Winter 2026, Volume 11, Issue 40 (37- 44) DOI: 10.22034/ppmj.2026.735672

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Investigation of Gene Expression and DNA Methylation of IGF2, PPARγ, LEP, and CDKN1C in Gestational Diabetes Mellitus

Mahsa Maqsoodi [1] , Abbas Ardalan [2] *

[1] **Department of Microbiology, ShK.C., Islamic Azad University, Shahrekord, Iran.**
[2] **Department of biology, faculty of science, Arak university, Arak, Iran.**

ARTICLE INFO

Paper Type: Original Article

Submitted: 2025-10-10
Accepted: 2026-03-08

Keywords:
Gestational diabetes mellitus
DNA methylation
Epigenetics
Gene expression
IGF2

Corresponding author:
Abbas Ardalan
Email: abbasardalan@rocketmail.com

ABSTRACT

Gestational diabetes mellitus (GDM) is a prevalent complication of pregnancy associated with adverse outcomes for both mother and fetus. Epigenetic modifications, particularly DNA methylation, may play a significant role in its pathogenesis. This study aimed to evaluate the expression and methylation status of IGF2, PPARγ, LEP, and CDKN1C in women with GDM. In this case control study, 50 women with GDM and 50 healthy pregnant women were included. Gene expression levels and DNA methylation patterns were analyzed, and clinical risk factors were assessed. Significant differences were identified in both expression and methylation profiles of the studied genes between GDM patients and controls. Pre-pregnancy BMI, high-fat diet, and family history of diabetes were significantly associated with GDM. These results indicate that GDM is influenced by metabolic, environmental, and epigenetic factors, and that altered expression and methylation of IGF2, PPARγ, LEP, and CDKN1C may contribute to its development.

How to Cite this Article:

M. Maqsoodi, A. Ardalan. "Autoimmune Diseases and Their Relationship with Environmental Pollution" Personalized & Precision Medicine Journal, Vol. 11, no. 40, pp. 37- 44.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as hyperglycemia first detected during pregnancy based on IADPSG/WHO criteria and represents one of the most common pregnancy complications, affecting about 14% of pregnancies worldwide (1–3). Poorly controlled GDM is associated with adverse maternal outcomes such as gestational hypertension, pre-eclampsia, and Caesarean delivery, as well as long-term risks including cardiovascular disease, obesity, and progression to Type 2 diabetes in both mother and offspring (4–7).

The pathogenesis of GDM remains incompletely understood and appears to involve complex interactions among genetic, metabolic, and environmental factors (8). Established risk factors include advanced maternal age, pre-pregnancy obesity, family history of diabetes, prior GDM, infections such as HIV, smoking, and socioeconomic conditions (9- 14). Mechanistically, GDM is linked to β-cell dysfunction, insulin resistance, adipose tissue dysfunction, gluconeogenesis, gut microbiota imbalance, and oxidative stress (15), with growing evidence highlighting the contribution of epigenetic regulation (16). Epigenetic mechanisms—including DNA methylation, histone modifications, and miRNA-mediated regulation—can alter gene expression without changing DNA sequence (17). DNA methylation, particularly at CpG sites, plays a major regulatory role, influencing gene expression depending on its genomic location (18), although its direct relationship with expression remains inconsistently reported (19).

Several studies have explored methylation changes in GDM, including genome-wide alterations prior to diagnosis and gene-specific promoter methylation in metabolic pathways (20–22). Among key genes, LEP regulates energy homeostasis and insulin secretion (23, 24), PPARγ is involved in adipogenesis and glucose metabolism and is linked to diabetes and pregnancy metabolic adaptation (25–27), IGF2 influences insulin sensitivity and fetal growth (28–30), and CDKN1C controls cell proliferation, including pancreatic β-cell expansion (31–33). Despite these findings, most studies have examined methylation or gene expression separately, with limited integration of clinical and lifestyle factors. Therefore, this study aimed to simultaneously assess methylation and expression of these genes alongside relevant clinical and lifestyle variables in pregnant women with GDM.

This study aimed to investigate the expression levels and DNA methylation status of key metabolic genes, including IGF2, PPARγ, LEP, and CDKN1C, in women with GDM compared with healthy pregnant controls. In addition, the study sought to evaluate the association between these molecular alterations and clinical as well as lifestyle-related risk factors in order to provide a more comprehensive understanding of the mechanisms underlying GDM pathogenesis.

