Pakistan J. Zool., pp 1-6, 2024. **DOI**: https://dx.doi.org/10.17582/journal.pjz/20231210184756

Effects of Insulin Intensification on FINS, CP, HOMA-IR, and HbA1c Levels in Patients with Gestational Diabetes Mellitus

Qian Liu*, Minhuan Sun and Zijuan Xu

Gynecology and Obstetrics, Shangrao Municipal Hospital, Shangrao, 334000, China.

ABSTRACT

The objective of this study was to evaluate the effects of insulin combined with metformin on glycemic control and fasting insulin (FINS), C-peptide (CP), homeostasis model assessment of insulin resistance (HOMA-IR) and glycated hemoglobin (HbA1c) levels in patients with gestational diabetes mellitus (GDM). Eighty-eight GDM patients from January 2020 to December 2022 were picked as study subjects and stochastically put into a control group (CG) and an observation group (OG). The OG received combined therapy, while the CG received single metformin therapy. The time to achieve fasting plasma glucose (FPG) target, 2-h postprandial plasma glucose (2hPG) target, and both FPG and 2hPG targets were recorded. FINS, CP, HOMA-IR, and HbA1c levels were also monitored and recorded. The time to achieve FPG target, 2hPG target, and both FPG and 2hPG targets in the OG were significantly lower than those in the CG (P<0.05). After treatment, the FINS, CP, HOMA-IR, and HbA1c levels in the OG were lower than the other's value (P<0.05). Additionally, the incidence of adverse maternal and neonatal outcomes in the OG was significantly lower than the other's value (P<0.05). Combined therapy had a significant glycemic control effect in GDM. The blood glucose control in the OG is superior to that in the CG, as evidenced by shorter time to achieve targets and decreased FINS, CP, HOMA-IR, and HbA1c levels. Therefore, insulin combined with metformin has an important clinical efficacy in GDM management, as it improves blood glucose control, reduces the occurrence of adverse outcomes, and provides effective treatment strategies for GDM patients.

Article Information
Received 10 December 2023
Revised 22 January 2024
Accepted 16 February 2024
Available online 03 May 2024
(early access)

Authors' Contribution
QL and MS conducted the experiments in this study. QL and ZX contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
Metformin, Insulin, Gestational diabetes mellitus, Glycemic control effect, Insulin resistance

INTRODUCTION

Gestational diabetes mellitus (GDM) is widely prevalent among pregnant women, which is one kind of diabetes (Butt *et al*., 2017). The incidence of this disease is rapidly increasing worldwide affecting pregnant women globally (Liu *et al*., 2021). GDM is associated with issues in insulin secretion and utilization in the pregnant woman's body, which bring the victims with elevated blood glucose levels (BGL) and potential risks to the mother and the infant. For pregnant women, having GDM may give them increasing diabetes and cardiovascular diseases risk, and may even lead to hypertension and pregnancy complications such as gestational hypertension (Paulo *et al*., 2021). Additionally, GDM is also associated with macrosomia infants and complications during delivery. This not only affects the pregnant women but may also give long-term health risk factors to the fetus (Wang *et al*., 2022). For the fetus, exposure to a high blood glucose environment may result in excessive fetal weight, leading to difficulties during delivery and the potential need for cesarean section (Ruszała *et al*., 2021). Moreover, high BGL may have negative effects on the fetal insulin secretion and metabolism, increasing the risk of diabetes and obesity in adulthood (Chatzakis *et al*., 2021). Therefore, finding effective treatment methods and control measures is crucial for improving the prognosis of GDM patients. Early diagnosis and appropriate management of GDM are essential in reducing maternal and infant risks (Sert and Ozgu-Erdinc, 2021).

Insulin therapy is a common treatment approach for GDM, aiming to control the high BGL that occur in pregnant women during pregnancy to ensure the parent and infant's health (Oskovi-Kaplan *et al*., 2021). Gestational diabetes typically manifests in the 2nd to 3rd pregancy trimester, partly due to inadequate insulin secretion, resulting in high BGL (Sert and Ozgu-Erdinc, 2021). Currently, commonly used insulins include rapid-acting insulin, intermediate-acting insulin, and insulin pumps (Timsit *et al*., 2022). Rapid-acting insulin is used

