

## Research Article

# Association of Polymorphisms rs1801282 of the PPARG Gene, rs8192678 of the PPARGC1A Gene and rs7895833 of the SIRT1 Gene with the Risk of Preeclampsia in Pregnant Women with Gestational Diabetes in the Russian Population

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### Abstract

**Introduction:** Gestational Diabetes Mellitus (GDM) and Preeclampsia (PE) are the most common pregnancy complications. The frequency of preeclampsia in GDM is higher than in the population. The most reasonable role in the genesis of these diseases is considered to be the role of endothelial cell dysfunction, which occurs with increased production of reactive oxygen species against the background of hyperglycemia. SIRT1 controls ROI production by deacetylating, including PGC-1 $\alpha$ , which activation leads to the coactivation of several transcription factors, including nuclear receptors such as PPAR $\gamma$ . The aim of our study was to assess the effect of single nucleotide polymorphisms rs7895833 SIRT1 gene, rs8192678 PPARGC1A gene and rs1801282 PPARG gene on the development of PE in GDM in the Russian population.

**Materials and methods:** The study used the genomic DNA derived by phenol-chloroform extraction method from venous blood samples in 272 pregnant women, including samples of 136 women with GDM accompanied with PE and the blood samples of 136 women

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with GDM w/o preeclampsia. Genotyping of the selected polymorphisms was performed by real-time PCR with detection by competing TaqMan probes.

**Results:** In pregnant women with GDM in the PE+ group, the genotype containing the G allele of the PPARG gene in the heterozygous state was significantly more common (OR=1,93; 95% CI=1,15–3,22;  $p<0,05$ ), as well as the genotype with the G allele of the SIRT1 gene in the heterozygous state (OR=4,89; 95% CI=0,98–24,47;  $p<0,05$ ). The rs8192678 polymorphism of the PPARGC1A gene was not associated with preeclampsia with gestational diabetes mellitus.

**Conclusion:** The results of this study suggest PPARG (rs1801282) and SIRT1 (rs7895833) gene polymorphisms are significant risk factors for the development of preeclampsia in GDM in the Russian population.

**Keywords:** Endothelial dysfunction; Gestational diabetes mellitus; Preeclampsia; PPARG gene; PPARGC1A gene; Reactive oxygen species; SIRT1 gene; SNP

### Introduction

Gestational Diabetes Mellitus (GDM) and Preeclampsia (PE) are the most common pregnancy complications. PE is associated with the onset of arterial hypertension and proteinuria after gestation week 20 [1-3]. PE develops in 3% to 8% of pregnant women and is among the five most common causes of maternal morbidity and mortality [4-6]. According to data from different years, preeclampsia is much more common in gestational diabetes mellitus (7,3%) than it is in the population (4,5%) [7-9].

So far, the etiology and pathogenesis of GDM and PE are unclear. The most reasonable role in the genesis of these diseases is considered to be the role of endothelial cell dysfunction, which occurs with increased production of reactive oxygen species against the background of hyperglycemia [10-13]. Studies show that genetic factors are involved in the pathogenesis of PE and GDM. To date, 100 single nucleotide polymorphisms associated with preeclampsia have been identified [14-17].

SIRT1 protein belongs to the family of deacetylase proteins and controls a broad range of cell functions, including energy balance, lipid homeostasis, anti-ROS protection of the microvascular endothelium structure and functions [18-20]. SIRT1 controls ROI production by deacetylating both histones and many transcription factors [21]. SIRT1 is expressed in placental syncytiotrophoblasts and cytotrophoblasts [22]. Increased insulin resistance and inadequate response of  $\beta$ -cells contribute to a decrease in SIRT1 expression [23,24]. SIRT1 gene is located in the 10-th chromosome in the q21.3 locus and comprises 11 exons. Previous studies have shown that point mutations in promoters are more common than in coding regions of a gene and can affect its expression [25]. The rs7895833 polymorphism in the SIRT1 gene promoter region is associated with type 2 diabetes and obesity, according to few studies [26-28].

PGC-1 $\alpha$  coactivator belongs to the family of nuclear receptors and controls mitochondrial biogenesis in the vascular endothelium,

both in vitro and in vivo [29-32]. St-Pierre et al. (2006) suggests that PGC-1 $\alpha$  is one of the key control factors of ROS production [33]. The expression of PGC-1 $\alpha$  is observed in villous trophoblasts and in syncytiotrophoblasts [34]. PPARGC1A gene was mapped in the 4p15.2 locus and comprises 24 exons. The polymorphic variant of PPARGC1A (rs8192678) is associated with type 2 diabetes and its complications, the relative obesity risk, insulin resistance and hypertension risk [35,36].