MATERIALS AND METHODS

Study design

This study included 50 pregnant women with GDM and 50 healthy pregnant women with normal blood glucose levels based on the IADPSG diagnostic criteria, and the two groups were matched for age and body mass index (BMI). People with metabolic diseases other than gestational diabetes and those taking certain medications, such as steroids, were excluded from the trial due to their potential impact on gene expression and methylation. All required information was collected with the consent of the participants in this study through a questionnaire and medical records.

Sampling and RNA extraction

5 ml of peripheral blood was collected from each participant in EDTA tubes and stored at -80°C until use. RNA was extracted from peripheral blood using the Blood RNA Isolation Kit (DENAzist co). The purified RNA was then converted to cDNA using the Reverse Transcription Kit (DENAzist co).

Real-Time Polymerase Chain Reaction

Real-time PCR analysis of adiponectin, IGF2, PPARγ, LEP, CDKN1C, and GAPDH (as the reference gene) was performed using the SYBR Green PCR Master Mix assay. Each reaction was carried out under specified conditions in a total volume of 10.0 µL, containing 5.0 µL of SYBR Green PCR Master Mix, 0.5 µL of forward primer and 0.5 µL of reverse primer for each target gene (Table 1) at a final concentration of 10 pmoL, 1.0 µL of cDNA template, and 3.0 µL of RNase-free water. The thermal cycling protocol consisted of denaturation at 95°C for 15 seconds, primer annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds. Data were analyzed using the ΔΔCt method.

DNA methylation screening

DNA extraction

DNA was extracted using the Blood DNA isolation kit (Denazist co) according to the protocol.

Bisulfite treatment

In this study, the Qiagen bisulfite treatment kit (EpiTect Bisulfite Kits) was used for DNA sequence treatment.

Methylation-specific PCR reaction

Methylation-specific polymerase chain reaction (MSP) is a technique that has facilitated the detection of promoter hypermethylation at CpG islands in cell lines and clinical samples (34). Specific primers were designed for methylated and unmethylated sequences of each gene (Table 1). Moreover, uni DNA and water were used as positive and negative controls. PCR reactions were performed in a thermocycler, and then the products were electrophoresed on a 2% agarose gel.

Statistical analysis

For comparative analysis of gene expression levels between groups, the relative expression ratio was used with the ΔΔCt method in Real-Time PCR. To compare quantitative variables between groups, an independent t-test was used, and to examine qualitative variables, chi-square test was used. Data were reported as Mean ± SD. To examine the association of risk factors with GDM, logistic regression model was used. Results were reported as Odds Ratio (OR) with 95% Confidence Interval (CI). A significance level of $p < 0.05$ was considered as the threshold of significance in all tests. All analyses were performed with SPSS version 26 software. GraphPad Prism software was also used to prepare visual graphs. In addition, the intensity of methylated and unmethylated bands was evaluated for semi-quantitative analysis by ImageJ software.

RESULTS

Patient characteristics

Participant characteristics are presented in Table 2. The age range of patients with Gestational diabetes mellitus (GDM) was 20 to 41 years (mean: 32.5

Table 1. Sequence of primers used and product size *M: methylated DNA, U: unmethylated DNA

q-PCR			
Gene	**Primer sequence**	**Tm ◦C**	**Product size (bp)**
IGF2	F: GTGGCATCGTTGAGGAGTG R; CACGTCCCTCTCGGACTTG	60	92
PPARY	F: ACCAAAGTGCAATCAAAGTGGA R: ATGAGGGAGTTGGAAGGCTCT	60	100
LEP	F: TGCCTTCCAGAAACGTGATCC R: CTCTGTGGAGTAGCCTGAAGC	61	164
CDKN1C	F: GTGAGCCAATTTAGAGCCCA R: CGGTTGCTGCTACATGAACG	59	104
GAPDH	F: GGAGCGAGATCCCTCCAAAAT R: GGCTGTTGTCATACTTCTCATGG	60	197
MSP			
IGF2-M	F: GACGTTAATTTTCGGGGACGTT R: AACGCGAAATAAAACGAACGTATACGA	55	363
IGF2-U	F: TTTTGGATGTTAATTTTTGGGGATGTT R: AAAAAAACACAAAATAAAACAAACATATACAA	64	373
PPARY-M	F: AAGACGGTTTGGTCGATC R: CGAAAAAAAATCCGAAATTTAA	52	124
PPARY-U	F: GGGAAGATGGTTTGGTTGATT R: TCCAAAAAAAAATCCAAAATTTAA	53	128
LEP-M	F: TTTGGAGGGATATTAAGGATTTTTC R: TACAACCGCTAACGCTACGAT	59	301
LEP-U	F: TTTGGAGGGATATTAAGGATTTTTT R: ACCTTACAACCACTAACACTACAAT	59	305
CDKN1C-M	F: GTTAGTTGGCGTAGGAGGTTTAC R: AAAACGCTACGAACGATAACG	55	257
CDKN1C-U	F: TTAGTTGGTGTAGGAGGTTTATGG R: TAAAAAACACTACAAACAATAACATA	55	259

