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Genetic and Clinical Predictors of PCOS: Role of PON1 Q192R Polymorphism in Infertile Women at Nigerian Tertiary IVF Center

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder associated with oxidative stress and metabolic dysfunction. Paraoxonase1 (PON1), an antioxidant enzyme, exhibits functional polymorphisms that may influence PCOS susceptibility. This study investigates the association between the PON1 Q192R polymorphism and PCOS among Nigerian women.

Methods: A total of 90 women aged 25-40 years were recruited, comprising 50 infertile women with PCOS and 40 age-matched fertile controls. Genomic DNA was extracted from peripheral blood, and genotyping performed using PCR-RFLP with the Mbol restriction enzyme. A subset of samples was validated via Sanger sequencing. Clinical parameters, including body mass index (BMI) and family history of infertility were recorded. Statistical analysis included Chi-square tests for genotype and allele frequencies, and binary logistic regression to assess independent risk factor.

Results: The frequency of RR genotype and R allele was significantly higher in women with PCOS compared to controls ($p< 0.01$). Women with the RR and QR genotype had increased risk of PCOS (OR = 5.33, 95% Cl: 1.72 – 16.45 for RR and OR = 4.38 for QR, 95% Cl: 1.82 – 10.51). Higher BMI and a positive family history of infertility were also significantly associated with PCOS ($p< 0.05$). Sequencing confirmed 100% concordance with PCR-RFLP results.

Conclusion: The PON1 Q192R polymorphism, particularly the RR genotype, is significantly associated with PCOS in Nigerian women. Elevated BMI and family history of infertility further contribute to the risk, suggesting a multifactorial interaction in the pathophysiology of PCOS. These results back the function of oxidative stress-related genetic variants in reproductive disorders and warrant further large-scale studies.

Keywords: PON1, Q192R, Polymorphism, PCR-RFLP, PCOS, Infertility, Oxidative stress, Nigeria.

INTRODUCTION

Infertility is believed to stem from multiple contributing factors, encompassing genetic and epigenetic abnormalities, the presence of reactive oxygen species, or endocrine disruption resulting from environmental pollution [(1)]. In females specifically, infertility can arise from diverse causes, including genetic irregularities like chromosomal defects or single gene mutations, as well as obesity. While there is no specific hereditary disorder directly linked to female infertility, lifestyle (obesity), genetic markers and variations have been associated with the condition. Single nucleotide polymorphisms (SNPs) in certain genes such as paraoxonase 1 (PON1) Q192R variant have been identified in individuals with PCOS and unexplained infertility, suggesting their involvement in the development of the condition [(2)].

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder, impacting an estimated 5-10% of women of reproductive age globally. It stands as a primary contributor to anovulatory infertility [(3)]. This syndrome is characterized by hyperandrogenism, persistent anovulation, and a polycystic appearance of the ovaries. PCOS develops from an excess of androgens, which promotes the accumulation of abdominal and visceral adipose tissue.

Which in turns, leads to compensatory hyperinsulinemia, insulin resistance (IR), and further stimulates androgen secretion by both the ovaries and adrenal glands [(4)]. The connection between hyperinsulinemia, IR, and hyperandrogenism, in relation with the dysfunction of the hypothalamic-pituitary, leads to the dysfunction of the ovaries resulting in anovulation and infertility [(5)]. Anovulation is a common cause of female infertility accounting for about 25% of couples and PCOS being the major cause of anovulation. PCOS is also associated with a range of metabolic disturbances, including insulin resistance, dyslipidemia, and increased oxidative stress [(6)]. These metabolic alterations not only contribute to reproductive dysfunction but also increase long term risk of cardiovascular disease and type 2 diabetes mellitus in affected women [(7)].

