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ORIGINAL RESEARCH

Association of WEE2 Gene Polymorphism with Fertilization Failure in Women Undergoing Intracytoplasmic Sperm Injection

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Background: Infertility and pregnancy loss are major concerns in reproductive medicine, often linked to genetic factors affecting oocyte maturation. The WEE2 gene, which encodes an oocyte-specific kinase critical for meiosis, plays a vital role in fertilization. Variants in WEE2 have been implicated in oocyte maturation arrest and total fertilisation failure (TFF), particularly in women undergoing assisted reproductive technologies. This study aimed to investigate the association between WEE2 gene polymorphism and fertilization failure in women undergoing intracytoplasmic sperm injection (ICSI).

Materials and Methods: This prospective comparative study enrolled 137 infertile women undergoing ICSI procedures. Peripheral blood samples were collected from all participants for genetic analysis. Genotyping of the WEE2 gene variant rs1476640 was performed using a polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay, which was specifically designed and optimised for this study.

Results: WEE2 gene polymorphism (rs1476640) showed a significant association with fertilization outcomes ($p < 0.0001$). The T allele was protective, while the C allele increased the risk of fertilization failure (OR = 9.06; 95% CI: 3.27–25.14). Significant differences were also observed in infertility duration, oocyte count, and endometrial thickness between pregnant and non-pregnant women ($p < 0.05$), but not in age or BMI.

Conclusion: The WEE2 rs1476640 polymorphism is significantly associated with fertilization failure in ICSI-treated women. Screening for this variant may help identify patients at risk and support personalised infertility treatment strategies.

Keywords: infertility, oogenesis, gene polymorphism of WEE2, fertilization failure

Introduction

Human reproduction is a complex and tightly regulated biological process involving gamete maturation, fertilization, embryo development, blastocyst formation, implantation, and ultimately, live birth. Disruption or arrest at any of these stages can result in reproductive failure.[1]

Infertility, defined as the inability to conceive after one year of regular, unprotected intercourse, affects an estimated 48 million couples worldwide.[2,3] Debate exists around the classification of infertility into primary and secondary types, but both contribute significantly to global reproductive health challenges. As infertility rates rise, increasing numbers of couples are turning to assisted reproductive technologies (ART), such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), success rates remain suboptimal, partly due to underlying genetic factors. Genetic abnormalities have been implicated in up to that contribute up to 30% of infertility cases.[4,5]

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Female fertility is critically dependent on successful oogenesis where immature oocytes undergo two meiotic divisions (meiosis I and II) to produce haploid gametes.[6] The oocyte arrest at meiosis II and completed the process when fertilization take place.[7,8]

Oocyte maturation involves two essential components: nuclear maturation, referring to chromosomal reduction via meiosis, and cytoplasmic maturation, which prepares the oocyte for fertilization, activation, and early embryonic development.[9]

The WEE2 gene (WEE1 homolog 2), located on chromosome 7q34, encodes a 567-amino acid oocyte-specific kinase belonging to the WEE family of protein kinases. It consists of 12 exons and is exclusively expressed in oocytes and zygotes.[10] WEE2 plays a vital role in maintaining meiotic arrest at the GV stage by inhibiting maturation-promoting factor (MPF) through CDK inactivation. Additionally, WEE2 is required for exit from metaphase II during fertilization.[11] Reduced expression of WEE2 has been associated with elevated MPF activity and impaired MII exit, leading to failure in pronucleus formation and fertilization.[12]

Given the critical role of WEE2 in oocyte maturation and fertilization, this study aimed to assess the association between WEE2 gene polymorphism and fertilization failure in women undergoing ICSI. To our knowledge, this represents the first study in Iraq investigating the relationship between WEE2 genetic variation and fertilization outcomes.

Materials and Methods

Study Design and Setting

This prospective comparative study was conducted between October 2024 and February 2025 at Tibacenter for Infertility in Babil, Iraq. A total of 137 infertile women undergoing intracytoplasmic sperm injection (ICSI) were enrolled.

Study Population

Eligible participants were women aged 20–35 years with primary or secondary infertility of 2–10 years' duration. All participants were undergoing ICSI cycles. Inclusion criteria encompassed women with no history of systemic diseases or chromosomal abnormalities. All male partners underwent standard semen analysis.

Clinical and Laboratory Evaluation

Comprehensive gynecological and general examinations were performed. Baseline fertility assessments included hormonal profiling on day 1 or 2 of the menstrual cycle, measuring FSH, LH, estradiol (E2), and progesterone (P4). Transvaginal ultrasound was performed on cycle day 2 to assess baseline ovarian status.