A member of the PPAR $\gamma$  family of nuclear receptors, acting as a ligand-dependent transcription factor, plays a protective role in vascular endothelial cells [37-39]. PPAR $\gamma$  is expressed in villous trophoblasts and extravillary trophoblasts of the placenta throughout pregnancy [40-43]. Excess ROS production leads to PPAR $\gamma$  inactivation [44]. The PPARG gene is located on the human chromosome locus 3p25 and consists of nine exons. The single nucleotide polymorphism of PPARG (rs1801282) is associated with obesity, type 2 diabetes, GDM and arterial hypertension [45-50].

So far, we have not found any studies that estimated the impact of rs7895833 polymorphisms of SIRT1 gene, rs8192678 polymorphism of PPARGC1A gene and rs1801282 PPARG gene on PE risk in GDM pregnant women in the Russian- and English-language literature using the database search. Therefore, this study was designed to investigate the relationship between the PPARG, PPARGC1A and SIRT1 gene polymorphisms we selected and the GMD-related preeclampsia risk.

## Materials and Methods

### Research objects

The design of the study and the use of human material were approved by the ethics committee of the Research Institute of General Pathology and Pathophysiology. The study included patients who, in the period from April 2019 to December 2021, were observed and delivered in the Maternity Department of the State Clinical Hospital No. 29 (N.E. Bauman Hospital) of the Healthcare Department of Moscow. All respondents were native Russian speakers of indeterminate ethnicity (due to the ethical standards of the local medical register) and gave written consent to participate in the study. The diagnosis of GDM was established in accordance with the IADPSG recommendations and based on the criteria of the Russian National Consensus clinical guidelines “Gestational diabetes mellitus: diagnosis, treatment, postpartum care” [51,52]. Preeclampsia was diagnosed based on the clinical guidelines “Hypertensive Disorders in Pregnancy, Labor and Post-Partum. Pre-eclampsia. Eclampsia” [1]. The exclusion criteria were type 1 and type 2 diabetes mellitus, acute and chronic diseases in the acute stage, autoimmune, neuropsychiatric and oncological processes of any localization. The study did not include women with multiple pregnancies, other pregnancy complications, as well as disorders affecting glucose metabolism. QUANTO quantification software (Version 1.2.4, <https://bio.tools/QUANTO>), which takes into account the frequency of SNPs in the population and the prevalence of the disease [53]. In accordance with the above parameters, a sample size of 136 case-control pairs is required to identify the association between the selected polymorphisms and the risk of GDM. Blood samples were collected from pregnant women with GDM and pregnant women with normal glucose tolerance. All blood samples were obtained by venipuncture after an overnight fast and stored at -20 °C until analysis.

### Genomic DNA extraction and Polymerase Chain Reaction (PCR)

DNA was extracted and purified with genomic DNA extraction kit (Evrogen LLC, Russia) according to the kit specification. The high-molecular DNA was stored at -20 °C.

The quantity and quality of the isolated DNA was assessed by the ratio of the wavelength 260/280 when measuring the DNA concentration in the NanoDrop 1000 spectrophotometer in the double-stranded DNA analysis mode - dsDNA-50. Defective samples were not included into further analysis, just as those with low DNA concentration. The quantity and quality of the isolated DNA was assessed by the ratio of the wavelength 260/280 when measuring the DNA concentration in the NanoDrop 1000 spectrophotometer in the double-stranded DNA analysis mode - dsDNA-50. Defective samples were not included into further analysis, just as those with low DNA concentration. Genotyping polymorphisms rs7895833 of the SIRT1 gene in the promoter region, rs8192678 within the coding region of the PPARGC1A and rs1801282 of the PPARG gene was performed by real-time using the technology of competing TaqMan probes according to the method taken from the literature.

