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ORIGINAL ARTICLE

Gene Polymorphisms of TCF7L2 and Risk of Preeclampsia in Pregnant Women

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SUMMARY

Background: **Preeclampsia (PE), a pregnancy complication, affects 10% of pregnancies worldwide. The development of PE has been attributed to multiple genetic variations. The aim of this study was to evaluate the possible association between TCF7L2 gene polymorphisms (rs12255372 and rs12243326) and risk of preeclampsia in Egyptian women with and without gestational diabetes mellitus (GDM) as well as to assess the discrimination values of these polymorphisms as biomarkers for PE.**

Methods: **This case-control study included 120 pregnant women allocated into two groups: 80 preeclamptic women (40 with GDM and 40 without GDM) and a control group that included 40 normotensive pregnant women. Genotyping of rs12255372 and rs12243326 was performed by real-time polymerase chain reaction (RT-PCR).**

Results: **The mutant TT and hetero GT genotypes of rs12255372 for the TCF7L2 gene were significantly associated with increased risk of preeclampsia, and the dominant model was significantly linked in PE ($p < 0.001$), with odds ratio (OR) = 6.1; 95 % confidence interval (CI) = 3.74 - 10.12. The mutant and hetero genotypes (CC and TC, respectively) of rs12243326 were considerably linked to a high risk of preeclampsia ($p < 0.001$) as well as the dominant model with a p-value of less than 0.001 and OR (95% CI) = 0.185 (0.09 - 0.39). Furthermore, there were significant differences between preeclamptic groups compared to controls according to the co-dominant model ($p < 0.001$), while there was no significant difference between PE women with and without GDM for rs12255372 ($p = 0.603$). The high predictive accuracies of TCF7L2 gene polymorphisms (rs12243326 and rs12255372) and their combination as probable indicators for PE (accuracy = 91.05%) were observed with the receiver operating characteristic curve (ROC) analysis ($p < 0.001$).**

Conclusions: **The genetic polymorphisms of rs12255372 and rs12243326 for the TCF7L2 gene were associated with the risk of preeclampsia in Egyptian women. Thus, they could be biochemical markers for PE.**

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KEYWORDS

preeclampsia (PE), gestational diabetes mellitus (GDM), gene polymorphisms, transcription factor 7-like 2 (TCF7L2)

INTRODUCTION

Preeclampsia (PE) is a multisystem disorder that occurs during pregnancy and is one of the main causes of maternal, fetal, and neonatal mortality, especially in low- and middle-income countries [1]. PE is commonly associated with a sudden increase in blood pressure with

concurrent development of a high level of protein in the urine (proteinuria) and can progress to eclampsia [2]. It affects 2% - 4% of pregnancies worldwide and is responsible for nearly 46,000 maternal deaths and around 500,000 fetal and neonatal deaths every year [3]. Based on the guidelines from various global organizations, specifically, the International Society for the Study of Hypertension in Pregnancy (ISSHP), the diagnostic definition of PE was broadened as gestational hypertension accompanied by proteinuria or other maternal end-organ dysfunction after 20 weeks of gestation [4]. This includes neurological complications, pulmonary edema, hematological complications, acute kidney injury, liver involvement, and uteroplacental dysfunction [5].

Although the exact cause of PE remains unclear, significant advancements have been made in understanding its underlying mechanisms [5]. Gestational diabetes mellitus (GDM) is recognized as a contributing factor to gestational hypertension, which can progress to more severe complications such as proteinuria, dyslipidemia, thrombocytopenia, and pulmonary edema-hallmarks of PE [6]. Moreover, women with GDM, as well as their offspring, face a heightened long-term risk of developing type 2 diabetes mellitus (T2DM) [7]. Therefore, early identification of individuals at risk for GDM and PE offers critical opportunities for enhanced monitoring, preventive education, lifestyle intervention, and early clinical management [2]. However, many biomarker studies have focused on identifying potential predictors using samples collected at the time of GDM or PE diagnosis. While such biomarkers may reflect disease-related alterations and provide valuable diagnostic insights, their predictive utility may be limited [8].