Women diagnosed with PCOS consistently demonstrate an elevated predisposition to a range of adverse pregnancy-related outcomes. This includes a significantly heightened risk of miscarriage, along with the increased likelihood of developing various other gestational complications, most notably the onset of gestational diabetes. These risks underscore the importance of specialized management for pregnant

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individuals with PCOS [8]. Research consistently indicates that oxidative stress plays a significant role in mediating the development of insulin resistance and the elevation of androgen levels that are commonly observed in patients with PCOS. This suggests a complex interplay between oxidative imbalance and the hormonal and metabolic disturbances characteristic of this endocrine disorder [9].

Oxidative stress is central to the pathophysiology of PCOS. It contributes to follicular dysfunction, compromises oocyte quality, and drives inflammatory responses within ovarian tissue [10]. This condition arises when the production of reactive oxygen species (ROS) and other radical species overwhelms the body's antioxidant defenses. Within the body, oxidative stress can lead to lipid peroxidation, structural and functional alterations in proteins and DNA, promote cell death, and increase the risk of cancer and other chronic diseases [11]. A delicate balance between antioxidants and ROS is essential throughout the female reproductive system. An increase in ROS in this system can result in various gynecological conditions, including infertility. One contributing factor to infertility is the overproduction of ROS within the peritoneal cavity, combined with the heightened sensitivity of gametes to ROS-induced damage [12]. Elevated levels of ROS, free radicals, and lipid peroxides create oxidative stress, which in turn negatively impacts fertilization rates, oocyte penetration, cell viability, and ultimately, implantation. All these factors collectively contribute to infertility.

Paraoxonase 1 (PON1) is an enzyme predominantly synthesized in the liver and is associated with high-density lipoprotein (HDL) particles. It plays a vital role in lipid metabolism and possesses significant antioxidant properties, which are believed to protect against oxidative stress and inflammation. The PON gene family comprises three genes: PON1, PON2, and PON3, all are located on the long arm of chromosome 7 [13]. PON1 was the first member of this gene cluster to be discovered. Alterations in the size and shape of HDL particles can profoundly affect PON1's binding affinity and stability, leading to a diminished antioxidative capacity [14].

Notably, PON1 prevents the oxidation of low-density lipoprotein (LDL) and hydrolyzes lipid peroxides, thereby offering protection against oxidative damage [15]. The Q192R variant in the paraoxonase 1 (PON1) gene is a common polymorphism that leads to an amino acid substitution from glutamine (Q) to arginine (R) at position 192 of the PON1 protein. This variant has been extensively studied due to its impact on PON1 enzymatic activity and its potential implications for various health conditions, including female infertility [16]. Some studies have suggested that the altered enzymatic activity of PON1 associated with the Q192R variant is believed to result in compromised antioxidant and anti-inflammatory functions, which may contribute to ovarian dysfunction, impaired folliculogenesis, and reduced oocyte quality, leading to infertility or subfertility [17]. The activity and expression of PON1 are significantly influenced by genetic polymorphisms, particularly the glutamine (Q) to arginine (R) substitution at position 192, known as Q192R (rs662) [18]. This polymorphism results in two common isoforms of the enzyme substrate specificities and enzymatic activities. The R allele has been associated with higher paraoxonase activity but potentially lower arylesterase activity compared to the Q allele, indicating differential functional consequences [13].

Emerging scientific evidence indicates that PON1 polymorphisms may play a role in modulating an individual's susceptibility to various diseases associated with oxidative stress. These conditions include significant public health concerns such as cardiovascular disease, diabetes and specifically female infertility. This suggests that genetic variations in the PON1 enzyme's structure or function could influence an individual's vulnerability to these oxidative-stress-mediated health challenges [19]. It is critical to note that the relationship between the Q192R variant, PON1 activity, and female infertility is still an active area of research, and findings have been somewhat inconsistent across different studies. Further investigations are required to fully understand the mechanisms underlying this association [20]. In addition, the clinical implications of the Q192R polymorphism in the context of PCOS remain poorly understood. A few studies have explored the association between PON1 gene variants and PCOS risk, with mixed findings regarding the role of the Q192R polymorphism in oxidative stress regulation and its impact on reproductive outcomes.