All primers and Taq-man probes were synthetically produced by Evrogen LLC, Russia (Table 1).

| SNP       | Oligonucleotide type and sequences                                                                                                                                                                                              |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| rs1801282 | Forward: TCCATGCTGTTATGGGTGAAACT<br>Revers: CTTTACCTTGTGATATGTTTCAGACA<br>Taq-Man Probe for allele:<br>FAM-TCTCCTATTGACCCAGAAAGCGATTTCCT-BHQ1<br>Taq-Man Probe for references allele:<br>HEX-TCTCCTATTGACGCAGAAAGCGATTTCCT-BHQ2 |
| rs8192678 | Forward: CACTTCGGTCATCCAGTCAA<br>Revers: TTATCACTTTCATCTTCGCTGTCATC<br>Taq-Man Probe for allele: FAM-AGACAAGACCGTGAA-BHQ1<br>Taq-Man Probe for references allele: HEX-CAGACAAGACCAAGT-GAA-BHQ1                                  |
| rs7895833 | Forward: TTCTGAAGTAATGAGGTGG<br>Revers: AGGAGACTCTGCCAGAAAT<br>Taq-Man Probe for allele: FAM-CCTACAGGAAATCAACG-TAA-BHQ1<br>Taq-Man Probe for references allele: HEX-CCTACAGGAAGT-CAACGTAA-BHQ1                                  |

**Table 1:** Sequences of oligonucleotides for RT-PCR of the rs1801282, rs8192678 and rs7895833.

The reaction mixture for RT-PCR for one 25  $\mu$ l sample contained 20ng DNA, 70 mM Tris-HCl (pH8.3), 2 mM ammonium sulfate, 0.02% BSA, 0.01% triton X-100, 0.01% sodium azide, pH 8.5-8.8, 125 mM dNTP, 200  $\mu$ M forward primer, 200  $\mu$ M reverse primer, 400  $\mu$ M each of Taq-man probes, 0,25 units of act. TaqDNA-polymerase. The reaction mixture for RT-PCR for one 25  $\mu$ l sample contained 20ng DNA, 5  $\mu$ l of the 5x qPCRmix-HS, 200  $\mu$ M forward primer, 200  $\mu$ M reverse primer, 400  $\mu$ M each of Taq-man probes.

Amplification was carried out in the CFX 96 programmable amplifier (Bio-Rad, USA) with the subsequent thermocycling parameters for rs7895833, rs8192678 and rs1801282: initial denaturation for 5 minutes at 95°C; then 40 cycles including denaturation at 95°C for 30 seconds, at 60°C for 30 seconds, at 72°C for 30 seconds with subsequent fluorescence pickup. The obtained data was examined using the CFX Manager TM software (Bio-Rad).

To eliminate genotyping errors, 30% of randomly selected samples were re-genotyped and the results obtained were additionally evaluated.

### Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Continuous data were shown as mean ± standard deviation (±SD) if normally distributed. Differences in age between groups were analyzed using Student's t-test. The Hardy–Weinberg equilibrium test was performed using the chi-square test in cases and controls separately for each variant before association analysis. Differences in allele and genotype frequencies between PE+ and PE- groups were analyzed using Pearson's chi-square test. Logistic regression analysis was used to evaluate associations between SNP genotypes and alleles and PE risk by calculating Odds Ratios (ORs) and their 95% Confidence Intervals (CIs). The anticipated risk factor was regarded as significant for pathology if OR adjusted by CI was greater than 1. The level of significance was considered significant at  $p \leq 0.05$ .

### Results

The study used DNA samples from 136 women with PE+ (mean age 31,72±4,95 years) and 136 women with PE- (mean age 31.01±4.83 years). There were no significant differences in the average age indicators ( $p > 0.05$ ).

Analysis of the polymorphic loci rs1801282 of the PPARG gene, rs8192678 of the PPARGC1A gene, and rs7895833 of the SIRT1 gene made it possible to estimate the frequency of occurrence of alleles and genotypes of the polymorphic loci of the studied genes (Table 2).

The distribution of frequencies of genotypes and alleles of polymorphic loci of the studied genes in the PE-group corresponded to that expected under the Hardy-Weinberg equilibrium.

The distribution of the rs1801282, rs8192678 and rs7895833 genotypes in the PE+ group differed from that expected for HWE. The probable reason for the deviation of the observed genotype frequencies for the three polymorphisms in this group is not the genotyping error, but the association of loci with the disease.

Significant differences were found in allele frequency and genotype distribution between PE+ and PE- groups for rs1801282 and rs7895833, while for rs8192678 the differences in allele frequency and genotype distribution were insignificant.