Controlled Ovarian Stimulation and ICSI Procedure

All patients underwent ovarian stimulation using a flexible GnRH antagonist protocol. Oocyte retrieval was performed 34–36 hours after administration of the ovulation trigger via transvaginal ultrasound-guided aspiration. Semen samples were collected on the same day and processed for ICSI.

The ICSI procedure involved microinjection of a single spermatozoon into the cytoplasm of each mature oocyte. Fertilization was confirmed 16–18 hours post-injection by the presence of two pronuclei (2PN) and two polar bodies (2PB). Abnormal fertilization was defined by the presence of 1PN, 3PN, or 4PN.

Embryo Evaluation and Transfer

Embryo grading was performed on day 3 based on standard morphological criteria:

Grade I: <10% fragmentation, stage-specific cell size, no multinucleation.
Grade II: 10–25% fragmentation, mostly stage-specific cell size, no multinucleation.
Grade III: >25% fragmentation, irregular cell size, presence of multinucleation.
Embryos graded I and II were selected for uterine transfer based on maternal age, embryo quality, and IVF history.

Table 1 Primer Sequences and Properties Used for Amplifying the WEE2 Gene (rs1476640 SNP)

SNP	Primer	Sequence (5′→3′)	Length (bp)	Template Strand	Start	Stop	Tm (°C)	GC%	Self-Complementarity	Self 3′ Complementarity
ZH2F	F	GGTTGCCTTCTTCTTCACCAC	21	Plus	141712312	141,712,332	59.93	52.38	3.00	0.00
ZH2R	R	GCCAAGGAATTGTGTGACCAC	22	Minus	141712640	141,712,619	60.35	50.00	4.00	2.00

Molecular Analysis

Sample Collection and DNA Extraction

Peripheral venous blood (2 mL) was collected into EDTA tubes and stored at −20°C until analysis. Genomic DNA was extracted using a standard phenol–chloroform protocol. DNA quantity and purity were assessed via NanoDrop spectrophotometry (BioDrop, UK), with absorbance ratios at 260/280 and 260/230. DNA integrity was confirmed by agarose gel electrophoresis.

Primer Design

Primers for rs1476640 of the WEE2 gene were designed using NCBI Primer-BLAST and validated for specificity using BLAST against the human genome. Secondary structure and self-complementarity were assessed using OligoCalc (Kibbe, 2007). Amplicon verification was performed using MFEprimer-2.0 (Qu et al, 2012). Primer sequences and characteristics are provided in Table 1.

PCR and Genotyping

PCR Amplification

PCR was optimized for annealing temperature and cycle number. Each 20 µL reaction included 8 µL 2X Master Mix, 1 µL forward primer (10 pmol), 1 µL reverse primer (10 pmol), 2 µL genomic DNA (10–20 ng/µL), 0.5 µL $MgCl_2$ (1%), and 7.5 µL nuclease-free water. The amplified product was confirmed on agarose gel prior to restriction digestion.

RFLP Analysis

The rs1476640 SNP was genotyped using NdeI enzyme digestion. The 20 µL reaction mix included 5 µL PCR product, 1.5 µL enzyme buffer, 0.5 µL NdeI, and 8 µL ddH_2O. Fragments were separated on 2.5% agarose gel and visualized under UV light.

Statistical Analysis

Statistical analyses were performed using SPSS version 26, Microsoft Excel 2010, and SNPStats (Sole et al, 2006). Independent samples *t*-tests were used for normally distributed continuous variables. The Kruskal–Wallis test was used for non-parametric comparisons. Chi-square tests assessed associations between categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between genotype and fertilization outcomes.

Ethical Approval

This study was approved by the Ethics Committee of the University of Babylon, Hammurabi College of Medicine, Iraq (Document No. 40, dated September 15, 2024). All participants provided informed verbal and written consent in accordance with the Declaration of Helsinki.

Results

Demographic Characteristics of Women Enrolled in the Present Study

The demographic characteristics of infertile patients are shown in Table 2. The Mean, Standard Deviation and Standard Error of female age with positive and negative pregnancy were 30.73, 5.025 and 0.649, and 29.88, 5.385 and 0.614, respectively, and the age was ranging from 20 to 39years and 18 to 39 years, respectively, and there was no significant difference ($p = 0.347$).