Given the complex relationship between oxidative stress, PON1 activity, and reproductive dysfunction in PCOS, investigating the serum level of Q192R variant polymorphism as a potential biomarker is of significant clinical interest. The objective of this study was to assess the distribution and serum expression of PON1 Q192R variant in infertile women with PCOS and assess its utility as a biomarker for disease susceptibility and severity. Understanding the genetic foundations of PON1 activity in PCOS could provide valuable insights into the molecular mechanisms of infertility and pave the way for personalized therapeutic strategies.

MATERIALS AND METHODS

Subjects: In this study a total of 90 women were involved which were then split into two groups. Group A of 50 infertile women with PCOS and group B of 40 fertile women as control group. The patients and controls were drawn from the same population of women attending National Hospital Abuja.

Inclusion criteria: All the patients were diagnosed for causes of infertility, all patients had a hysteroscopy, and were negative of chronic endometriosis. The infertile group were established to have PCOS according to the European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) Rotterdam 2003 criteria. At least two out of the three features must be present (1) oligomenorrhea and/or anovulation, (2) Clinical and/or biochemical signs of hyperandrogenemia, and (3) PCOS identified through ultrasound. The study controls were 25-40 age match, who were menstruating regularly, without any biochemical or clinical cause of infertility with normal ovaries by ultrasound.

Exclusion criteria: Participant on any form of medication. Infertile women of known cause, such as male factor, hormonal, structural, coagulation and immunological abnormalities.The investigations of the patients were completed before their enrollment into the study.

Sample collection: The peripheral blood sample (2-3 ml) were collected from women who were diagnosed with PCOS, before the patients commence down regulation (IVF treatment). The samples were collected in EDTA-coated tubes, which were used for the DNA extraction. The samples were processed by centrifugation and the supernatant was removed using a sterile Pasteur pipette and the serum was aliquot into two cryogenic vials and frozen at about -80 °C until when ready for the assays. The vials were labeled for easy identification of each of the participating patients and record was taken. The serum was used to run the DNA extraction.

Genotyping: Genomic DNA was isolated from serum samples leveraging on Accu prep Genomic DNA extraction kit from (Accupower Hotstart PCR premix (Bioneer) according to the manufacturer's protocols. PCR Amplification of PON1 Q192R Region. A specific region of the PON1 gene encompassing the Q192R polymorphism (rs662) was analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The following primers were used: rs662 (Q192R). Forward: 5'-GGG-ACC-TGA-GCA-CTT-TTA-TGG-C-3'. Reverse: 5'- CAT-CGG-GTG-AAA-TGT-TGATTC-C -3'. The PCR was performed with 20 µL reaction mixture. The 5'-3´ of oligonucleotide sequence of rs662 (Q192R) polymorphism sequence was GGG-ACC-TGA-GCA-CTT-TTA-TGG-C and 30 -50 sequence of oligonucleotide was CAT-CGG-GTG-AAA-TGT-TGATTC-C were used in polymerase chain reaction (PCR). The primers were designed by means of Oligo7 software (version 7.54, USA).

The PCR thermal conditions for PON1 were as follows: Pre- Denaturation at 95°C for 5minutes, cycle condition of 35 cycles for 40 seconds at 94°C, Annealing at 54°C for 40 seconds, Extension at 72 °C for 40 seconds. The products of PCR (238bp) were visualized on 3 % agarose gel stained with ethidium bromide and photographed under UV light box.The DNA was qualitatively analyzed by Gel electrophoresis then analyzed for restriction fragment length polymorphism (RFLP). 5 U of MboI restriction enzyme (New England Biolabs) was used to digest the DNA at the concern restriction site at position 192 in rs662 polymorphism amplicon. Sequencing was performed by (Inqaba Biotechnical Industries, Pretoria, South Africa). To validate the PCR-RFLP results, Sanger sequencing was performed on a subset of 30 DNA samples (10 for each genotype: QQ, QR, RR), using primers designed for the PON1 rs662 (Q192R) polymorphic site. Sequencing was conducted using forward and reverse oligonucleotide primers targeting exon 6 of the PON1 gene. Chromatogram analysis confirmed:

- Homozygous QQ (C/C): Cytosine peak at codon 192.2.
- Homozygous RR (G/G): Guanine peak.
- Heterozygous QR (C/G): Overlapping C and G peaks.