years), while in the healthy control group it ranged from 22 to 43 years (mean: 33.4 years). The findings indicated significant associations between pre-pregnancy BMI, high-fat diet, and family history of diabetes with GDM (P=0.04, Odds ratio: 2.062, 95% CI: 1.009–4.213; P=0.000, Odds ratio: 0.193, 95% CI: 0.081–0.459; P=0.011, Odds ratio: 3.777, 95% CI: 1.342–10.628). In contrast, no significant associations were found between GDM and maternal age, systolic blood pressure, physical activity, gestational weight gain, or smoking.

Comparison of the expression status

Based on the results obtained, IGF2 gene expression was increased 1.6-fold in the GDM group (P=0.0.041). Regarding the PPARγ gene, a 0.44-fold decrease in expression was observed in the GDM group (P=0.039). The LEP gene showed a 1.8-fold increase in expression

Table 2. Association between clinical characteristics of control and GDM groups and risk factors with GDM

Clinical characteristics/risk factors	GDM (n=50)	Control (n=50)	p-value*
Maternal age (Mean ± SD)	32.5±3.2	33.4±2.8	0.923
Pre-pregnant BMI (kg/m2) (Mean ± SD)	30.2±3.1	16.6 ± 2.5	**0.04**
Systolic blood pressure (mmHg) (Mean ± SD)	120 ± 12	116 ± 10	0.887
Physical activity			
Yes	18(36%)	24(48%)	0.225
No	32(64%)	26(52%)	
Diet			
High-fat	31(62%)	12(24%)	**0.000**
Low-fat	19(38%)	38(76%)	
Weight gain during pregnancy (kg) (Mean ± SD)	18 ± 4	12 ± 3	0.337
Smoking	4(8%)	5(10%)	0.727
Non-smoking	46(92%)	45(90%)	
Family history of diabetes			
Yes	١٧(34%)	6(12%)	**0.011**
No	33(66%)	44(88%)	

in the GDM group compared to the control group (P=0.0.036). A 0.5-fold decrease in expression was observed in the GDM group for the CDKN1C gene (P=0.028) (fig 1).

Comparison of the DNA methylation status

Table 3 shows the methylation status of IGF2, PPARγ, LEP, and CDKN1C genes in the control and GDM groups.

IGF2 gene

The methylation level was significantly reduced in the GDM group. In the GDM group, 38% of the samples were methylated, while in the control group this value was 64% (P=0.01, Odds ratio: 0.344, 95 % CI: 0.153-0.776).

PPARγ gene

No significant difference was observed in the methylation level of the PPARγ gene between the two groups. The methylation percentage in the GDM group was 52%, and in the control group was 56%.

LEP gene

Reduced methylation levels were observed in the LEP gene promoter in the GDM group. 36% of patient samples were methylated, while in the control group this value was 68% (P=0.001, Odds ratio: 3.777, 95 % CI: 1.649-8.651).

CDKN1C gene

Increased methylation of the CDKN1C gene was observed in the GDM group. 60% of samples in the GDM group were methylated, while this value was 28% in the control group (P=0.001, Odds ratio: 0.259, 95 % CI: 0.112-0.599).

In figure 2, the results of the bands obtained from 2% gel electrophoresis related to the 4 genes IGF2, PPARγ, LEP, and CDKN1C using the MSP-PCR technique, along with positive and negative controls, can be seen.

DISCUSSION

GDM is a multifactorial disorder shaped by genetic, epigenetic, and environmental influences (35). In the present study, the expression and methylation status of four key genes IGF2, PPARγ, LEP, and CDKN1Cwere examined in patients with GDM and compared with those in the control group. The findings revealed significant alterations in both expression and methylation patterns of these genes in GDM, highlighting their potential involvement in the pathophysiology of the disease.