* Corresponding author: lqlq15180347665@163.com
0030-9923/2024/0001-0001 $ 9.00/0

to rapidly lower BGL and is typically injected before meals to address postprandial blood glucose elevation (Basu *et al*., 2021). Intermediate-acting insulins have a longer duration of action and help maintain basal BGL. Examples include NPH insulin and long-acting insulins such as glargine (Yin *et al*., 2022). Some women may opt for insulin pumps, which are portable devices that deliver insulin regularly to maintain stable BGL (Martín-Estal and Castorena-Torres, 2022). A novel approach currently being explored is the combination of metformin and insulin therapy to enhance glycemic control in GDM (Lu and Hu, 2022). Metformin is an herbal medicine with potential hypoglycemic effects, although its specific mechanisms and effects are not fully understood (Rafaqat *et al*., 2023). Insulin glargine, on the other hand, is a long-acting insulin used to maintain basal BGL (Mathiesen *et al*., 2023). This study is to investigate the glycemic control of combined therapy in GDM and evaluate its impact on fasting insulin, insulin resistance index, and long-term glycemic control indicators. Understanding these effects will help develop individualized treatment plans for GDM patients to improve blood glucose control, reduce complications risk, and ensure the mother and infant's safety.

The innovation of this study lies in the combination therapy of metformin and insulin, with metformin providing sustained blood glucose control as a long-acting insulin and insulin glargine exerting a rapid effect in lowering postprandial BGL. This combined treatment strategy aims to better mimic the natural insulin secretion pattern and achieve more precise blood glucose control. Additionally, this study also focuses on the changes in indicators such as fasting insulin (FINS), C-peptide (CP), homeostasis model assessment of insulin resistance (HOMA-IR), and glycated hemoglobin (HbA1c) to comprehensively evaluate the treatment effectiveness and improvement in metabolic status.

MATERIALS AND METHODS

General information

Among pregnant women diagnosed with GDM who received treatment at the Shangrao Municipal Hospital from December 2020 to December 2022, a total of 88 GDM patients were enrolled and stochastically put into a control group (CG) for and an observation group (OG), with 44 cases in each. Inclusion criteria: Pregnant women (i) diagnosed with GDM during pregnancy, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations; (ii) of 18 years and above; (iii) with complete medical records, laboratory test results, and treatment and (iv) who voluntarily participated and agreed in writing an informed consent form. However pregnant women (i) with other types of diabetes, such as type 1 or 2; (ii) with severe heart disease, kidney disease, or other serious illnesses; (iii) with pregnancy complications such as gestational hypertension, placental insufficiency, etc.; (iv) who have received treatment with other antidiabetic medications or insulin therapy; and (v) with a history of allergy or adverse reactions to metformin or insulin glargine were excluded from the study.

Methods

All enrolled pregnant women received the same GDM education and underwent appropriate dietary control and aerobic exercise. At the same time, their fingertip BGL were monitored, including pre-meal levels at 30 min, 2 h' post-meal, and 03:00 in the early morning. After 3-5 days of monitoring, it was found that the BGL before meals, during the night, and after meals exceeded the BGL control targets for pregnancy.

The CG received treatment with insulin glargine, which was administered subcutaneously before meals. The total daily dose was controlled between 0.3-0.8 U/kg. The insulin glargine used in this study was manufactured by Novo Nordisk Pharmaceutical Co., Ltd. (National Drug Approval Number: J20150073; Specification: 3 mL:300U). The OG received combination therapy with insulin glargine and insulin aspart. The administration method of insulin glargine was the same as in the CG. Insulin aspart, also manufactured by Novo Nordisk (China) Pharmaceutical Co., Ltd. (National Drug Approval Number: J20140107; Specification: 3 mL:300U), was administered to the OG patients at bedtime with a dose of 0.1-0.2 U/kg.

The dosage of insulin glargine was adjusted reasonably based on the fluctuation of postprandial BGL. The dosage of insulin as part was adjusted based on fasting BGL and pre-meal BGL, with a dose adjustment of 2-4 U per adjustment and an interval of 2-3 days for each adjustment. The goal of the adjustment was to stabilize the patient's BGL within the target range. After achieving stable blood glucose control, fasting BGL and postprandial BGL were monitored once a week on different dates. After 6 weeks of continuous medication, BGL were checked again to ensure that they remained within the target range until the delivery stage.

Observation indicators

The glycemic control effect was measured by the time to achieve target BGL, including the time to achieve fasting plasma glucose (FPG) target, the time to achieve 2-h postprandial glucose (2h PG) target, and the time to achieve both targets. FPG target was defined as fasting BGL ≤5.1 mmol/L (92 mg/dL), and 2hPG target was defined as 2-h postprandial BGL ≤8.5 mmol/L (153 mg/dL).