Transcription factor 7-like 2 (TCF7L2), a member of the high mobility group-box family of transcription factors, is expressed in pancreatic β-cells and plays a key role in regulating glucose metabolism and maintaining glucose homeostasis [9]. Genetic variants in the TCF7 L2 gene have been consistently identified as major risk factors for T2DM, and emerging evidence also implicates these variants in the development of GDM [9,10]. Given the common pathophysiological features between T2DM and GDM, particularly in relation to β-cell dysfunction and insulin resistance, it is conceivable that TCF7L2 polymorphisms may also contribute to the onset of GDM and potentially PE [11]. Accordingly, the current study aimed to examine the association between two TCF7L2 single nucleotide polymorphisms (SNPs), rs12255372 and rs12243326, and susceptibility to GDM and PE in pregnant women. These polymorphisms have previously been linked to T2DM but remain underexplored, with inconclusive findings in the context of GDM and PE. A secondary objective was to assess their potential utility as biomarkers for identifying the risk of developing PE.

MATERIALS AND METHODS

The cross-sectional study was conducted on pregnant women recruited from the Department of Obstetrics and Gynecology, El Galaa Teaching Hospital, Egypt. All participants signed an informed consent form. The study proposal was approved by the Hospital Review Board of El Galaa Teaching Hospital, Egypt (HG000090). This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. A total sample size of n = 120 pregnant women were allocated into two groups: preeclamptic patients (n = 80) and normotensive pregnant women (n = 40). Preeclamptic women were further subdivided into 40 without GDM and 40 with GDM as a risk factor of PE.

Preeclampsia was diagnosed using the criteria of the National High Blood Pressure Education Program Working Group [12] with systolic and diastolic blood pressure ≥ 140 mm Hg and ≥ 90 mm Hg, respectively, and the presence of proteinuria ≥ 300 mg in 24-hour urinary collection or ≥ 30 mg/dL protein in a random urine sample (1+ reaction on a standard urine dipstick), which occurs after 20 weeks of gestation in a woman with previously normal blood pressure. Pregnant women without a previous diagnosis of T2DM were screened for GDM, and the diagnosis of GDM was performed according to the International Association of Diabetes and Pregnancy Study Groups [13]. Women with a history of chronic hypertension, diabetes, cardiac and renal diseases, pregnancies with deformed fetuses, and multiple pregnancies were excluded from the study. The normal control group included (n = 40) age- and parity-matched pregnant women with no hypertension or proteinuria with the same inclusion and exclusion criteria as the preeclamptic group.

DNA extraction

Genomic DNA was extracted from whole blood by QIA amplification extraction kit (Qiagen GmbH, USA) according to the manufacturer's instructions. The isolated DNA was quantified via UV absorption at 260 nm and 280 nm and stored at -20°C until use.

Genotyping of TCF7L2 (rs12243326 C/T) and (rs12255372 G/T) gene polymorphism

Genotyping of SNPs rs12243326 C/T and rs12255372 G/T for TCF7L2 was carried out on real-time PCR-amplified DNA by allelic discrimination using TaqMan from Applied Biosystems (Foster City, CA, USA). Real-time PCR was done using 12.5 µL of TaqMan® Universal PCR Master Mix, 1.25 µL of SNP genotyping assay mix, and 1 µL of DNA, with a final reaction volume of 25 µL. The cycling conditions were as follows: initial denaturation at 95°C for 10 minutes, 40 cycles of 92°C for 15 seconds (denaturation), and 60°C for 1 minute (annealing/extension). PCR was achieved using a 2,700 real-time PCR system (Applied Biosystems, USA).

