most exciting research topics in female infertility female genetics's genetics. Genetic polymorphisms in essential genes are considered potential risk factors that may affect women fertility. Many polymorphic variants have been reported in female infertility, but not all studies have shown the same results. The main reasons for these differences are the study's size and composition, the techniques used, the type of polymorphism, the heterogeneity of female infertility phenotypes, ethnic differences, and geographical area that contribute to genetic variation. The phenotypic effects of gene polymorphism are modulated by other genetic and environmental factors, an example of gene-environment interaction. Therefore, it is possible that genetic polymorphisms with a specific genetic background or environmental factors can affect fertility potential in the female.

ESR1 PvuII T/C (rs2234693) variant and the process of female reproductive

ESR1 is a very polymorphic gene, in which most of the 44,710 ESR1 variants (97.8%) occur in intronic regions (10). The ESR1 genetic variants are associated with various diseases including cancer, severe preeclampsia, endometriosis and infertility (11, 12). Moreover, some of the variants of the ESR1 gene are related to the disorders in reproductive processes (10, 13, 14). Based on the results of the studies, ESR1 PvuII T/C (rs2234693) polymorphism can be associated with controlled ovarian hyperstimulation, pregnancy rate following in vitro fertilization, predisposition to endometriosis, spontaneous abortions, preeclampsia and infertility (5, 7, 10, 11) (Figure 1). The polymorphism of PvuII T/C (rs2234693) can aaffect the expression levels of gene and may with other mutations of ESR be linkage and probably influence ER function (7, 12). Moreover, in the promoter of ESR1 gene, the genomic organization is very complex and intermittent sites to splice exist in multiple promoter sequences. This can produce the various estrogen protein transcripts that subsequently can influence the generation and function of ESR protein. Thus, this variant may impact the normal function of estrogen and its receptors.

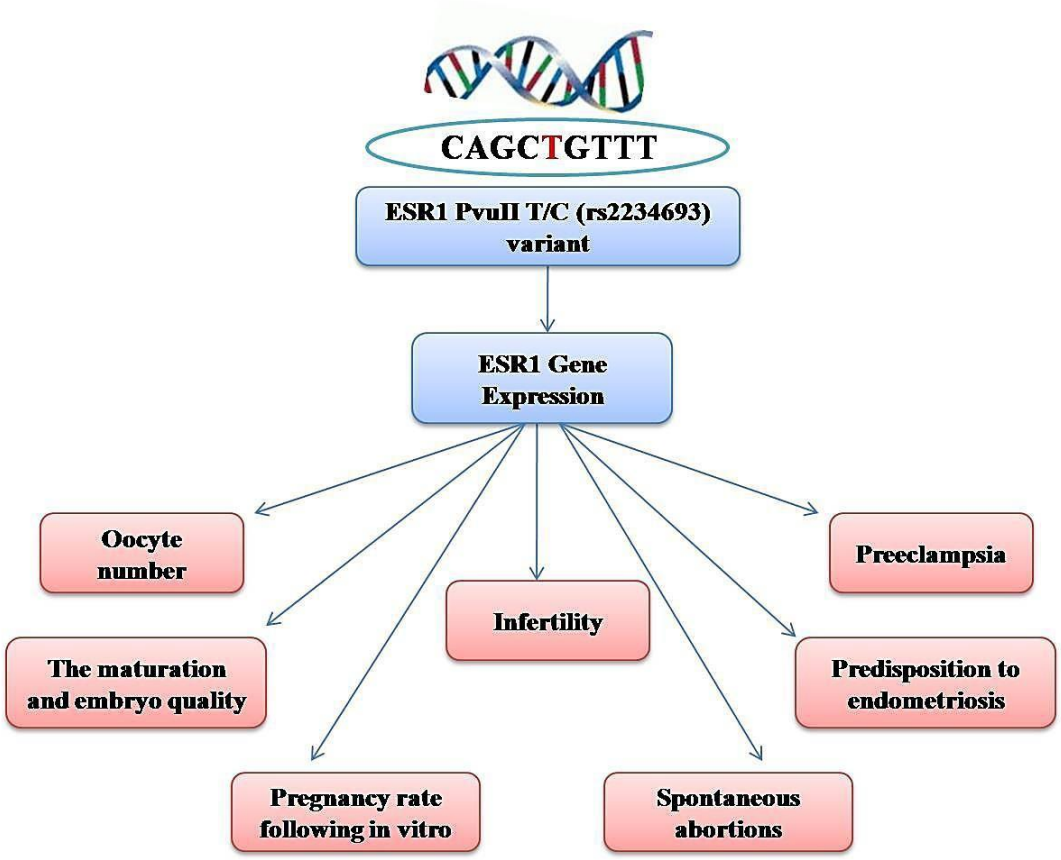

Figure 1. The probable effects of ESR1 PvuII T/C variant on various aspects of the female reproductive.