The sequencing results were 100% concordant with PCR-RFLP data, affirming genotyping accuracy.

Genotype identification: Chromas and BioEdit software were used to analyze the sequencing results. The Q192R polymorphism corresponds to a substitution of adenine (A) to guanine (G) at codon 192, resulting in a glutamine (Q) to arginine (R) amino acid change.

Genotype patterns:

- QQ (homozygous wild-type): single 238 bp band (no cut).
- QR (heterozygous): three bands at 238 bp, 175 bp, and 63 bp.
- RR (homozygous mutant): two bands at 175 bp and 63 bp.

Quality control: The assays for DNA extraction, PCR, and agarose gel electrophoresis were performed at the DNA Laboratory Ltd, Kaduna,Nigeria. And the product of PCR were sent for DNA sequencing at Inqaba Biotecnical Industry, South Africa, which validated the outcome of our PCR-RFLP results.

Ethical approval and consent to participate: All subjects signed informed written consents for using data before their enrolment into this study. This study was reviewed and approved by The Department of Health Research Ethics Committee (HREC) of National Hospital

Abuja with License number (NHA/EC/068/2022). The scope, nature, aims and objectives of this study were explained to the patients attending IVF center National Hospital, Abuja. All procedures were performed according to the Declaration of Helsinki.

Statistical Analysis

All statistical analysis were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Genotype and allele frequencies of PON1 Q192R polymorphism were determined by direct counting. Chi-square (x^2) tests were used to compare genotype and allele distributions between infertile women with PCOS and fertile controls. Hardy-Weinberg equilibrium was tested in both groups. Continuous variables such as age and BMI were expressed as mean ± standard deviation and analyzed using independent t-tests. The association between PON1 Q192R genotypes and PCOS was further evaluated using binary logistic regression, adjusting for potential confounders such as age, BMI, and family history of infertility. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

The present study comprised 50 infertile patients with PCOS and 40 fertile control subjects. The genotype frequencies of the PON1 Q192R polymorphism showed a significant difference between PCOS patients and fertile controls (Table 1).

Table (1): Genotype distribution of PON1 Q192R in infertile women with PCOS and fertile control

Genotype	PCOS Group (n = 50)	Control Group (n = 40)	p-value (Chi-square)
QQ (wild-type)	9 (18%)	24 (60%)	
QR (heterozygous)	27 (54%)	9 (22.5%)	
RR (homozygous mutant)	14 (28%)	7 (17.5%)	
Total	50 (100%)	40 (100%)	< 0.01

*Chi-square test used to compare genotype distributions between groups

In the PCOS group, the frequencies of QQ, QR, and RR genotype were 18%, 54%, and 28%, respectively, whereas in the control group, the frequencies were 60%, 22.5%, and 17.5%, respectively ($p < 0.01$). Figure (1) illustrated the genotype distribution of PON1 Q192R among PCOS vs fertile control groups, showing significantly higher QR and RR genotypes in the PCOS.

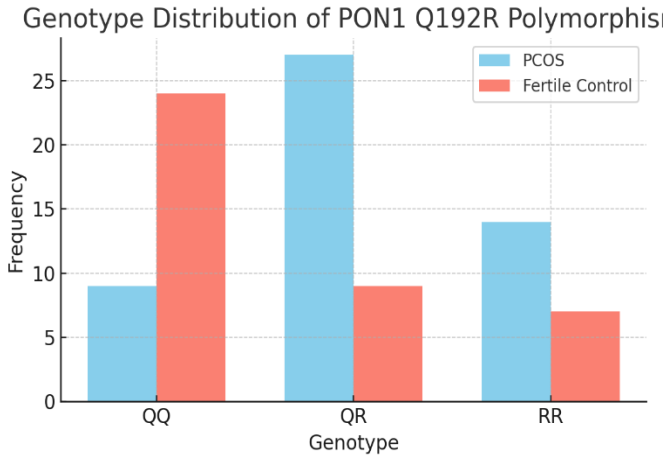

Figure (1): Distribution of PON1 Q192R genotypes in PCOS and control groups.