Table 2 Demographic Characteristics of Female Enrolled in the Present Study

Status	Groups	N	Mean	Std. Deviation	Std. Error Mean	T.test	MD	P-value
Age	Positive group	60	30.73	5.025	0.649	0.944	0.850	0.347 I
	Negative group	77	29.88	5.385	0.614			NS
BMI	Positive group	60	29.073	4.2801	0.5526	−1.106	−0.855	0.271 I
	Negative group	77	29.929	4.6466	0.5295			NS
Duration	Positive group	60	6.90	4.387	0.566	2.092	1.471	0.038 I
	Negative group	77	5.43	3.833	0.437			NS

Note: I significant at $p \leq 0.05$.
Abbreviations: N,number of cases; SD, standard deviation; BMI, body mass index; MD, Mean Difference; I, Independent sample *t*-test; NS, not significant.

In addition, there was no significant difference in mean of BMI between positive pregnancy group and negative pregnancy groups ($p = 0.271$).

Regarding the duration of infertility, there was significant difference between positive pregnancy and negative pregnancy groups ($p = 0.038$). The Mean, Standard Deviation and Standard Error of Duration with positive and negative pregnancy were 6.90, 4.387 and 0.566, and 5.43, 3.833 and 0.437, respectively.

Comparison of Total Oocyte Count Between Positive Pregnancy Group and Negative Pregnancy Group

The Mean and Standard Deviation of total oocyte count with positive and negative pregnancy were 12.67 and 4.990 and 10.82 and 5.241, respectively, and the Standard Error was 0.644 and 0.597), respectively; the result showed significant association between pregnancy group and negative pregnancy group (0.038) Table 3.

Comparison of Endometrial Thickness Between Positive Pregnancy Group and Negative Pregnancy Group

The Mean and Standard Deviation of Endometrial thickness with positive and negative pregnancy were 11.84 and 2.763, and 10.83 and 2.897, respectively, and the Standard Error was 0.357, and 0.330) respectively; the difference in mean rank was statistically significant ($p = 0.04$) Table 4.

Table 3 Comparison of Total Oocyte Count Between Positive Pregnancy Group and Negative Pregnancy Group

Status	Groups	N	Mean	Std. Deviation	Std. Error Mean	T.test	MD	P-value
No of Oocyte	**Positive group**	60	12.67	4.990	0.644	2.091	1.848	0.038
	Negative group	77	10.82	5.241	0.597			

Note: Significant at $p \leq 0.05$.
Abbreviations: *n*, number of cases; I, Independent sample *t*-test; MD, Mean Difference.

Table 4 Comparison of Endometrial Thickness Between Positive Pregnancy Group and Negative Pregnancy Group

Status	Groups	N	Mean	Std. Deviation	Std. Error Mean	T.test	MD	P-value
Endometrial thickness	**Positive group**	60	11.84	2.763	0.357	2.072	1.0131	0.04
	Negative group	77	10.83	2.897	0.330			

Note: significant at $p \leq 0.0$.
Abbreviations: *n*, number of cases; I, Independent sample *t*-test; MD, Mean Difference; SD, Standard Deviation.

Amplification of WEE2 Gene

In this study, the PCR technique was used to detect *WEE2 gene*. Gel electrophoresis results indicated the size of the amplicons as 329 bp for WEE2 gene, compared with the DNA ladder (Figures 1–2). The genotypes of SNP rs1676760 were determine by PCR-RFLP method (Figure 3).

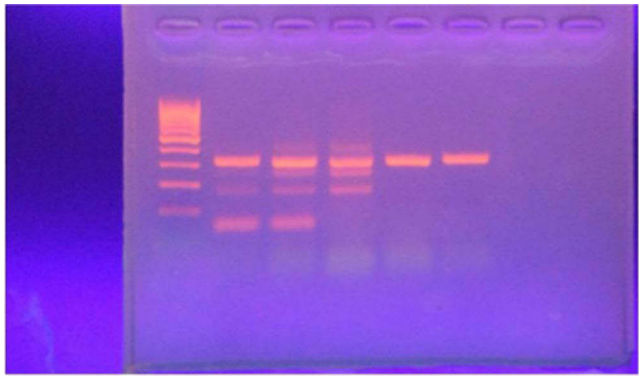

Figure 1 Optimization of PCR by gradient annealing temperature. Lane L 100bp step DNA ladder; other lanes represent different annealing temperature as indicated on each lane.

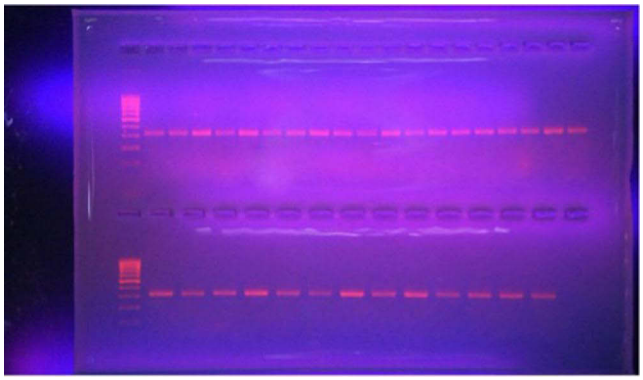

Figure 2 PCR amplification of 329bp amplicon for rs1476640 genotyping. The product was resolved on 2% agarose gel. lane L 100bp step DNA ladder. This product was subjected to restriction enzyme analysis.