The different studies have investigated PvuII T/C (rs2234693) polymorphism with the various aspects of reproduction in females (Table 1)**.** For example, Liaqat et al. suggested that PvuII T/C (rs2234693) variant is strongly related to infertility risk in the Pakistanian population (5). Moreover, Ayvaz et al., demonstrated that between ESR1 genotypes and infertility risk and some IVF parameters such as maturation and fertilization rates exist a significant relationship (4). Recently, Pagard et al. showed that in women population in northwest of Iran, rs2234693 polymorphism may related to implantation failure (15). Also, it has been reported that in Indian population, in the women under IVF-treated, the genotypes combination of rs2234693 with some genotypes may decrease a negative outcome (16). In another study by Boudjenah et al. suggested that in a person under IVF treatment, ESR-α variant have related to ovarian response to follicle stimulating hormone (17).

Table 1. The characteristics of included studies in this review.

Author	Method	Final Result
Molvarec et al., (11)	PCR-RFLP	The risk of severe preeclampsia is enhanced in the carriers of homozygous T-A haplotype in PvuII and XbaI variants.
Ayvaz et al., (4)	PCR-RFLP	ESR1 PvuII variant is associated with risk of infertility
Song et al., (18)	PCR-RFLP	In women under IVF-treat , the variants combining PvuII and FSHR307 are the marker in predicting poor response of ovarian
Liaqat et al., (5)	PCR-RFLP	ESR1 PvuII (rs2234693) variant is associated with infertility risk.
Swaminathan et al., (7)	PCR-RFLP	PvuII variant demonstrated no significant association between studied groups.
Ganesh et al., (16)	PCR and Sanger Sequencing	Decreased of negative outcome in the women under IVF-treated in the presence of the genotypes combination of rs2234693 with some genotypes
Bahia et al., (10)	Allelic exclusion method on Real-time PCR	ESR1variant (rs2234693) is associated with risk enhancement of recurrent pregnancy loss.
Qin et al., (15)	Tetra-ARMS PCR	ESR-α (rs2234693) variant might have a significant role in the implantation failure
Ramesh et al., (19)	PCR-RFLP	PvuII (rs2234693) variant can be a potential biomarker in postmenopausal women with low levels of circulating estradiol

Bahia et al., also showed that specific ESR1variant (rs2234693) significantly is associated with risk enhancement of unexplained recurrent pregnancy loss in North African Arab population (10). In addition it has been demonstrated that the severe preeclampsia risk is enhanced in the individuals with homozygous T-A haplotype in PvuII and XbaI variants (11)**.** Another study showed the relationship between ESR1 and FSHR variants with the ovarian response to gonadotropin in females undergoing IVF treatment and the genotypes combining PvuII T/C and FSHR307 introduced as markers to predicting the poor response of ovarian in these women (18)**.** Moreover, in a study on Indian women proposed the PvuII T allele as a potential biomarker in postmenopausal women with low levels of circulating estradiol (19). Inthe field of reproduction, especially infertility, various polymorphic variants have been reported, but not all reports have shown the same results (7, 20, 21). The primary reasons for these differences as above mentioned, are the size and composition of the study and the geographical area etc. The phenotypic effects of gene variants are moderated by other genetic factors and environmental factors, which is a clear example of gene-environment interaction in specific phenotypic development (22). Thus, it is likely that genetic variants, along with a specific genetic background or environmental factors, lead to the dysfunction in biological processes including reproduction process**.**

Conclusion

Infertility treatment is an essential issue in different populations, so the identification of genetic biomarkers in this field is important. Genetic polymorphisms in key genes can be important biomarkers in the female reproductive process. Based on previous studies, PvuII T/C (rs2234693) variant that occurs in intron 1 of ESR1 gene can be related to the reproductive disorders in women. In fact, this variant can associated with ovarian hyperstimulation, numbers of oocyte, pregnancy rate in vitro fertilization, spontaneous abortions, endometriosis, preeclampsia, the maturation and embryo quality and infertility in women. Therefore, targeting ESR1 PvuII T/C (rs2234693) variant due to the effects on reproductive process and its association with the environmental factors as a example of gene-environment interaction could be of great importance in the potential of female fertility.

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