Based on the results of comparing clinical characteristics and some risk factors between the GDM and control groups in this study, significant associations were observed between BMI, High-fat diet and family history of diabetes and GDM. These risk factors likely exacerbate the observed epigenetic and gene expression changes. This associations have

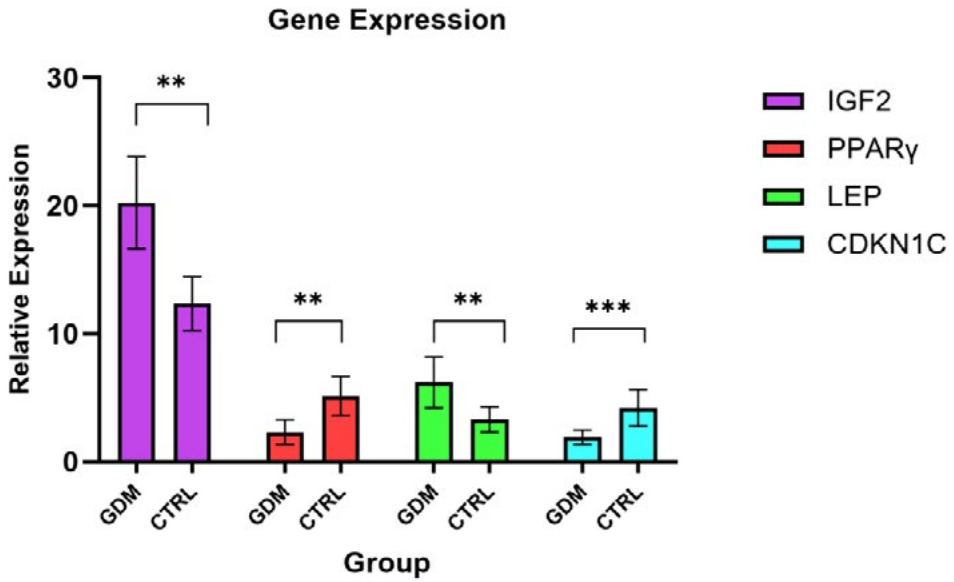

Fig 1. Schematic diagram comparing the expression levels of IGF2, PPARγ, LEP, and CDKN1C genes between the control and GDM groups using real-time PCR technique.

Table3. Comparison of methylation of IGF2, PPARγ, LEP and CDKN1C genes in control and GDM groups.

gene	methylation in the GDM group (n=50)	methylation in the control group (n=50)	odds ratio 95 % CI	P-value*
IGF2	19(38%)	32(64%)	0.344 0.153-0.776	**0.010**
PPARγ	26(52%)	28(56%)	0.851 0.3874-1.870	0.688
LEP	18(36%)	34(68%)	3.777 1.649-8.651	**0.001**
CDKN1C	30(60%)14(28%)	14(28%)	0.259 0.112-0.599	**0.001**

also been noted in other studies (36, 37, 38). In fact, it can be said that pre-pregnancy obesity and high BMI are among the most important risk factors for GDM and lead to increased insulin resistance and chronic inflammation (36). Changes in lipid profile (such as increased LDL cholesterol and triglycerides), which can be caused by obesity and an unhealthy, high-fat diet, are a characteristic of GDM and can affect the health of the mother and fetus (37). These types of diets lead to inflammation and insulin resistance (38). Also, advanced maternal age at the time of pregnancy and a family history of diabetes are strong risk factors for GDM (39).

Based on the findings, IGF2 gene expression was approximately 1.6-fold higher in the GDM group compared with the control group. In a study investigating alterations in the IGF axis during pregnancy, elevated serum IGF2 levels were reported in women with GDM, suggesting that increased IGF-2 may influence maternal and fetal metabolic processes (30). In contrast, another study examining IGF-I and IGF-II levels in mothers and fetuses and their association with fetal growth and gestational diabetes found no significant difference in maternal IGF-II levels between diabetic and non-diabetic groups (40). Additionally, Wei et al. reported increased IGF2 expression in placental tissues from patients with diabetes (including gestational diabetes and Type 2 diabetes) compared to controls, suggesting that this upregulation may represent an adaptive response to the intrauterine hyperglycemic environment (41). Elevated IGF2 expression may contribute to the development or exacerbation of GDM by promoting insulin resistance, impairing placental function, and enhancing nutrient

transfer to the fetus. Furthermore, studies in both murine and human samples demonstrated that increased IGF2 expression is associated with higher body weight, and that IGF2 levels in maternal peripheral blood and fetal cord blood are independently linked to macrosomia. These findings highlight the important role of IGF-2 in regulating growth and glucose–lipid metabolism during pregnancy and the postpartum period (42).