Statistical analysis

All statistical analyses were conducted using SPSS 27.0 (IBM, USA). Statistical power and sample size were calculated by PASS 11. Quantitative data were expressed as mean ± SD (standard deviation), while qualitative data were expressed as frequencies and relative percentages. Parameters were compared between groups using Student's *t*-test and the χ^2 test for categorical data. The ability of TCF7L2 gene polymorphisms to detect PE and GDM was tested using the receiver operating characteristic (ROC) curve. The p-value was considered statistically significant at $p < 0.05$.

RESULTS

The characteristics and clinical features of preeclampsia (PE) patients with and without gestational diabetes mellitus (GDM) and controls are demonstrated in Table 1. There was a significant difference regarding the age between PE patients with GDM and both PE without GDM and normal controls. Systolic and diastolic blood pressure was significantly higher in both groups of cases (PE with and without GDM) than in the control group ($p < 0.001$), but there was no significant difference regarding blood pressure in PE with GDM compared to PE without GDM. Besides, proteinuria was significantly higher in GDM preeclampsia than in preeclampsia ($p < 0.001$). The TCF7L2 G/T (rs1255372) and TCF7L2 T/C (rs12243326) genotype distributions in controls and in total PE women are displayed in Table 2. As regards the TCF7L2 G/T (rs1255372), the TT mutant genotype and GT hetero-genotype were significantly higher in PE patients than in controls. Regarding the TCF7L2 T/C (rs12243326), the genotype frequencies of mutant (CC) and hetero (TC) were considerably increased in PE cases in comparison to the control group. The genotype frequencies for TCF7L2 (rs 1255372 and rs12243326) in PE cases (with and without GDM) and controls were examined (Table 3). There were significant differences between the PE groups and the control group for the codominant, dominant, and recessive models of rs1255372 and rs12243326. Moreover, rs12243326 in the two models (codominant and recessive) revealed a significant difference among PE with and without GDM cases. However, the genotype distribution for rs1255372 showed non-significant differences between the two PE groups (PE with and without GDM). In order to evaluate the discriminating values of TCF7L2 (rs1255372 and rs12243326) as markers for preeclampsia and GDM accompanied by PE, the receiver operating characteristic (ROC) curve was applied. The predictive accuracies of TCF7L2 gene polymorphisms (rs1255372 and rs12243326) and their combination as probable indicators for PE were determined using ROC curve analysis as shown in Table 4 and Figures 1 and 2.

DISCUSSION

Preeclampsia (PE) is frequently diagnosed in the later stages of pregnancy, often when severe clinical manifestations are already present, complicating timely intervention. Therefore, early detection is critical for enhancing patient management and enabling prompt therapeutic measures, ultimately improving both maternal and neonatal outcomes [14,15]. Beyond clinical factors, genetic predispositions have also been implicated in the pathogenesis of gestational diabetes mellitus (GDM), a condition increasingly recognized as a risk factor for PE. Among the genetic contributors, the transcription factor 7-like 2 (TCF7L2) gene has emerged as one of the most consistently associated loci for type 2 diabetes mellitus (T2DM) across various ethnic populations. Numerous genome-wide association studies (GWAS) have identified and validated TCF7L2 as a major susceptibility gene in diverse cohorts [16,17]. The current investigation aimed to explore whether the TCF7L2 polymorphisms rs12243326 (C/T) and rs12255372 (G/T) are associated with an increased risk of both PE and GDM in pregnant women. To the best of our knowledge, this is the first study to assess these associations within a sample of the Egyptian population.

