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GESTATIONAL DIABETES – MANAGEMENT STRATEGIES INCLUDING PHARMACOLOGICAL TREATMENT AND LIFESTYLE INTERVENTIONS

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ABSTRACT

Diabetes is a chronic disease, characterized by elevated blood glucose levels, resulting from insulin resistance and inadequate insulin production. Among many types of diabetes, gestational diabetes (GDM) is a unique kind, correlated with numerous metabolic changes occurring during pregnancy, it develops around second trimester of the gestation and in most cases resolves after delivery. The prevalence of gestational diabetes is rising globally and becomes a significant public health concern. [48] According to the World's Health Organization's classification GDM is, apart from the diabetes mellitus type 1 (DM1) and diabetes mellitus type 2 (DM2), one of the main clinical forms of carbohydrate metabolism disorders occurring during pregnancy. So far, epidemiological data are ambiguous regarding GDM prevalence, this study estimates GDM frequency at 4–12%. [1] The aim of this article is to provide a comprehensive analysis of the topic of gestational diabetes, its prevalence, risk factors, importance of early detection, methods of glycemia monitoring and management strategies, including lifestyle interventions and pharmacological treatment. Referring to the treatment, it also describes the preparation for pregnancy of people with preexisting DM1 and DM2 and the necessity to modify foregoing management strategies. Furthermore, it describes the most frequent early complications resulting from GDM as well as long-term outcomes for both mother and offspring.

Keywords: gestational diabetes, gestational diabetes treatment, lifestyle modification, pharmacological treatment

INTRODUCTION

The term diabetes during pregnancy includes pre-pregnancy diabetes what means diabetes that occurred before the conception of the child, and hyperglycemia first diagnosed during pregnancy. According to WHO 2013 classification hyperglycemia first diagnosed during pregnancy includes diabetes in pregnancy and gestational diabetes mellitus. [23] This article focuses on gestational diabetes mellitus (GDM) which is a form of diabetes which develops during pregnancy, often is diagnosed and manifests fully in the second trimester of pregnancy and usually resolves after childbirth. The physiological changes that occur during pregnancy lead to the development of GDM and one of the mechanisms include producing hormones antagonistic to insulin such as human placental lactogen (hPL) and progesterone which leads to impaired glucose tolerance. [39] GDM is associated with many complications including

infant macrosomia, large for gestational age (LGA), preterm birth, cesarean section and maternal and infant morbidity. Moreover, gestational diabetes is associated with the risk of developing diabetes mellitus type 2 in the future and increased risk of cardiovascular diseases. [2]

DIAGNOSTIC CRITERIA

The measurement of the fasting glucose level should be carried out during the first appointment of the pregnant women at the doctor's office. Any abnormal result obtained during the measurement requires urgent further diagnostics which means conducting an oral glucose tolerance test (OGTT) or fasting glucose level. If the results are within the normal range the glycemia measurement is repeated between 24 and 28th week of pregnancy by performing OGTT. When a woman is at risk of gestational diabetes i.e. had a past medical history of GDM, OGTT must be carried out during the first visit at the doctor's office, instead of fasting glucose measurement. [41]

Hyperglycemia first diagnosed during pregnancy diagnosed and verified according to WHO 2013 classification distinguishes diabetes in pregnancy - when the general criteria of recognition diabetes mellitus are fulfilled and gestational diabetes mellitus with specific diagnostic criteria.

Criteria for diagnosing diabetes in pregnancy:

1. fasting blood glucose ≥ 7,0 mmol/l (126 mg/dl)
2. glycemia in 2nd hour of OGTT ≥ 11,1 mmol/l (200 mg/dl)
3. random glycemia ≥11,1 mmol/l (200mg/dl) and at the same time clinical symptoms of hyperglycemia

Meeting any of these criteria is enough to diagnose diabetes in pregnancy. [42]
Criteria for diagnosing gestational diabetes based on an oral glucose tolerance test with 75 g of glucose (WHO 2013):

1. fasting blood glucose 5.1–6.9 mmol/l (92–125 mg/dl)
2. glycemia in 1 h OGTT ≥ 10 mmol/l (180 mg/dl)
3. glycemia in 2 h OGTT 8.5–11.0 mmol/l (153–199 mg/dl)