The expression of the PPARγ gene was significantly reduced in the GDM group, reaching 0.44 relative to the control group. This observation is in agreement with previous studies reporting an association between decreased PPARγ expression and disturbances in lipid and glucose metabolism (43). Given the key role of this gene in modulating insulin sensitivity, alterations in its expression may contribute to increased insulin resistance and the progression of GDM (44).

The expression level of the LEP gene was significantly increased in the GDM group compared to the control group (1.8-fold). The increased expression of this gene in GDM usually occurs due to insulin resistance and inflammatory changes. LEP is secreted by fat cells and in GDM, the level of this hormone is also increased due to hyperglycemia and increased adipose tissue (45). These results are consistent with previous studies investigating the role of leptin in insulin resistance and inflammation. For example, a study examined the association between maternal plasma LEP levels in early pregnancy and the risk of GDM. According to the study, early pregnancy LEP levels were significantly associated with an increased risk of GDM. It also introduced LEP as a predictive marker for GDM and emphasized the need for more extensive studies in this field (46). Another study has implicated LEP as a key adipokine in the development of GDM through insulin resistance and placental inflammatory processes. Alterations in the levels of this hormone disrupt fetal metabolic development, increase the risk of birth defects and intrauterine growth restriction, and increase the likelihood of developing metabolic diseases in the future (47).

Unlike IGF-2 and leptin, the expression of the CDKN1C gene in the present study was reduced by half in the GDM group compared to the control group. The change in the expression of this gene could be due to epigenetic effects and molecular pathways. Since the product of this gene is a cell cycle inhibitor, the change in its expression level could lead to an increase in uncontrolled cell division in some tissues and impaired placental development. It also indirectly increases the risk of metabolic complications in infants born to mothers with GDM (48). While the provided papers do not directly associate CDKN1C with gestational diabetes mellitus (GDM), they offer insights into its broader implications in metabolic regulation and growth disorders, which could indirectly relate to GDM. CDKN1C's role in regulating β-cell proliferation and its involvement in growth syndromes suggest potential pathways through which it might influence conditions like GDM (49, 50, 51).

REFERENCES

1. Buchanan, T.A.; Xiang, A.H.; Page, K.A. Gestational Diabetes Mellitus: Risks and Management during and after Pregnancy. Nat. Rev. Endocrinol. 2012, 8, 639–649.
2. Crowther, C.A.; Hiller, J.E.; Moss, J.R.; McPhee, A.J.; Jeffries, W.S.; Robinson, J.S.; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N. Engl. J. Med. 2005, 352, 2477–2486.
3. Wang, H.; Li, N.; Chivese, T.; Werfalli, M.; Sun, H.; Yuen, L.; Hoegfeldt, C.A.; Elise Powe, C.; Immanuel, J.; Karuranga, S.; et al. IDF Diabetes Atlas: Estimation of Global and Regional Gestational Diabetes Mellitus Prevalence for 2021 by International Association of Diabetes in Pregnancy Study Group's Criteria. Diabetes Res. Clin. Pract. 2022, 183, 109050.
4. Kondracki, A.J.; Valente, M.J.; Ibrahimou, B.; Bursac, Z. Risk of large for gestational age births at early, full and late term in relation to pre-pregnancy body mass index: Mediation by gestational diabetes status. Paediatr. Perinat. Epidemiol. 2022, 36, 566–576.
5. Lee, K.W.; Ching, S.M.; Ramachandran, V.; Yee, A.; Hoo, F.K.; Chia, Y.C.; Sulaiman, W.A.W.; Suppiah, S.; Mohamed, M.H.; Veettil, S.K. Prevalence and risk factors of gestational diabetes mellitus in Asia: A systematic review and meta-analysis. BMC Pregnancy Childbirth 2018, 18, 494.
6. McIntyre, H.D.; Catalano, P.; Zhang, C.; Desoye, G.; Mathiesen, E.R.; Damm, P. Gestational diabetes mellitus. Nat. Rev. Dis. Primers 2019, 5, 47.
7. Lenoir-Wijnkoop, I.; Van Der Beek, E.M.; Garssen, J.; Nuijten, M.J.C.; Uauy, R.D. Health economic modeling to assess short-term costs of maternal overweight, gestational diabetes, and related macrosomia A pilot evaluation. Front. Pharmacol. 2015, 6, 103.
8. Plows, J.F.; Stanley, J.L.; Baker, P.N.; Reynolds, C.M.; Vickers, M.H. The Pathophysiology of Gestational Diabetes Mellitus. Int. J. Mol. Sci. 2018, 19, 3342. [Google Scholar] [CrossRef]
. W., Kinabo J., Ramaiya K., and Feskens E. J., Gestational diabetes mellitus in sub-Saharan Africa: systematic review and metaregression on prevalence and risk factors, Tropical Medicine & International Health. (2015) 20, no. 8, 983–1002,
10. Cypryk K., Szymczak W., Czupryniak L., Sobczak M., and Lewiński A., Gestational diabetes mellitus