The present study identified maternal age as a significant contributing factor to PE with GDM cases, with a highly significant association ($p < 0.001$). Additionally, marked differences were observed in systolic and diastolic blood pressure, as well as in proteinuria levels, between the PE with and without GDM groups ($p < 0.001$). These findings align with previous research indicating that advanced maternal age increases the risk of GDM onset [6,14,15]. Other contributing factors, such as multiple pregnancies, have also been implicated in the development of PE among women with early-onset GDM [16]. Supporting these associations, Alfadhli et al. reported a high prevalence of GDM among Saudi women, primarily linked to older maternal age and hypertension [17]. A cohort study further revealed that the risk of developing PE is approximately eightfold higher when GDM is diagnosed by the 20th week of gestation [18]. In a related study, Aziz et al. found that women with both GDM and PE commonly presented at 26 - 28 weeks of gestation, suggesting that late-onset GDM may exacerbate PE progression [6]. These findings indicate that increasing maternal age and gestational age may collectively contribute to the manifestation of GDM and its complications, including PE. According to a recent global report from the International Diabetes Federation (IDF), GDM affects up to 80.3% of all pregnancies worldwide [19]. It is also a major risk factor for gestational hypertension, which is responsible for approximately 30,000 maternal deaths annually [20]. The current study also suggests a potential link between increased proteinuria and the onset of PE in women with GDM. This is in agreement with findings by Magee et al., who emphasized proteinuria as a key diagnostic indicator in cases of gestational hypertension and pre-

Table 1. Characteristics and clinical features of studied subjects.

Variables	Controls (n = 40)	PE without GDM (n = 40)	PE with GDM (n = 40)	p1	p2	p3
Age (years)	28.4 ± 5.2	30.35 ± 6.6	37 ± 2.8	0.247	< 0.001	0.007
Gestational age (weeks)	32.65 ± 1.7	31.45 ± 3.9	33.25 ± 1.6	0.191	0.618	0.139
Systolic BP (mmHg)	119.5 ± 6.05	157.5 ± 18.03	156.25 ± 7.4	< 0.001	< 0.001	0.815
Diastolic BP (mmHg)	74.5 ± 5.1	98.25 ± 8.8	99.38 ± 1.77	< 0.001	< 0.001	0.697
Platelets count (mm^3 x 10^3)	226.9 ± 72.1	217.25 ± 60.76	218.63 ± 45.4	0.635	0.758	0.959
Hemoglobin (g/dL)	10.56 ± 1.61	10.695 ± 1.015	10.7 ± 0.915	0.752	0.804	0.993
INR:	1.04 ± 0.065	1.035 ± 0.054	1.057 ± 0.055	0.937	0.401	0.369
Parity (PG/MP)	6/34 15%/85%	12/28 30%/70%	5/35 12.5%/87.5%	0.252	0.863	0.311
History of preeclampsia	0 (0%)	4 (10%)	5 (12.5%)	0.09	0.107	0.847
Family history of PE	0 (0%)	12 (30%)	0 (0%)	0.008	-	0.031
Proteinuria:						
Negative	40 (100%)	0 (0%)	0 (0%)	< 0.001	< 0.001	< 0.001
+	0 (0%)	20 (50%)	5 (12.5%)			
++	0 (0%)	14 (35%)	20 (50%)			
+++	0 (0%)	6 (15%)	15 (37.5%)			

PE - preeclampsia, GDM - gestational diabetes mellitus, BP - blood pressure, PG/MP - primigravida/multipara.
Underlined values indicate significant differences < 0.05.
p1 - control versus PE without GDM, p2 - control versus PE with GDM, p3 - PE without GDM versus PE with GDM.

Table 2. Genotype distributions of the studied TCF7L2 polymorphisms in women with preeclampsia and gestational diabetes mellitus.