Figure (2) showed Agarose gel electrophoresis image that showed PON1 Q192R genotypes as determined by PCR-RFLP using MboI enzyme. Lane M: DNA marker (100 bp ladder); Lanes 1–2: QQ genotype (238 bp); Lanes 3–4: QR genotype (238, 175, 63 bp); Lanes 5–6: RR genotype (175, 63 bp). The QR and RR genotype were significantly more frequent among the women with PCOS. Genotyping of 192 Q/R was done by PCR-RFLP method (Figure 2).

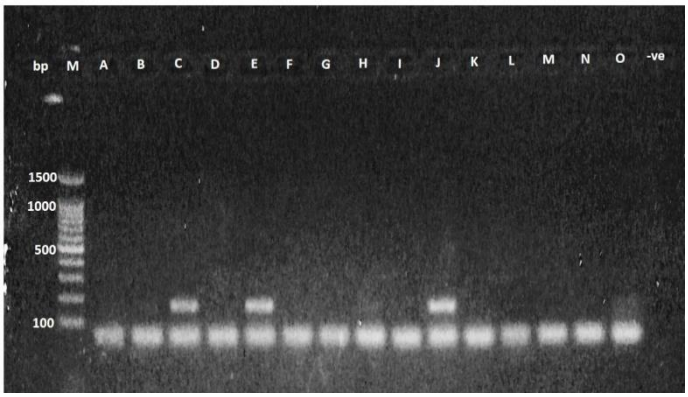

Figure (2): Genotyping of 192 Q/R done by PCR-RFLP method.

The allele distribution also differed significantly between groups (Table 2).

Table (2): Allele frequencies of PON1 Q192R polymorphism

Allele	PCOS Group (n = 100 alleles)	Fertile Control (n = 80 alleles)	p-value
Q	45 (45%)	57 (71.25%)	
R	55 (55%)	23 (28.75%)	< 0.01

*Chi-square test used to compare allele frequencies.

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The R allele was more prevalent in the PCOS group (55%) compared to the control group (28.75%) ($P < 0.01$), implying that the R allele might play a part in the development of PCOS. When stratified by age and BMI. PCOS patients with the RR genotype had significantly higher BMI (30.5 ± 2.5) and were more frequent in the 30 – 40 age group. A positive family history of infertility was reported more often in PCOS individuals with QR and RR genotypes compared to controls ($p < 0.01$). These findings support a multifactorial influence, where both genetic and clinical risk factors contribute to PCOS susceptibility (Table 3).

Table (3): Genotype distribution by Age, BMI, and family history

Group	Genotype	Age 20-29	Age 30-40	BMI Mean ± SD	Family History Positive	Family History Negative	p-value
PCOS	QQ	4	5	30.1 ± 2.9	3	6	< 0.05
PCOS	QR	13	14	29.8 ± 3.1	12	15	< 0.05
PCOS	RR	3	7	30.5 ± 2.5	7	3	< 0.01
Fertile Control	QQ	15	9	24.0 ± 2.6	4	20	< 0.01
Fertile Control	QR	3	6	24.3 ±	3	6	< 0.01
Fertile Control	RR	1	6	24.5 ± 2.9	1	6	NS

Table (4): Logistic regression analysis confirmed R allele carrier and BMI as an independent predictor of infertility in PCOS