an analysis of risk factors, Endokrynologia Polska. (2008) 59, no. 5, 393–397, 18979449.
11.Ganapathy A., Holla R., Darshan B. B., Kumar N., Kulkarni V., Unnikrishnan B., Thapar R., Mithra P., and Kumar A., Determinants of gestational diabetes mellitus: a hospital-based case control study in coastal South India, International Journal of Diabetes in Developing Countries. (2021) 41.
12.Jao J., Wong M., Van Dyke R. B., Geffner M., Nshom E., Palmer D., Muffih P. T., Abrams E. J., Sperling R. S., and LeRoith D., Gestational diabetes mellitus in HIV-infected and -uninfected pregnant women in Cameroon, Diabetes Care. (2013) 36, no. 9, e141–e142.
13.Muche A. A., Olayemi O. O., and Gete Y. K., Prevalence and determinants of gestational diabetes mellitus in Africa based on the updated international diagnostic criteria: a systematic review and meta-analysis, Archives of Public Health. (2019) 77, no. 1.
14.Zhang Y, Xiao CM, Zhang Y, Chen Q, Zhang XQ, Li XF, Shao RY, Gao YM. Factors associated with gestational diabetes mellitus: a Meta-analysis. Journal of diabetes research. 2021;2021(1):6692695.
15.Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci 2018; 19:3342.
16.Dalfrà MG, Burlina S, Del Vescovo GG, Lapolla A. Genetics and epigenetics: new insight on gestational diabetes mellitus. Frontiers in endocrinology. 2020 Dec 1;11:602477.
17.Barker DJ. The fetal and infant origins of adult disease. BMJ (1990) 301:1111–22.
18.Hernando-Herraez I, Garcia-Perez R, Sharp AJ, Marques-Bonet T. DNA methylation: insights into human evolution. PLoS Genet. 2015;11(12):e1005661e1005661.
19.Lee, D.D.; Leão, R.; Komosa, M.; Gallo, M.; Zhang, C.H.; Lipman, T.; Remke, M.; Heidari, A.; Nunes, N.M.; Apolónio, J.D.; et al. DNA hypermethylation within TERT promoter upregulates TERT expression in cancer. J. Clin. Investig. 2019, 129, 223–229.
20.Wu P, Farrel WE, Haworth KE, Emes RD, Kitchen MO, Glossop JR, et al. Maternal genome-wide DNA methylation profile in gestational diabetes shows distinctive disease-associated changes relative to matched healthy pregnancies. Epigenetics (2018) 13(2):122–8.
21.Bouchard L, Thibault S, Guay SP, Santure M, Monpetit A, St-Pierre J, et al. Leptin Gene Epigenetic Adaptation to Impaired Glucose Metabolism During Pregnancy. Diabetes Care (2010) 33:2436–41.
22.Bouchard L, Hivert MF, Guay SP, St-Pierre J, Perron P, Brisson D. Placental Adiponectin Gene DNA Methylation Levels Are Associated With Mothers' Blood Glucose Concentration. Diabetes (2012) 61:1272–80.