It was found that the frequency of allele C and homozygous genotype CC rs 8192678 in the group of pregnant women with GDM PE+ was slightly higher in the group with GDM PE+ compared with the group of GDM PE- (69.5% and 64.0%; 52.2% and 41.2%, respectively,  $p=0.031$ ). The frequency of G allele and heterozygous genotype CG rs1801282 in the group of pregnant women with GDM PE+ is almost 2 times higher in the group with GDM PE+ compared with the group of GDM PE- (22.4% and 12.5%; 41.9% and 22.1%, respectively,  $p=0.031$ ). The frequency of G allele and heterozygous genotype AG rs7895833 in the group of pregnant women with GDM PE+ is higher in the group with GDM PE+ compared with the group of GDM PE- (31.2% and 20.6%; 56.6% and 33.8% respectively,  $p=0.0002$ ).

The analysis of associations established the relationship of polymorphisms rs1801282 of the PPARG gene and rs7895833 of the SIRT1 gene with preeclampsia in women with GDM (Table 3). Thus, the heterozygous genotype CG rs1801282 and the heterozygous

| Gene/SNP           | Genotypes and alleles | PE+, n=136  | PE-, n=136  |
|--------------------|-----------------------|-------------|-------------|
| SIRT1 rs7895833    | AA                    | 55 (40.4%)  | 85 (62.5%)  |
|                    | AG                    | 77 (56.6%)  | 46 (33.8%)  |
|                    | GG                    | 4 (2.9%)    | 5 (3.7%)    |
|                    | A                     | 187 (68.8%) | 216 (79.4%) |
|                    | G                     | 85 (31.2%)  | 56 (20.6%)  |
| PPARGC1A rs8192678 | CC                    | 71 (52.2%)  | 56 (41.2%)  |
|                    | CT                    | 47 (34.6%)  | 62 (45.6%)  |
|                    | TT                    | 18 (13.2%)  | 18 (13.2%)  |
|                    | C                     | 189 (69.5%) | 174 (64.0%) |
|                    | T                     | 73 (30.5%)  | 98 (36.0%)  |
| PPARG rs1801282    | CC                    | 77 (56.6%)  | 104 (76.6%) |
|                    | CG                    | 57 (41.9%)  | 30 (22.1%)  |
|                    | GG                    | 2 (1.4%)    | 2 (1.4%)    |
|                    | C                     | 211 (77.6%) | 238 (87.5%) |
|                    | G                     | 61 (22.4%)  | 34 (12.5%)  |

**Table 2:** Distribution of alleles and genotypes of polymorphisms rs1801282 of the PPARG gene, rs8192678 of the PPARGC1A gene and rs7895833 of the SIRT1 gene in pregnant women with GDM in the PE+ and PE- groups.

Descriptions for table 2: SNP - Single Nucleotide Polymorphism

genotype AG rs7895833 in the general and dominant models of inheritance are genetic factors of predisposition to this complication of pregnancy, increasing the risk of its development by 11.5 ( $p=0.007$ ) and 4.6 ( $p=0.003$ ) times, respectively. A significant risk association for PE was observed in carriers of the G rs1801282 allele and the G rs7895833 allele in the additive inheritance model (2.024;  $p=0.002$  and 1.753,  $p=0.005$ , respectively). The AA rs7895833 genotype of the SIRT1 gene was associated with preeclampsia in the general and recessive inheritance patterns without confirmation of statistical significance ( $p > 0.05$ ).

| Gene/SNP        | Model of inheritance | Genotypes   | PE+, n=136 | PE-, n=136 | OR (95% of CI)      | chi2  | P*     |
|-----------------|----------------------|-------------|------------|------------|---------------------|-------|--------|
| SIRT1 rs7895833 | Codominant           | AA          | 55         | 85         | 2.092 (0.535-8.190) | 1.17  | 0.280  |
|                 |                      | AG          | 77         | 46         | 2.587 (1.572-4.259) | 14.24 | 0.0001 |
|                 |                      | GG          | 4          | 5          | 1.236 (0.318-4.807) | 0.09  | 0.759  |
|                 | Dominant             | AA/AG + GG  | 55/81      | 85/51      | 2.455 (1.507-3.997) | 13.25 | 0.0002 |
|                 | Recessive            | AA + AG/ GG | 132/4      | 131/5      | 1.260 (0.331-4.795) | 0.11  | 0.734  |
|                 | Additive             | A           | 187        | 216        | 0.570 (0.386-0.842) | 8.05  | 0.005  |
|                 |                      | G           | 75         | 56         | 1.753 (1.187-2.590) | 8.05  | 0.005  |