Gestational diabetes mellitus (GDM) is diagnosed when at least 1 of 3 criteria are met [42]

RISK FACTORS

Knowledge of GDM risk factors allows for early identification of women endangered with this disease and gives an opportunity to implement different preventive actions. [8] Obesity is one of the main risk factors due to the overproduction of pro-inflammatory cytokines by adipocytes which results in a chronic inflammatory process. This leads to metabolic imbalance and subsequently to insulin resistance and hyperglycemia in both maternal and fetal blood. [6]. Not only high initial BMI defined as BMI ≥25 kg/m2 but also gestational BMI gain from conception to 15–20 weeks of pregnancy was correlated with an increased risk of GDM. [8] Apart from obesity other well-documented factors for GDM are maternal age (especially pregnancy after the age of 35), family history of diabetes mellitus type 2, macrosomic childbirths, stillbirths and previous birth of a child with congenital anomaly in the past medical history. [23,44]. Women giving birth to a macrosomic babies, when macrosomia is defined as a birth weight of 4-4,5 kg, have a higher possibility of developing GDM in the future compared to women giving birth to an infant within the range up to the 90th percentile of normal gestational weight [8]. In this study, [11] the age of pregnant individuals in the GDM group was older than that in non-GDM group, and the risk of GDM was increased by 12.5% at each increasing age of 1 year. Genetics is considered as a risk factor as well, this study revealed that the risk of GDM was increased significantly among pregnant women with history of diabetes mellitus in first-degree relatives when compared with patients without record of diabetes mellitus among family members. [12] This leads to the point that both women with GDM in their medical history as well as their offspring have an increased risk of developing a DM2 in the future. [16] Other risk factors are endocrine diseases and chronic diseases including hypertension. [23] GDM and different thyroid dysfunctions are two most frequent endocrinopathies during gestation and may co-occur together. What is more, these thyroid dysfunctions including hypothyroidism and presence of thyroid antibodies in the blood may be starting points for GDM development due to the imbalances in glucose metabolism and insulin resistance. [17] According to growing evidence, GDM complicates 40 % of polycystic ovary syndrome (PCOS) pregnancies, suggesting that PCOS may be a risk factor for GDM. PCOS predisposes to the development of GDM due to

the fact that it is often associated with obesity, dyslipidemia and metabolic disorders such as hyperinsulinemia and insulin resistance. [30]

PREVENTION OF GDM AND PRECONCEPTION COUNSELING

Preconception counseling plays a significant role in comprehensive preparation for pregnancy among patients with preexisting type 1 or type 2 diabetes and should be conducted multidisciplinary among the specialists in the field of diabetology, gynecology, endocrinology and clinical nutritionists. [43] First of all, it is essential to keep glucose levels in recommended values, especially glycated hemoglobin (A1C) <6.5% (<48 mmol/mol), to minimize the risk of congenital anomalies, macrosomia, preeclampsia or preterm birth and other complications affecting fetus and woman. [13, 15] This study revealed that increases in A1C levels during the first 10 weeks of pregnancy were associated with the higher risk of congenital anomalies. [14] Given numerous studies, patients with DM should be educated on the topic of family planning and the importance of meeting glycemic targets before conception. [13] Apart from an optimal diabetes control, patients with diagnosed DM should maintain proper body mass (BMI within the normal range 18,5-24,99 kg/m2). When planning a pregnancy, it is recommended to supplement with folic acid (minimum 0.4 mg/day) for a period of at least 6 weeks before conception until the 12th week of pregnancy. [23] Patients without preexisting DM are also obliged to lead a healthy lifestyle, reduce excess body weight, implement regular physical activity and correct nutritional deficiencies.