23.R.N. Kulkarni, Z.L. Wang, R.M. Wang, J.D. Hurley, D.M. Smith, M.A. Ghatei, D.J. Withers, J.V. Gardiner, C.J. Bailey, S.R. Bloom. Leptin rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice J. Clin. Invest., 100 (1997), pp. 2729-2736
24.C. Lesseur, D.A. Armstrong, A.G. Paquette, D.C. Koestler, J.F. Padbury, C.J. Marsit. Tissue-specific Leptin promoter DNA methylation is associated with maternal and infant perinatal factorsMol. Cell. Endocrinol., 381 (2013), pp. 160-167
25.Fajas L, Auboeuf D, Raspe E, Schoonjans K, Lefebvre AM, Saladin R, et al. The organization, promoter analysis, and expression of the human PPARgamma gene. J Biol Chem. 1997;272(30):18779–89.
26.Wójcik M, Mac-Marcjanek K, Nadel I, Woźniak L, Cypryk K. Gestational diabetes mellitus is associated with increased leukocyte peroxisome proliferator-activated receptor γ expression. Archives of Medical Science. 2015 Aug 12;11(4):779-87.
27.Bayramci NS, Acik L, Kalkan Ç, Yetkin İ. Investigation of glucocorticoid receptor and calpain-10 gene polymorphisms in Turkish patients with type 2 diabetes mellitus. Turkish Journal of Medical Sciences. 2017;47(5):1568-75.
28.A.C. Moses, et al. Recombinant human insulin-like growth factor I increases insulin sensitivity and improves glycemic control in type II diabetes Diabetes, 45 (1) (1996), pp. 91-100
29.Martín-Estal I, Castorena-Torres F. Gestational diabetes mellitus and energy-dense diet: what is the role of the insulin/IGF axis?. Frontiers in Endocrinology. 2022 Jun 23;13:916042.
30.Anderlová K, Cinkajzlová A, Šimják P, Klouèková J, Kratochvílová H, Lacinová Z, Kaválková P, Krejèí H, Mráz M, Paøízek A, Haluzík M. Insulin-like growth factor axis in pregnancy and gestational diabetes mellitus. Physiological research. 2019 Sep 1;68(5):807-16.
31.Arboleda VA, Lee H, Parnaik R, Fleming A, Banerjee A, Ferraz-de-Souza B, Délot EC, Rodriguez-Fernandez IA, Braslavsky D, Bergadá I, Dell'Angelica EC. Mutations in the PCNA-binding domain of CDKN1C cause IMAGe syndrome. Nature genetics. 2012 Jul;44(7):788-92.
32.Kristy, Ou., Ming, Yu., Nicholas, G., Moss., Yue, J., Wang., Amber, W., Wang., Son, C., Nguyen., Connie, L., Jiang., Eseye, Feleke., Vasumathi, Kameswaran., Eric, F., Joyce., Ali, Naji., Benjamin, Glaser., Dana, Avrahami., Klaus, H., Kaestner. Targeted demethylation at the CDKN1C/p57 induces human β cell replication. Journal of Clinical Investigation, (2018).;129(1):209-214.
33.Diaz-Meyer N, Day CD, Khatod K, Maher ER, Cooper W, Reik W, Junien C, Graham G, Algar E, Der Kaloustian VM, Higgins MJ. Silencing of CDKN1C