Insulin resistance level was evaluated using FINS, CP, HOMA-IR, and HbA1c. Venous blood samples were collected and centrifuged to obtain serum or plasma for testing. The results were reported in unit concentrations (e.g., ng/mL or pmol/L). CP measurement was performed with ELISA. FPG, 2hPG, FINS, and HbA1c levels were tested with an automated biochemical analyzer (Mindray BS-850).

The occurrence of maternal hypertension, preterm birth, and cesarean section was recorded. The occurrence of macrosomia, fetal distress, and neonatal jaundice in newborns was also recorded.

Statistical analyses

SPSS 25.0 was utilized for data analysis. Continuous variables were presented as mean±standard deviation. The t-test was employed to analyze differences between groups and within groups. Categorical variables were expressed as percentages, and the chi-square test was used to analyze differences. A *p-value* under 0.05 was recognized as statistically significant.

RESULTS

From the 88 enrolled people, the age distribution was 28.7±1.17 with a M(SD) BMI of 23.0±1.00 kg/m^2 in the CG and 29.0±1.17 with a M(SD) BMI of 23.1±1.05kg/m^2 in the OG (see Table I). Table I shows demographic and clinical-related variables of the pregnant women who were enrolled in the study. As the table shows, there are no significant differences between the CG and the OG so it can be concluded that they are homogenous groups.

The time to achieve target FPG, 2hPG, and both FPG and 2hPG were lower in the OG than the value in the CG (P<0.05), which is displayed in Table II. Both FPG and 2hPG showed a decreasing trend with treatment duration in both groups. However, the decrease in BGL was faster in the OG, indicating a significant advantage in blood glucose control.

Table I. General information ($\bar{x}$±s [n(%)]).

General information	OG (n=44)	CG (n=44)	χ^2/t	p
Age (years)	29.0±1.17	28.7±1.17	1.203	0.232
BMI (kg/m^2)	23.1±1.05	23.0±1.00	0.457	0.648
Duration of diabetes(years)	2.0±0.92	2.0±0.93	0.001	0.999
Gestational weeks	29.0±1.47	29.1±1.59	0.306	0.760
Primiparous (%)	25(56.82)	23(57.50)	0.004	0.949

Table II. Time to achieve target blood glucose ($\bar{x}$±s, d).

Target	OG (n=44)	CG (n=44)	t
FPG	4.8±2.23	6.8±2.52	3.942
2hPG	4.1±2.54	8.4±2.95	8.465
FPG and 2hPG	7.1±3.12	10.9±3.20	5.639

FPG, fasting plasma glucose; 2hPG, 2-h postprandial plasma glucose.

No significant difference was detected in insulin resistance level between the OG and the CG before treatment (P>0.05). However, after treatment, FINS, CP, HOMA-IR, and HbA1c were smaller the OG compared to the CG (P<0.05), which is displayed in Table III. According to the results, both groups showed a significant decrease in insulin resistance indicators after treatment. However, the decrease in insulin resistance was significantly higher in the OG, indicating an advantage in reducing insulin resistance levels.

The adverse outcome incidence in both mothers and newborns is displayed in Table IV, which was significantly lower in the OG than the CG. The proportion of mothers and newborns without adverse reactions in the OG is significantly higher than in the CG, indicating a significant advantage of the OG in terms of treatment safety.

Table III. Effect of insulin + metformin on FINS, CP, HOMA-IR and HbA1c of GDM patients showing comparison of insulin resistance ($\bar{x}$±s).

Indicator	OG (n=44)		CG (n=44)		t	P
	Time 0	Time 1	Time 0	Time 1		
FINS(mU/L)	9.15±0.51	8.08±0.51	9.06±0.61	8.39±0.58	2.662	0.009
CP(nmol/L)	0.79±0.11	0.40±0.06	0.80±0.12	0.60±0.04	18.397	0.000
HOMA-IR	4.57±0.62	2.03±0.32	4.52±0.63	4.08±0.47	23.915	0.000
HbA1c(%)	9.56±0.55	5.31±0.37	9.45±0.63	7.00±0.60	15.903	0.000

FINS, fasting insulin; CP, C-peptide; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycated hemoglobin.

Table IV. Comparison of adverse maternal and neonatal outcomes [n(%)].