Variable	Adjusted OR	95% Cl	p-value	Interpretation
QR Genotype	4.38	1.82 – 10.51	0.001	Significantly associated with PCOS
RR Genotype	5.33	1.72 – 16.45	0.004	Strongly associated with PCOS
BMI (per unit increase)	1.21	1.08 – 1.36	0.001	Higher BMI increases PCOS risk
Family History of Infertility	3.07	1.29 – 7.28	0.011	Significant independent predictor
Age (30 – 40) vs (20 – 29)	1.18	0.56 – 2.51	0.66	Not significantly significant

Figure (3): Represents sequencing chromatograms validating the PON1 rs662 (Q192R) genotypes. QQ genotype shows homozygous C peak, QR genotype shows overlapping C/G peaks, and RR genotype displays a homozygous G peak at codon 192. The chromatograms confirm accurate genotyping by PCR-RFLP.

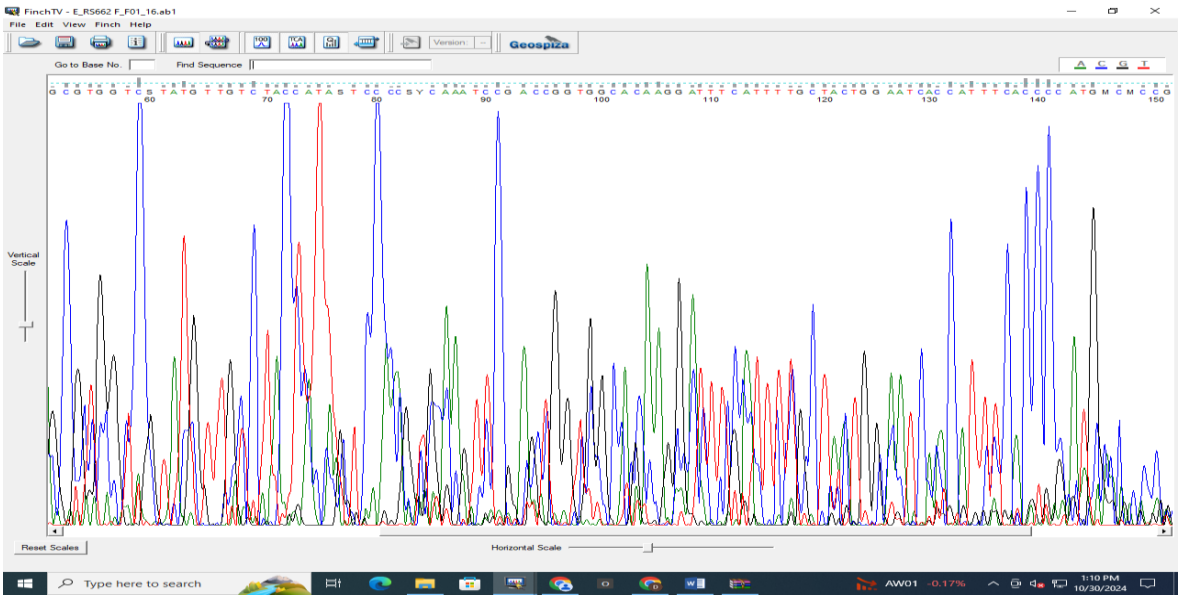

Figure (3): Sanger sequencing analysis for rs662 polymorphism of QQ, QR. and RR.

DISCUSSION

PCOS is a prevalent endocrine disorder with severe metabolic and reproductive consequence on affected women. Insulin resistance (IR), oxidative stress and obesity are common pathogenesis of PCOS. Numerous etiological factors have been involved in PCOS such as gene-gene interaction, or gene- environment interaction, although no consensus has been reached to rule out a particular genetic marker for PCOS. Identification of some specific variants in genes such as PON1 that may affect its expression or protein function helps to delineate the genetic architecture of this multifactorial disorder [(21)]. The genetic basis of PCOS was first established by **Cooper *et al.*** [(22)].