(p57KIP2) is associated with hypomethylation at KvDMR1 in Beckwith–Wiedemann syndrome. Journal of medical genetics. 2003 Nov 1;40(11):797-801.
34.Licchesi JD, Herman JG. Methylation-specific PCR. Methods Mol Biol. 2009;507:305-23. doi: 10.1007/978-1-59745-522-0_22. PMID: 18987823.
35.Ustianowski Ł, Udzik J, Szostak J, Gorący A, Ustianowska K, Pawlik A. Genetic and Epigenetic Factors in Gestational Diabetes Mellitus Pathology. International Journal of Molecular Sciences. 2023 Nov 22;24(23):16619.
36.Fan Y, Li W, Liu H, Wang L, Zhang S, Li W, Liu H, Leng J, Shen Y, Tuomilehto J, Yu Z. Effects of obesity and a history of gestational diabetes on the risk of postpartum diabetes and hyperglycemia in Chinese women: Obesity, GDM and diabetes risk. Diabetes research and clinical practice. 2019 Oct 1;156:107828.
37.Lappas M. Effect of pre-existing maternal obesity, gestational diabetes and adipokines on the expression of genes involved in lipid metabolism in adipose tissue. Metabolism. 2014 Feb 1;63(2):250-62.
38.Manitta E, Fontes Marques IC, Stokholm Bredgaard S, Kelstrup L, Houshmand-Oeregaard A, Dalsgaard Clausen T, Groth Grunnet L, Reinhardt Mathiesen E, Torp Dalgaard L, Barrès R, Vaag AA. DNA Methylation and Gene Expression in Blood and Adipose Tissue of Adult Offspring of Women with Diabetes in Pregnancy A Validation Study of DNA Methylation Changes Identified in Adolescent Offspring. Biomedicines. 2022 May 26;10(6):1244.
39.Sun M, Luo M, Wang T, Wei J, Zhang S, Shu J, Zhong T, Liu Y, Chen Q, Zhu P, Qin J. Effect of the interaction between advanced maternal age and pre-pregnancy BMI on pre-eclampsia and GDM in Central China. BMJ Open Diabetes Research and Care. 2023 Apr 1;11(2):e003324.
40.Luo ZC, Nuyt AM, Delvin E, Audibert F, Girard I, Shatenstein B, Cloutier A, Cousineau J, Djemli A, Deal C, Levy E. Maternal and fetal IGF-I and IGF-II levels, fetal growth, and gestational diabetes. The Journal of Clinical Endocrinology. 2012 Mar 14;97(5):1720-8.
41.Wei Yumei, Zhang Jing, Yang Huixia. Expression and imprinting status of insulin growth factor 2 and its interactive imprinted gene H19 in placenta of diabetic pregnant women[J]. Chinese Journal of Diabetes, 2012, 4(7): 416-420. 42.Zhang Q, Qin S, Huai J, Yang H, Wei Y. Overexpression of IGF2 affects mouse weight and glycolipid metabolism and IGF2 is positively related to macrosomia. Frontiers in Endocrinology. 2023 Apr 19;14:1030453.
43.Catalano PM, Nizielski SE, Shao J, Preston L, Qiao L, Friedman JE. Downregulated IRS-1 and PPARγ in obese women with gestational diabetes: relationship to FFA during pregnancy. American Journal of Physiology-Endocrinology and Metabolism. 2002 Mar 1;282(3):E522-33.
44.Knabl J, Hüttenbrenner R, Hutter S, Günthner-Biller M, Vrekoussis T, Karl K, Friese K, Kainer F, Jeschke U. Peroxisome proliferator-activated receptor-gamma (PPARγ) is down regulated in trophoblast cells of gestational diabetes mellitus (GDM) and in trophoblast tumour cells BeWo in vitro after stimulation with PPARγ agonists. Journal of perinatal medicine. 2014 Mar 1;42(2):179-87.
45.Ray A, editor. Gestational Diabetes Mellitus: An Overview with Some Recent Advances.
46.Qiu C, Williams MA, Vadachkoria S, Frederick IO, Luthy DA. Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus. Obstetrics & Gynecology. 2004 Mar 1;103(3):519-25.
47.Świrska J, Zwolak A, Dudzińska M, Matyjaszek-Matuszek B, Paszkowski T. Gestational diabetes mellitus—literature review on selected cytokines and hormones of confirmed or possible role in its pathogenesis. Ginekologia polska. 2018;89(9):522-7.
48.Asahara SI, Etoh H, Inoue H, Teruyama K, Shibutani Y, Ihara Y, Kawada Y, Bartolome A, Hashimoto N, Matsuda T, Koyanagi-Kimura M. Paternal allelic mutation at the Kcnq1 locus reduces pancreatic β-cell mass by epigenetic modification of Cdkn1c. Proceedings of the National Academy of Sciences. 2015 Jul 7;112(27):8332-7.
49.Kerns SL, Guevara-Aguirre J, Andrew S, Geng J, Guevara C, Guevara-Aguirre M, Guo M, Oddoux C, Shen Y, Zurita A, Rosenfeld RG. A novel variant in CDKN1C is associated with intrauterine growth restriction, short stature, and early-adulthood-onset diabetes. The Journal of Clinical Endocrinology & Metabolism. 2014 Oct 1;99(10):E2117-22.
50.Van de Pette M, Tunster SJ, John RM. Loss of imprinting of Cdkn1c protects against age and diet-induced obesity. International Journal of Molecular Sciences. 2018 Sep 12;19(9):2734.
51.Stampone E, Caldarelli I, Zullo A, Bencivenga D, Mancini FP, Della Ragione F, Borriello A. Genetic and epigenetic control of CDKN1C expression: importance in cell commitment and differentiation, tissue homeostasis and human diseases. International journal of molecular sciences. 2018 Apr 2;19(4):1055.