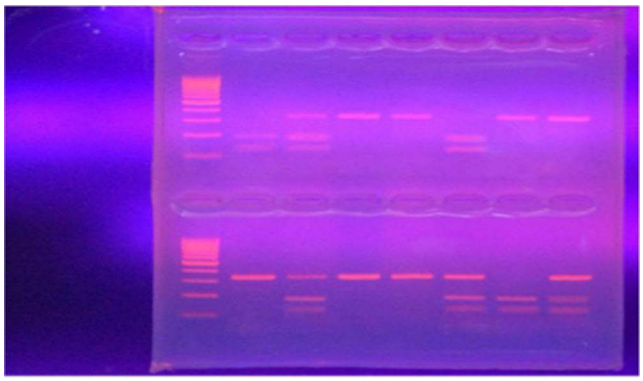

Figure 3 Genotyping of rs1476640 polymorphism by PCR-RFLP technique. PCR product were digested by NdeI restriction enzyme lanes L 100bp step DNA ladder: lanes 1, 5 and 13 show the TT genotype; lanes 2, 9, 12 and 14 show the TC genotype; lanes 3, 4, 6, 7, 8, 10 and 11 show the CC genotype.

Genetic Association of T and C Alleles Between the Positive Pregnancy Group and Negative Pregnancy Group

The results showed that there was significant allele frequency difference between the positive pregnancy group and negative pregnancy group (Table 5).

Association of rs1476640 Genotypes with Pregnancy Outcome in Female Under ICSI

The difference in T\T between positive and negative pregnancy was statistically highly significant Codominance TT (reference) is 50.6% and 18.3%, respectively, C/T is 37.7%, and 43.3%), respectively, and C/C is 11.7%, 38.3%, respectively (p = < 0.0001). Dominant C/ T-C/C 39 (50.6%), 49 (81.7%), respectively (p = 1e-04). Recessive C/C 9 (11.7%), 23 (38.3%), respectively (p = 2e-04) (Table 6).

Comparison of Oocyte Maturation and Genotype Between the Positive Pregnancy Group and Negative Pregnancy Group

There was significant difference in Germinal vesicle oocyte between positive and negative pregnancy median (IQR) CC 3 (2), CT 0 (2), TT 0 (2) respectively; (p < 0.001). In addition there was no significant difference in (metaphase I, MI) oocytes between pregnant and non pregnant ladies (Table 7).

In addition, there was significant difference in the number of germinal vesicle (GV) oocytes in pregnant ladies (p < 0.001). There was also no significant difference in the number of immature (metaphase I, MI) oocytes in pregnant.

A statistically significant difference in Germinal vesicle oocyte in nonpregnant ladies (p < 0.001). However, the stage of oocyte maturation includes metaphase I (MI) which showed no significant difference in negative group.

Table 5 Genetic Association of T and C Alleles Between the Positive Pregnancy Group and Negative Pregnancy Group

Allele	Positive Pregnancy		Negative Pregnancy		OR (95% CI)	P-value
	Count	Proportion	Count	Proportion		
T	107	0.69	48	0.4	0.293 (0.177–0.483)	P < 0.0001
C	47	0.31	72	0.6	3.415 (2.069–5.636)	

Note: Significant at $p \leq 0.05$.
Abbreviations: C, chi-square test; NS, not significant; OR, odds ratio; CI, confidence interval.

Table 6 Association of rs1476640 Genotypes with Pregnancy Outcome in Female Under ICSI

Model	Genotype	Positive Pregnancy	Negative Pregnancy	OR (95% CI)	P-value
Codominant	T/T	39 (50.6%)	11 (18.3%)	Reference	<0.0001
	C/T	29 (37.7%)	26 (43.3%)	3.18 (1.35–7.46)	
	C/C	9 (11.7%)	23 (38.3%)	9.06 (3.27–25.14)	
Dominant	T/T	39 (50.6%)	11 (18.3%)	Reference	0.0001
	C/T-C/C	38 (49.4%)	49 (81.7%)	4.57 (2.07–10.09)	
Recessive	T/T-C/T	68 (88.3%)	37 (61.7%)	Reference	0.0002
	C/C	9 (11.7%)	23 (38.3%)	4.70 (1.97–11.19)	

Note: Significant at $p \leq 0.05$.
Abbreviations: C, chi-square test; NS, not significant; OR, odds ratio; CI, confidence interval.