Paraoxonase 1 (PON1), an enzyme with antioxidative properties, play a vital role in the detoxification of lipid peroxides and protection against oxidative stress, which has been implicated as a key factor in the development of PCOS-related reproductive dysfunction. The Q192R polymorphism results in an amino acid substitution (glutamine to arginine) at position 192 that influences substrate specificity and enzymatic efficiency, with the allele typically exhibiting greater activity against some substrate but also differing in its protective capacity against lipid oxidation [(20)]. The association between oxidative stress and female infertility, particularly in conditions such as PCOS, endometriosis, and unexplained infertility, has been well documented [(23)]. Obesity is known to aggravate oxidative stress and insulin resistance, thereby altering the activity of PON1 and also increase the expression of other metabolic comorbidities. Patients diagnosed with PCOS have been demonstrated to present with an intrinsic pro-oxidant status. Notably, this oxidative imbalance appears to manifest independently of the presence of either insulin resistance or the broader metabolic syndrome, indicating a distinct pathophysiological component in PCOS [(9)].

Evidence from prior investigations has consistently and robustly documented a notable reduction in the enzymatic activity of **Paraoxonase 1 (PON1)** among individuals diagnosed with PCOS. This observed decrease in PON1 activity, which is crucial for antioxidant defense, has been specifically reported across distinct patient cohorts originating from diverse geographical regions, including Egypt [(24)], Saudi Arabia [(25)], and Turkey [(26)]. Such recurrent findings strongly suggest a potentially widespread and clinically significant association between altered PON1 function and PCOS pathophysiology.

The findings of this study indicated a significant association between the PON1 Q192R polymorphism and susceptibility to PCOS in infertile women. The QR and RR genotype were significantly more prevalent in the PCOS group compared to fertile controls. The R allele frequency was notably higher among PCOS risk, potentially through mechanisms involving oxidative stress and metabolic dysfunction. These findings are consistent with prior studies. For example, a study by **Jiang *et al.*** [(16)] also reported a higher prevalence of the R allele and RR genotype among women with PCOS in an Asians and Caucasians population, suggesting a link between the polymorphism and increased oxidative stress levels. Similarly, **Liu *et al.*** [(27)] observed that women with PCOS had significantly reduced paraoxonase 1 enzyme activity, and this reduction was particularly pronounced in individuals carrying the RR genotype, implying a functional relevance of the polymorphism. Our results support these associations, indicating that the PON1

Q192R polymorphism may contribute to impaired antioxidant defence in PCOS, thereby promoting ovarian dysfunction and metabolic complications. The current study improved upon this by using a well characterized cohort and incorporating additional clinical variables such as BMI and family history, which strengthened the observed associations.

The logistic regression analysis in our study confirmed that both OR and RR genotypes were independently associated with PCOS even after controlling for confounders. The increased odds (aOR = 4.38 for QR and aOR = 5.33 for RR) suggest a genotype-independent risk gradient, which is particularly compelling. Moreover, BMI and positive family history of infertility were also found to be significant predictors, supporting the notion that PCOS is a complex disorder influenced by both genetic and environmental factors. In contrast to some findings, **Dadachanji *et al.*** [28] specifically observed an association between the L55M polymorphism and PCOS, rather than the Q192R polymorphism. This divergence in findings is likely attributable to inherent variations in the genetic background or ethnic composition of the study populations examined. Importantly, the significant interaction between the RR genotype and higher BMI observed in this study supports the idea of gene-environment interplay, where genetic predisposition may exacerbate the impact of metabolic risk factors. This is consistent with the findings from **Shahrokhi *et al.*** [29] who reported that metabolic syndrome is more prevalent among PCOS patients with higher BMI and low antioxidant enzyme activity, pointing to the relevance of oxidative stress pathways.