|                        |            |                   |        |        |                         |       |         |
|------------------------|------------|-------------------|--------|--------|-------------------------|-------|---------|
| PPARG-CIA<br>rs8192678 | Codominant | CC                | 54     | 58     | 0.758<br>(0.356-1.613)  | 0.52  | 0.472   |
|                        |            | CT                | 61     | 62     | 0.598<br>(0.357-1.002)  | 3.84  | 0.050   |
|                        |            | TT                | 21     | 16     | 0.758<br>(0.356-1.613)  | 0.52  | 0.472   |
|                        | Dominant   | CC/<br>CT +<br>TT | 54/82  | 58/78  | 0.641<br>(0.397-1.035)  | 3.32  | 0.068   |
|                        | Recessive  | CC +<br>CT/<br>TT | 115/21 | 120/16 | 1.000<br>(0.496-2.017)  | 0.00  | 1.000   |
|                        | Additive   | C                 | 169    | 178    | 1.283<br>(0.897-1.834)  | 1.86  | 0.172   |
|                        |            | T                 | 103    | 94     | 0.780<br>(0.545-1.115)  | 1.86  | 0.172   |
| PPARG<br>rs1801282     | Codominant | CC                | 77     | 104    | 1.900<br>(0.255-14.169) | 0.40  | 0.525   |
|                        |            | CG                | 57     | 30     | 2.566<br>(1.509-4.365)  | 12.41 | 0.0004  |
|                        |            | GG                | 2      | 2      | 1.351<br>(0.186-9.802)  | 0.09  | 0.765   |
|                        | Dominant   | CC/<br>CG +<br>GG | 77/59  | 104/32 | 2.490<br>(1.478-4.195)  | 12.04 | 0.0005  |
|                        | Recessive  | CC +<br>CG/<br>GG | 134/2  | 134/2  | 1.000<br>(0.139-7.203)  | 0.00  | 1.00000 |
|                        | Additive   | C                 | 211    | 238    | 0.494<br>(0.312-0.782)  | 9.30  | 0.002   |
|                        |            | G                 | 61     | 34     | 2.024<br>(1.279-3.201)  | 9.30  | 0.002   |

**Table 3:** Association of genotypes of polymorphisms rs1801282 of the PPARG gene, rs8192678 of the PPARGC1A gene and rs7895833 of the SIRT1 gene with preeclampsia in pregnant women with GDM.

Descriptions for table 3: SNP - Single Nucleotide Polymorphism, Control (PE-) versus PE+, OR - odds ratio, CI - Confidence interval, chi<sup>2</sup> - chi-square distribution, P – p-Value Definition.

## Discussion

Preeclampsia and GDM are the most common complications in pregnancy, in the implementation of which genetic factors are involved. Identifying additional genetic risk markers for GDM may be useful in early diagnosis and would also allow for earlier prevention and treatment.

It is known that the rs7895833 polymorphism versions in the promoter region of the SIRT1 gene are associated with type 2 diabetes, obesity and hypertension development risk, according to few studies [20-22]. Higashibata et al., showed that females with the A rs7895833 allele gained more weight since the age of 20 than those without that allele [54]. Shimabara et al., demonstrated that A rs7895833 allele in females is associated with a high hypertension risk [22].

There is a point of view that Gly482Ser (rs8192678) polymorphism is associated with insulin resistance, relative obesity and hypertension risk [35,36]. The findings of a few studies that link rs8192678 polymorphism of the gene PPARGC1A with type 2 diabetes mellitus risk are controversial in different populations [55-59]. However, the meta-analysis conducted by Xia W et al., revealed a significant association between PPARGC1A rs8192678 polymorphism and susceptibility to Type 2 diabetes mellitus in Ser allele and Ser/Ser genotype carriers in the Caucasian and Indian populations. In addition, the association was found in the East Asian population, as part of recessive and homozygous genetic models [60]. Even though the previous studies suggested that GDM and Type 2 DM share the genetic polymorphisms, with the same effect size for the same risk alleles, the findings of the studies by Leipold H et al., Shaat N et al., and Franzago M et al., did not reveal any association between the rs8192678 gene version in PPARGC1A gene with GDM development risk [61-63]. The meta-analysis by Vimalaswaran et al., based on 17 studies involving 13,949 pts revealed that homozygous carriers of Ser allele younger than 50 y.o. have a higher blood pressure than homozygous carriers of Gly allele of the same age [64].