Polymorphism	Model of inheritance	Genotype	Preeclampsia (n = 80)	Controls (n = 40)	OR (95% CI)	p-value
rs1255372	co-dominant	GG	13 (16.25%)	40 (100%)		
		GT	35 (43.75%)	0 (0%)		
		TT	32 (40%)	0 (0%)		< 0.001
	dominant	GG	13 (16.25%)	40 (100%)		
		GT + TT	67 (83.75%)	0 (0%)	6.1 (3.74 - 10.12)	< 0.001
	recessive	TT	32 (40%)	0 (0%)		
		GT + GG	48 (60%)	40 (100%)	1.67 (1.4 - 1.99)	< 0.001
rs12243326	co-dominant	TT	15 (18.8%)	34 (85%)		
		TC	50 (62.5%)	6 (15%)		
		CC	15 (18.8%)	0 (0%)		< 0.001
	dominant	TT	15 (18.75%)	34 (85%)		
		TC + CC	65 (81.25%)	6 (15%)	0.185 (0.09 - 0.39)	< 0.001
	recessive	CC	15 (18.75%)	0 (0%)		
		TC + TT	65 (81.25%)	40 (100%)	1.23 (1.1 - 1.37)	0.003

Data are expressed as number (percentage %), OR - odds ratio, CI - confidence interval.
Underlined values indicate significant difference with p-values < 0.05.

Table 3. Genotype distribution of SNPs of TCF7L2 gene in control and preeclampsia with and without gestational diabetes mellitus groups.

Polymorphism	Model of inheritance	Genotype	PE (n = 40)	PE + GDM (n = 40)	Controls (n = 40)	p1	p2	p3
rs1255372	co-dominant	GG	8 (20%)	5 (12.5%)	40 (100%)			
		GT	20 (50%)	15 (37.5%)	0 (0%)			
		TT	12 (30%)	20 (50%)	0 (0%)	< 0.001	< 0.001	0.603
	dominant	GG	8 (20%)	5 (12.5%)	40 (100%)			
		GT + TT	32 (80%)	35 (87.5%)	0 (0%)	< 0.001	< 0.001	0.640
	recessive	TT	12 (30%)	20 (50%)	0 (0%)			
		GT + GG	28 (70%)	20 (50%)	40 (100%)	0.008	0.004	0.318
rs12243326	co-dominant	TT	10 (25%)	5 (12.5%)	34 (85%)			
		TC	30 (75%)	20 (50%)	6 (15%)			
		CC	0 (0%)	15 (37.5%)	0 (0%)	< 0.001	< 0.001	0.015
	dominant	TT	10 (25%)	5 (12.5%)	34 (85%)			
		TC + CC	30 (75%)	35 (87.5%)	6 (15%)	< 0.001	< 0.001	0.466
	recessive	CC	0 (0%)	15 (37.5%)	0 (0%)			
		TC + TT	40 (100%)	25 (62.5%)	40 (100%)	-	0.004	0.003

PE - preeclampsia, GDM - gestational diabetes mellitus.
Underlined values indicate significant differences < 0.05.
p1 - PE without GDM versus control, p2 - PE + GDM versus control, p3 - PE + GDM versus PE without GDM.

Table 4. ROC analysis for differentiating pregnant women with preeclampsia from healthy pregnant women.

Variables	AUC	Sensitivity	Specificity	Accuracy	p-value	95% CI
Total PE vs. C						
TCF7L2 rs1255372	0.911	82.1%	100%	91.05%	< 0.001	0.82 - 0.999
TCFL2 rs12243326	0.826	78.6%	85%	81.8%	< 0.001	0.7 - 0.95
TCF7L2 combined	0.915	82.1%	100%	91.05%	< 0.001	0.83 - 1
PE vs. C						
TCF7L2 rs1255372	0.9	80%	100%	90%	< 0.001	0.79 - 1
TCFL2 rs12243326	0.8	75%	85%	80%	0.001	0.66 - 0.95
TCF7L2 combined	0.91	80%	100%	90%	< 0.001	0.81 - 1
PE + GDM vs. C						
TCF7L2 rs1255372	0.938	87.5%	100%	93.5%	< 0.001	0.8 - 1
TCFL2 rs12243326	0.891	87.5%	85%	86.25%	0.001	0.74 - 1
TCF7L2 combined	0.947	87.5%	100%	93.5%	< 0.001	0.83 - 1

ACU - area under the curve, CI - confidence interval.
Underlined p-values represent significant differences at p < 0.05.
Total PE - PE pregnant women with and without GDM (n = 80).
PE - PE pregnant women without GDM (n = 40).
PE + GDM - PE pregnant women with GDM (n = 40).

eclampsia [21].