Outcomes	OG (n=44)	CG (n=44)	x^2	P
Adverse maternal	6(13.6)	29(65.9)	22.342	0.000
Hypertension	1	8		
Preterm birth	0	6		
Cesarean section	5	15		
Adverse neonatal	3(6.8)	16(36.4)	9.973	0.001
Macrosomia	2	6		
Fetal distress	0	2		
Neonatal jaundice	1	8		

DISCUSSION

FINS is one of the indicators used to measure pancreatic function. It reflects the secretion capacity of insulin. In GDM, the level of FINS can help evaluate the secretion status of insulin (Ravid *et al*., 2023). Higher levels of FINS may indicate increased insulin secretion in response to elevated BGL, while lower levels of FINS may suggest insufficient pancreatic function. Therefore, monitoring FINS can provide insights into the status of pancreatic function and guide the treatment and management of GDM. CP is also one of the indicators used to assess pancreatic function. It is a byproduct produced by the cleavage of proinsulin molecules and can reflect the secretion of insulin. In GDM, the level of CP can be used to evaluate the secretion capacity of insulin (Mlotshwa *et al*., 2022). Monitoring CP can provide insights into the secretion status of insulin and is of significant importance in the treatment and management of GDM. HOMA-IR is a calculated index used to assess the degree of insulin resistance. It is derived by combining fasting blood glucose and fasting insulin levels. Insulin resistance is a common characteristic of GDM, referring to a reduced response of the body to insulin. A high HOMA-IR value indicates a higher degree of insulin resistance, which may require more insulin to maintain normal BGL. Monitoring HOMA-IR can help assess the degree of insulin resistance and guide the treatment and management of GDM.

HbA1c can reflect the average blood glucose level in recent months. In GDM, measuring HbA1c can be used to assess long-term blood glucose control. High HbA1c may indicate poor long-term blood glucose control, while lower value of this indicate better blood glucose control. Monitoring HbA1c can provide insights into the long-term blood glucose control of GDM patients and guide adjustments in treatment and management. This study's outcomes told that no significant difference was located in insulin resistance levels between the OG and the CG before treatment (P>0.05), and FINS, CP, HOMA-IR, and HbA1c levels were significantly lower in the OG compared to the CG after treatment (P<0.05). The reasons for this analysis may be as follows: Insulin sensitivity refers to the degree of response of the body to insulin. GDM patients often have insulin resistance, which means a reduced response of cells to insulin. The combination of metformin and insulin can improve insulin sensitivity and increase the response of cells to insulin, thereby reducing insulin resistance levels (Li *et al*., 2023). In addition, combination therapy can promote insulin secretion. Metformin provides sustained insulin coverage, helping to control fasting BGL. insulin, on the other hand, can rapidly lower postprandial BGL. By using these two insulins in combination, it can better mimic the natural pattern of insulin secretion, stimulate insulin secretion, and lower BGL. Combination therapy may also lower BGL by inhibiting hepatic glucose output (Jaffar *et al*., 2022). Metformin can reduce the release of glucose in the liver, decrease the liver's demand for insulin, and reduce hepatic glucose output. insulin, on the other hand, can suppress hepatic glucose output by increasing insulin supply. The combination of these two insulins can work synergistically to effectively reduce hepatic glucose output and lower BGL. Combination therapy may also lower BGL by improving glucose metabolism. Insulin is an important hormone that regulates BGL, promotes glucose utilization and storage, and inhibits glucose production. Combination therapy can enhance the potency and utilization efficiency of insulin, improve glucose metabolism, and lower BGL (Mirabelli *et al*., 2021).

GDM can give adverse outcomes for both pregnant females and infants. A study recorded adverse outcomes such as gestational hypertension, preterm birth, and others in GDM females (Hillier *et al*., 2021). Corresponding outcomes told that the incidence of adverse outcomes in the OG, both for mothers and newborns, was under the CG (P<0.05). This can be explained by the following reasons: Combination therapy helps to better control BGL in parents. A well regulated BGL can bring down the gestational hypertension, preterm birth, and cesarean section risks in pregnant women (Vasile *et al*., 2021). At the same time, blood glucose control can also reduce the likelihood of macrosomia, fetal distress, and neonatal jaundice in newborns. By using a combination of metformin and insulin, more comprehensive and individualized blood glucose control can be achieved, thereby reducing the incidence of adverse outcomes (Newman and Dunne, 2022). GDM is often associated with insulin resistance. The combination of metformin and insulin can improve insulin resistance and reduce the insulin demand in pregnant women. The

reduction in insulin resistance may help reduce the risk of gestational hypertension and the occurrence of adverse outcomes in mothers. The combination of metformin and insulin can better mimic the natural pattern of insulin secretion, providing more precise blood glucose control. This combination therapy can stabilize BGL, avoiding excessive or low blood glucose fluctuations, thereby reducing the risks faced by pregnant women and newborns and reducing the occurrence of adverse outcomes (Bao *et al*., 2021).