Table 7 Comparison of Oocyte Maturation and Genotype Between the Positive Pregnancy Group and Negative Pregnancy Group

Group	Characteristic	Genotype			*P*
		CC	CT	TT	
All cases	**Germinal vesicle oocyte**				
	Median (IQR)	3 (2)	0 (2)	0 (2)	<0.001 K S***
	Metaphase I (MI) oocytes				
	Median (IQR)	1 (2)	0 (2)	1 (2)	0.637 K NS
	Metaphase II (MII) oocytes				
	Median (IQR)	6 (6)	7 (5)	7.5 (6)	0.550 K NS
Positive	**Germinal vesicle oocyte**				
	Median (IQR)	3 (2)	1 (2)	0 (2)	<0.001 K S ***
	Metaphase I (MI) oocytes				
	Median (IQR)	0 (2)	0 (2.25)	1 (1)	0.992 K NS
	Metaphase II (MII) oocytes				
	Median (IQR)	6 (6)	6 (6.5)	5 (7)	0.944 K NS
Negative	**Germinal vesicle oocyte**				
	Median (IQR)	3 (2)	0 (2)	0 (2)	<0.001 K S***
	Metaphase I (MI) oocytes				
	Median (IQR)	1.5 (1)	0 (2.25)	1 (2)	0.288 K NS
	Metaphase II (MII) oocytes				
	Median (IQR)	6 (9.25)	8 (6)	8 (6)	0.451 K NS

Notes: *** Highly significant at $p \leq 0.0001$.
Abbreviations: K, Kruskal Wallis test; NS, not significant; IQR, inter-quartile rang.

Discussion

This study investigated the association between WEE2 gene polymorphism and fertilization outcomes in infertile women undergoing intracytoplasmic sperm injection (ICSI). The findings revealed no statistically significant difference in the mean age or BMI between pregnant and non-pregnant groups, consistent with previous studies that suggest age and BMI may not be sole predictors of ICSI success in populations where cultural norms encourage early marriage.[13–15]

However, the duration of infertility showed a significant association with pregnancy outcome, in agreement with prior studies indicating that prolonged infertility may negatively impact clinical success rates in ART procedures.[16]

Importantly, the number of mature oocytes retrieved was significantly higher in the pregnant group, reinforcing the well-established link between oocyte yield and fertilization success.[17] Endometrial thickness also showed a significant association with pregnancy, with thicker endometria correlating with improved implantation rates, consistent with findings from earlier studies.[18,19]

Beyond clinical parameters, our study highlights the critical role of genetic factors, specifically WEE2 gene polymorphisms, in determining ICSI outcomes. The codominant model revealed a higher frequency of C/C and C/T genotypes in non-pregnant women, while the T/T genotype was more common in those who achieved pregnancy, suggesting a protective role of the T allele and a pathogenic effect of the C allele. These observations are in line with

previous reports that have linked WEE2 mutations to total fertilization failure (TFF) due to their impact on oocyte maturation and MII exit.[20–22]

WEE2 encodes an oocyte-specific kinase that regulates meiotic arrest at the GV stage and is essential for exit from metaphase II following fertilization. Mutations or reduced expression of WEE2 impair this process, resulting in abnormal oocyte activation and fertilization failure.[23,24] Studies have shown that up to 20.8% of women with TFF carry WEE2 mutations, while other investigations report a prevalence of approximately 6%.[24–26] Our findings support this association and emphasize the gene's role in regulating oocyte competence.

Furthermore, the data are consistent with reports by Jin et al (2021), who identified compound heterozygous WEE2 mutations in patients with unexplained infertility, and other studies confirming that WEE2 defects can halt oocyte development at the GV stage or block MII progression.[24,27]

Collectively, these findings underscore the importance of WEE2 in human oocyte development, meiotic regulation, and successful fertilization. Identifying polymorphisms in this gene could enhance early diagnosis of genetic infertility, inform patient counseling, and potentially guide personalized treatment strategies in ART.

Conclusion

Polymorphisms in the WEE2 gene, particularly the rs1476640 variant, are significantly associated with fertilization failure in women undergoing ICSI. The presence of the C allele may impair oocyte maturation by disrupting the meiotic process, thereby reducing the fertilization potential. Genetic screening for WEE2 variants may offer a valuable tool for identifying patients at risk of ART failure and improving individualized infertility treatment approaches.

Disclosure

The authors report no conflicts of interest in this work.

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