The present study found a significant difference ($p < 0.001$) in the distribution of the TT mutant and GT heterozygous genotypes of the TCF7L2 rs12255372 (G/T) polymorphism between preeclamptic patients and healthy controls. This association was observed consistently across co-dominant, dominant, and recessive genetic models and among the three groups studied, controls,

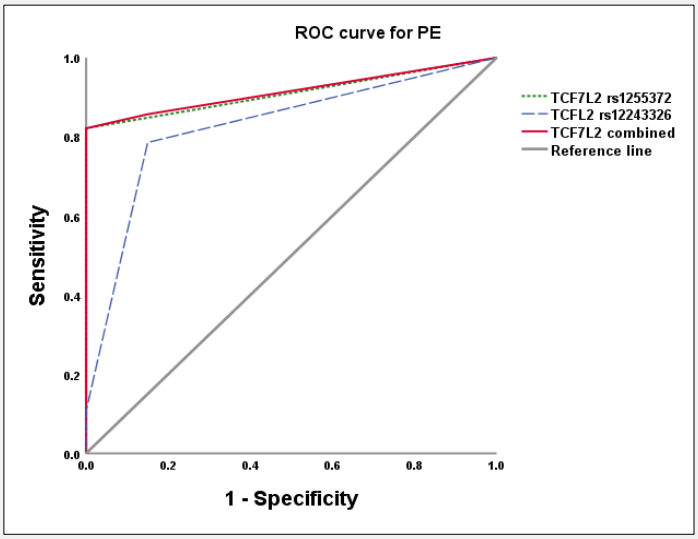

Figure 1. ROC curve for differentiating pregnant women with preeclampsia from healthy pregnant women.

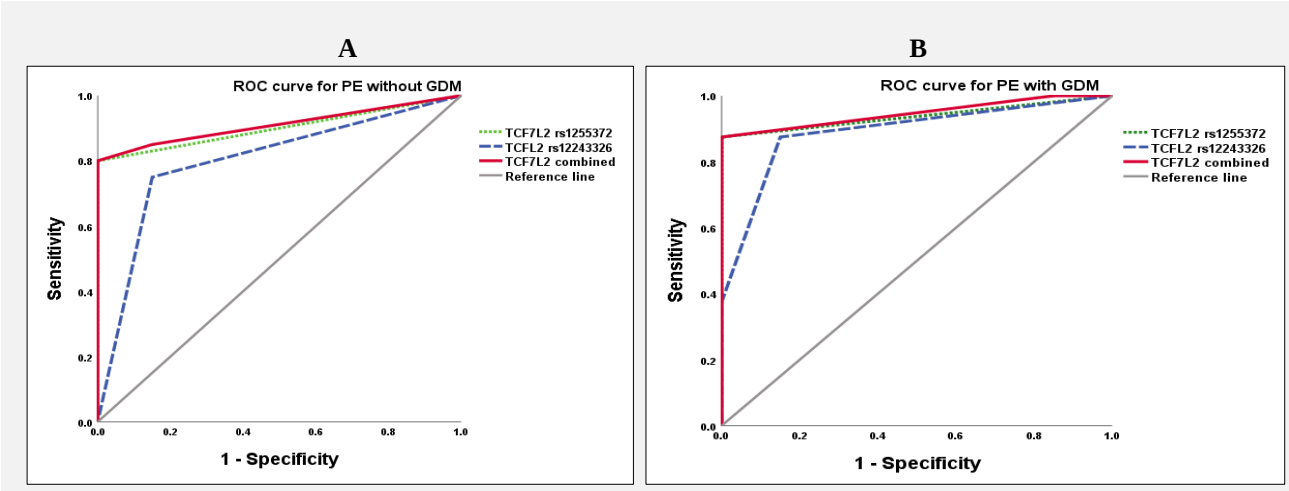

Figure 2. ROC curve for differentiating pregnant women with preeclampsia (PE) with and without gestation diabetes mellitus (GDM) from healthy pregnant women.