CONCLUSION

In summary, the combination therapy of metformin and insulin has shown positive results in terms of glycemic control and its impact on FINS, CP, HOMA-IR, and HbA1c levels in GDM. This provides important guidance for clinical practice and offers new perspectives and methods for the management of GDM patients. Further research and efforts will continue to refine the treatment strategies for GDM, improve maternal and infant health, and achieve better clinical outcomes and quality of life for GDM patients. We encourage healthcare professionals to actively explore and adopt this combination therapy approach in the treatment of GDM to maximize patient disease management and quality of life.

ACKNOWLEDGMENTS

Thanks to the members from Shangrao Municipal Hospital, the group collected samples, obtained data, and theoretical guidance.

Funding

Not applicable.

IRB approval

This study was approved by the Advanced Studies Research Board of Shangrao Municipal Hospital, Shangrao, 334000, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of Shangrao Municipal Hospital, Shangrao, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Bao, L.X., Shi, W.T. and Han, Y.X., 2021. Metformin versus insulin for gestational diabetes: A systematic review and meta-analysis. *J. Matern. Fetal Neonatal Med.*, **34**: 2741-2753. https://doi.org/10.1080/14767058.2019.1670804

Basu, A., Feng, D., Planinic, P., Ebersole, J.L., Lyons, T.J. and Alexander, J.M., 2021. Dietary blueberry and soluble fiber supplementation reduces risk of gestational diabetes in women with obesity in a randomized controlled trial. *J. Nutr.*, **151**: 1128-1138. https://doi.org/10.1093/jn/nxaa435

Butt, A., Malik, U., Waheed, K., Khanum, A., Firdous, S., Ejaz, S., Randhawa, F. and Shakoori, T., 2017. Low serum cobalamin is a risk factor for gestational diabetes. *Pakistan J. Zool*., **49**: 1963-1968. https://doi.org/10.17582/journal.pjz/2017.49.6.1963.1968

Chatzakis, C., Cavoretto, P. and Sotiriadis, A., 2021. Gestational diabetes mellitus pharmacological prevention and treatment. *Curr. Pharm. Des.*, **27**: 3833-3840. https://doi.org/10.2174/1381612827666210125155428

Hillier, T.A., Pedula, K.L., Ogasawara, K.K., Vesco, K.K., Oshiro, C.E., Lubarsky, S.L. and Van Marter, J., 2021. A pragmatic, randomized clinical trial of gestational diabetes screening. *N. Engl. J. Med.*, **384**: 895-904. https://doi.org/10.1056/NEJMoa2026028

Jaffar, F., Laycock, K. and Huda, M.S., 2022. Type 1 diabetes in pregnancy: A review of complications and management. *Curr. Diabetes Rev.*, **18**: 49-63. https://doi.org/10.2174/1573399818666211105124829

Li, J., Liu, H. and Shang, L., 2023. Tert-butylhydroquinone mitigates renal dysfunction in pregnant diabetic rats via attenuation of oxidative stress and modulation of the iNOs/NFkB/TNF alpha signalling pathway. *Endocr. Metab. Immune Disord. Drug Targets*, **23**: 633-646. https://doi.org/10.2174/1871530322666220908153118

Liu, Y., Liu, S., Wang, H. and Su, W., 2021. Protective effect of caffeic acid on streptozotocin induced gestational diabetes mellitus in rats: Possible mechanism. *Pakistan J. Zool.*, **53**: 1045-1052. https://doi.org/10.17582/journal.pjz/20200106060120

Lu, W. and Hu, C., 2022. Molecular biomarkers for gestational diabetes mellitus and postpartum diabetes. *Chin. med. J.*, **135**: 1940-1951. https://doi.org/10.1097/CM9.0000000000002160

Martín-Estal, I. and Castorena-Torres, F., 2022.