This research examined the link between PON1 Q192R polymorphism and infertile women with PCOS, with a focus on reproductive age group (25 – 40 years). Our findings demonstrated a significantly higher frequency of the heterozygous QR genotype and R allele in the PCOS group compared to infertile controls without PCOS, suggesting a potential genetic contribution of this variant to PCOS. Women with PCOS exhibited significantly higher BMI, consistent with the known metabolic derangements associated with the syndrome. The significant difference in genotype distribution ($p = 0.045$) and allele frequency ($p = 0.032$) between the groups suggests a potential role of the PON1 Q192R polymorphism, particularly the R allele, in the pathophysiology of PCOS-related infertility. Our findings are consistent with previous reports indicating a possible link between the R allele and adverse reproductive outcomes in PCOS. For instance, the altered PON1 enzymatic profile may exacerbate oxidative stress in ovarian tissue, impairing folliculogenesis, oocyte quality, and endometrial receptivity-factors crucial for successful conception [17].

Another key finding was the significantly higher BMI among women with PCOS, which is consistent with the well-established relationship between obesity and PCOS. Elevated BMI may exacerbate insulin resistance hormonal imbalances, compounding the reproductive dysfunction in affected women. A number of earlier investigations have sought to assess the significance of PON1 polymorphisms in relation to PCOS and infertility, but findings varied. A research by **Wang *et al*.** [30] reported a higher prevalence of the R allele in women with PCOS, which is aligning with our current findings. Studies in PCOS women have found higher frequencies of the R allele, which correlate with altered lipid profiles and higher oxidative stress markers [31]. Moreover, the R allele has been linked to decreased arylesterase and paraoxonase activities, reducing the enzyme's ability to neutralize oxidative damage in ovarian tissue [32]. Our study strengthens the association by specifically focusing on infertile women, a subset of PCOS patients often exhibiting more severe phenotypes and metabolic disturbances.

The observed association between the PON1 Q192R polymorphism and PCOS may also reflect broader metabolic implications. PON1 is closely linked to HDL function and cardiovascular health, and its impairment has been associated with increased systemic inflammation and insulin resistance, both of which are prevalent in PCOS and negatively impact fertility [33]. It is therefore possible that PON1 Q192R polymorphism acts as both a marker and a functional contributor to PCOS and reproductive dysfunction. Furthermore, although the Q192R polymorphism is not a direct causative factor, it may serve as a genetic marker for increased susceptibility to PCOS-related infertility [15]. This is particularly relevant in populations with a high prevalence of the polymorphism, suggesting a need for population-specific genetic screening strategies.

Importantly, our study adds to the growing body of evidence suggesting that genetic screening of antioxidants enzyme variants may have clinical utility in stratifying PCOS patients according to their risk for infertility. Identification of high-risk genotypes could guide personalized management strategies, including antioxidant therapy, lifestyle interventions aimed at reducing oxidative stress or earlier fertility referral.

LIMITATIONS

Despite the novel insights offered by our study, some limitations were acknowledged. The sample size was moderate, and larger multicentre studies are needed to confirm these associations. Moreover, enzyme activity assays were not conducted in this study, which would be useful for validating the functional impact of the PON1 genotype observed. Nevertheless, our findings provide a

strong rationale for further investigation into PON1 as a potential biomarker therapeutic target in PCOS.

CONCLUSION

This study demonstrated a significant association between PON1 Q192R polymorphism and susceptibility to PCOS among infertile women. Specifically, the QR and RR genotypes were found at significantly higher frequencies in PCOS patients compared to fertile controls, suggesting a potential role of this genetic variant in the pathophysiology of PCOS. Furthermore, elevated body mass index (BMI) and a positive family history of infertility were identified as independent predictors of PCOS, reinforcing the multifactorial nature of the syndrome. Our findings support the hypothesis that oxidative stress-related genes such as PON1 may contribute to the complex aetiology of PCOS, possibly through impaired antioxidative defence mechanisms. These results underscored the importance of integrating genetic screening and lifestyle factors in the clinical evaluation and risk stratification of women at risk of PCOS. Furthermore, it is necessary to conduct extensive multi-ethnic studies to confirm these associations and investigate PON1's potential genotyping as a biomarker for early diagnosis or targeted interventions in PCOS management.

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Conflicts of Interest: None.

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