preeclamptic women without GDM, and those with both PE and GDM, indicating a potential link between this SNP and increased susceptibility to preeclampsia. However, no significant genotypic difference was observed between the two patient subgroups (PE with and without GDM), suggesting that while rs12255372 may contribute to PE risk, it does not distinguish between PE cases based on GDM status. The progression of GDM may be partially attributed to a genetic predisposition to pancreatic islet β-cell dysfunction, which is exacerbated by the increasing insulin resistance associated with pregnancy [22]. Among the key genetic factors implicated in GDM susceptibility, the TCF7L2 gene plays a central role in β-cell function regulation [23]. TCF7L2

is highly expressed in pancreatic β-cells and belongs to the high mobility group-box family of transcription factors, which are crucial for maintaining glucose homeostasis. Supporting this, Watanabe et al. demonstrated an association between the rs12255372 polymorphism in TCF7L2 and GDM, showing that this variant influenced insulin response following oral glucose intake in affected individuals [24,25]. A systematic review of four studies also identified a significant correlation between this SNP and GDM risk [26]. Similarly, recent research in a Moroccan population confirmed the rs12255372 (G/T) variant's association with increased susceptibility to T2DM [27]. In contrast, other studies conducted across various ethnic groups have produced conflicting results, suggesting that the association may be population-specific [28-30].

Findings from this study revealed that the mutant CC and heterozygous TC genotypes of the rs12243326 SNP in the TCF7L2 gene were more prevalent among preeclamptic women compared to healthy controls and were significantly associated with an elevated risk of both PE and GDM. This association may be explained by prior studies suggesting that TCF7L2 mutations impair insulin secretion and glucose regulation, thereby increasing susceptibility to T2DM [31]. Numerous studies have further supported the link between TCF7L2 polymorphisms and T2DM, implicating the Wnt signaling pathway in disease development across various populations [32-34]. Given the overlapping pathophysiology between GDM and T2DM, including shared genetic risk factors [35], it is plausible that rs12243326 contributes to GDM susceptibility and, by extension, increases the likelihood of developing PE [36]. Both PE and GDM are prevalent pregnancy complications that exhibit similar clinical risk profiles and underlying mechanisms [37].

Receiver operating characteristic (ROC) analysis revealed that the TCF7L2 gene polymorphisms rs12243326 and rs12255372, both individually and in combination, demonstrated strong predictive accuracy with high statistical significance ($p < 0.001$). These findings suggest that these variants of the transcription factor 7-like 2 gene may serve as potential genetic biomarkers for susceptibility to both PE and GDM.

We should take into account the study's limitations, which include the sample size and the impact that environmental interactions play in the pathophysiology of preeclampsia. Preeclampsia risk may be influenced by a number of environmental factors. Because Egypt has several genetically diverse communities, the study's findings cannot be applied to the entire Egyptian population. Since we made an effort to establish stringent selection criteria and only included similar ethnic people from a small geographic area, these results might be representative of the community under study. It is advised that larger research be done to validate these results. Preventive measures could therefore be implemented to lower the morbidity and mortality associated with preeclampsia.

CONCLUSION

This study identified the TCF7L2 gene polymorphisms rs12243326 (C/T) and rs12255372 (G/T) as potential genetic risk factors for preeclampsia in pregnant women. These findings may offer new insights into the genetic predisposition to both preeclampsia and gestational diabetes mellitus, supporting further investigation of their roles in maternal health.

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Declaration of Interest:
The authors declare that they have no conflicts of interests.

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