Gestational diabetes mellitus and energy-dense diet: What is the role of the insulin/IGF axis? *Front. Endocrinol.*, **13**: 916042. https://doi.org/10.3389/fendo.2022.916042

Mathiesen, E.R., Alibegovic, A.C., Corcoy, R., Dunne, F., Feig, D.S., Hod, M., Jia, T., Kalyanam, B., Kar, S., Kautzky-Willer, A. and Marchesini, C., 2023. Insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes (EXPECT): An open-label, multinational, randomised, controlled, non-inferiority trial. *Lancet Diab. Endocrinol.*, **11**: 86-95. https://doi.org/10.1016/S2213-8587(22)00307-2

Mirabelli, M., Chiefari, E., Tocci, V., Greco, E., Foti, D. and Brunetti, A., 2021. Gestational diabetes: Implications for fetal growth, intervention timing, and treatment options. *Curr. Opin. Pharmacol.*, **60**: 1-10. https://doi.org/10.1016/j.coph.2021.06.003

Mlotshwa, C., Burger, J.R., Vorster, M., Rakumakoe, D.M. and Cockeran, M., 2022. Individual case safety reports analysis for patients with diabetes mellitus on insulin in Africa and the Middle East. *Curr. Drug Saf.*, **17**: 225-234. https://doi.org/10.2174/1574886316666211108103301

Newman, C. and Dunne, F.P., 2022. Metformin for pregnancy and beyond: the pros and cons. *Diabet. Med.*, **39**: e14700. https://doi.org/10.1111/dme.14700

Oskovi-Kaplan, Z.A. and Ozgu-Erdinc, A.S., 2021. Management of gestational diabetes mellitus. *Adv. exp. Med. Biol.,* **1307**: 257-272. https://doi.org/10.1007/5584_2020_552

Paulo, M.S., Abdo, N.M., Bettencourt-Silva, R. and Al-Rifai, R.H., 2021. Gestational diabetes mellitus in Europe: a systematic review and meta-analysis of prevalence studies. *Front. Endocrinol.*, **12**: 691033. https://doi.org/10.3389/fendo.2021.691033

Rafaqat, S., Sattar, A., Khalid, A. and Rafaqat, S., 2023. Role of liver parameters in diabetes mellitus–a narrative review. *Endocr. Regul.*, **57**: 200-220. https://doi.org/10.2478/enr-2023-0024

Ravid, D., Kovo, M., Leytes, S., Yagur, Y., Fakterman, M. and Weitzner, O., 2023. Insulin detemir versus glibenclamide in gestational diabetes mellitus: A retrospective cohort study. *Isr. med. Assoc. J.*, **25**: 398-401.

Ruszała, M., Niebrzydowska, M., Pilszyk, A., Kimber-Trojnar, Ż., Trojnar, M. and Leszczyńska-Gorzelak, B., 2021. Novel biomolecules in the pathogenesis of gestational diabetes mellitus. *Int. J. mol. Sci.*, **22**: 11578. https://doi.org/10.3390/ijms222111578

Sert, U.Y. and Ozgu-Erdinc, A.S., 2021. Gestational diabetes mellitus screening and diagnosis. *Adv. exp. Med. Biol.,* **1307**: 231-255. https://doi.org/10.1007/5584_2020_512

Timsit, J., Ciangura, C., Dubois-Laforgue, D., Saint-Martin, C. and Bellanne-Chantelot, C., 2022. Pregnancy in women with monogenic diabetes due to pathogenic variants of the Glucokinase gene: lessons and challenges. *Front. Endocrinol.*, **12**: 802423. https://doi.org/10.3389/fendo.2021.802423

Vasile, F.C., Preda, A., Ștefan, A.G., Vladu, M.I., Forțofoiu, M.C., Clenciu, D., Gheorghe, I.O., Forțofoiu, M. and Moța, M., 2021. An update of medical nutrition therapy in gestational diabetes mellitus. *J. Diabetes Res.*, **2021**: 5266919. https://doi.org/10.1155/2021/5266919

Wang, H., Li, N., Chivese, T., Werfalli, M., Sun, H., Yuen, L., Hoegfeldt, C.A., Powe, C.E., Immanuel, J., Karuranga, S. and Divakar, H., 2022. 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.*, **183**: 109050. https://doi.org/10.1016/j.diabres.2021.109050

Yin, Y., Pan, Y., He, J., Zhong, H., Wu, Y., Ji, C., Liu, L. and Cui, X., 2022. The mitochondrial-derived peptide MOTS-c relieves hyperglycemia and insulin resistance in gestational diabetes mellitus. *Pharmacol. Res.*, **175**: 105987. https://doi.org/10.1016/j.phrs.2021.105987