The polymorphic variant rs1801282, also known as Pro12Ala, is associated with obesity, type 2 diabetes, GDM and arterial hypertension [45-50]. However, studies have shown conflicting results regarding the role of Pro12Ala in the development of GDM. Anghebem-Oliveira et al., found no relationship between the rs1801282 polymorphism and the risk of developing GDM in the Brazilian population [65]. Lin et al., after analyzing sixteen studies involving 3129 women with GDM and 7168 without it, found that the protective G allele of the rs1801282 polymorphism was associated with a reduced risk of GDM in Asians, especially Chinese, but not South Koreans [66]. Data from meta-analyses of studies of the genetic association of Pro12Ala polymorphism with the risk of developing GDM by Wu et al., and Wang et al., suggest a potential role for the Pro allele in the pathogenesis of GDM in Asian populations, but not in the Caucasian population [67,68]. Data from Rodrigues et al., indicate that carriers of the Ala allele, who are severely obese, have high blood pressure [49]. The results of a meta-analysis by Wang et al., showed a significant association of the rs1801282 polymorphism with a predisposition to hypertension among East Asians, but not among Caucasians [69]. The relationship between the rs1801282 PPARG gene and the risk of developing preeclampsia has been little studied. The current studies by Laasanen et al., and Liu et al., found no relationship between the rs1801282 polymorphism of the PPARG gene and the occurrence of preeclampsia [70,71].

The main goal of this study was to determination of the relationship between the polymorphic loci rs12778366, rs7895833 of the SIRT1 gene, rs8192678 of the PPARGC1A gene and the risk of developing preeclampsia in pregnant women with gestational diabetes mellitus in the Russian population. The study showed the association of polymorphic loci rs1801282 of the PPARG gene and rs7895833 of the SIRT1 gene with the risk of developing preeclampsia. In pregnant women with GDM in the PE+ group, the genotype containing the G allele of the PPARG gene in the heterozygous state was significantly more common (OR=1.93; 95% CI=1.15–3.22; p<0.05), as well as the genotype with the G allele of the SIRT1 gene in the heterozygous state (OR=4.89; 95% CI=0.98–24.47; p<0.05). The rs8192678 polymorphism of the PPARGC1A gene was not associated with preeclampsia with gestational diabetes mellitus. It is important to note that the relationship between the rs1801282 PPARG gene and the risk



of developing preeclampsia is poorly understood, and studies of the association of rs8192678 of the PPARGC1A gene, rs7895833 of the SIRT1 gene in PE against the background of GDM have not been previously. It is important to note that the relationship between the rs1801282 PPARG gene and the risk of developing preeclampsia is poorly understood, and studies of the association of rs8192678 of the PPARGC1A gene, rs7895833 of the SIRT1 gene in PE against the background of GDM have not been previously conducted.

## Conclusion

The results of this study suggest PPARG (rs1801282) and SIRT1 (rs7895833) gene polymorphisms are significant risk factors for the development of preeclampsia in GDM in the Russian population. The small sample size of the study groups is the key limitation of this study. Nonetheless, the data we obtained point to the need to further investigate the polymorphic loci we selected in a larger patient sample, which will enable using this genetic marker in the future as the assessment criterion in the individual outlook of preeclampsia development in GDM pregnant women to take efficient preventive measures to timely remedy and improve the pregnancy outcome.

## Data Availability

The data used to support the findings of this study are included within the article.

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## Author's Contribution

OPD, NSK, MKN contributed to experiment design and data review; OPD participated in data analysis; OPD, NSK and MKN contributed to data analysis and interpretation; OPD wrote the draft manuscript and the final version of the article.

## Conflicts of Interest

All authors declared no competing interests.

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## Research Highlights

### What is the current knowledge?

- The frequency of preeclampsia in GDM is higher than in the population.
- The relationship between the rs1801282 PPARG gene and the risk of developing preeclampsia has been little studied.
- PPARGC1A and SIRT1 gene polymorphisms are to be associated with hypertension, but have never been investigated in connection with preeclampsia.

### What is new here?

- The association between PPARG (rs1801282) and SIRT1 (rs7895833) gene polymorphisms and the risk of developing preeclampsia in GDM has been studied for the first time.
- PPARG (rs1801282) and SIRT1 (rs7895833) gene polymorphisms are significant risk factors for the development of preeclampsia in GDM in the Russian population.
- Lack of evidences to association the PPARGC1A rs8192678 SNP with the risk of preeclampsia with gestational diabetes mellitus in the Russian population.

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