TREATMENT OF GESTATIONAL DIABETES

Treatment of gestational diabetes in most cases is based on lifestyle interventions such as appropriate dietary modification and regular physical activity. In other cases pharmacological treatment should be added in order to maintain an optimal glycemic control and avoid complications related to hyperglycemia for both the mother and the fetus. [19] Treatment should be coordinated in clinical centers specialized in the treatment of gestational diabetes. [13] During pregnancy, diabetes consultations are recommended approximately once a month and in justified cases every 2–3 weeks. For women with preexisting diabetes it is related, among other factors, with the changing demand for insulin and the need to monitor body weight, kidney function, eyesight and blood pressure values. [23]. Insulin is the medication of

choice for treating hyperglycemia in GDM and some studies suggest that up to 70–85% of individuals diagnosed with GDM are able to manage diabetes with lifestyle modification alone. [13] This percentage varies depending on the population and conclusions from different studies, but still remains high and emphasizes the importance of a well-balanced diet and physical activity. Including the insulin therapy into GDM management is necessary when glycemic goals are not accomplished or any signs of excessive fetal growth have been observed. [22] Human insulins are preferred [47] as they are characterized by the least immunogenicity compared to other insulins available on the market. This is especially important because using insulin preparations of low antigenicity significantly reduces the transplacental transport of insulin antibodies. Two rapid-acting insulin analogs, aspart and lispro, have been investigated during gestation and the results revealed their effectiveness, non-significant transfer across the placenta and no signs of teratogenesis. They improve postprandial glucose levels in comparison to human insulin and may be related with lower risk of delayed postprandial hypoglycemia. [22] Demand for insulin decreases rapidly after delivery and most women with hyperglycemia during pregnancy can discontinue insulin administration while maintaining glycemic control. [23]

TREATMENT OF PREEXISTING DM1 AND DM2 DURING PREGNANCY

Insulin is the preferred agent for management of both DM1 and DM2 during pregnancy and none of the human insulin preparations have been proved to cross the placenta. The recommended method is intensive insulin therapy using multiple injections or using a personal insulin pump. [13] The best moment to start pump therapy is at the planning stage or in early pregnancy (up to the 12th week), subsequent implementation only in exceptional cases, when it is impossible to achieve optimal metabolic control by repeated insulin injections. [23] The physiology of pregnancy requires frequent titration of insulin in order to adapt to the changing glycemia and daily and regular blood glucose monitoring is essential. In early pregnancy, insulin sensitivity slightly increases and therefore hypoglycemia may occur in pregnant women with so far, well-adjusted insulin dosage. From the 16th week of pregnancy, insulin resistance increases and this requires regular increases in insulin doses according to metabolic needs. [50] DM1 during pregnancy is associated with the higher risk of diabetic ketoacidosis (DKA), which is a condition leading to stillbirths. [42] It is advisable for patients to equip themselves with strips tests for the presence of ketones in urine. DM2 often co-occurs with obesity, therefore, dietary modification and achieving optimal body

weight may be beneficial. Meeting glycemic goals is more simple comparing to DM1 although management of DM2 requires greater insulin dosage. [13] Oral antidiabetic drugs, such as metformin, are not currently recommended for the treatment of diabetes due to the fact that they cross the placenta and many studies indicate their negative impact on the long-term development of the offspring. [49] There is still too little evidence of safety for other oral glucose-lowering medications and non insulin injectable drugs. [13] Among women taking oral antidiabetic drugs, it is recommended to replace metformin with insulin when planning pregnancy, at the latest in the first trimester. [23] Using metformin is acceptable for women suffering from both DM2 and polycystic ovary syndrome or insulin resistance during preconception period but has to be discontinued by the end of the first trimester. Patients with type 2 diabetes can safely use metformin during lactation period, current studies show that metformin passes into breast milk in very small amounts and does not exceed 1% of concentration in maternal blood. [23] Patients with pre-gestational diabetes should be prescribed acetylsalicylic acid at a dose of 1 mg/kg body weight. (100–150 mg/day) from the 12th to the 36th week of pregnancy in order to prevent preeclampsia. [23] Currently, there is insufficient data on whether the use of aspirin specifically in pregnant women with pre-existing diabetes ultimately reduces the incidence of preeclampsia [13], although a meta-analysis revealed that, overall, in high-risk groups, aspirin intake reduced the incidence of preeclampsia. [24] Therefore, the decision of implementing acetylsalicylic acid depends on the gynecologist.

DIETARY RECOMMENDATIONS AND WEIGHT CONTROL

Diet plays a significant role in the management of gestational diabetes, influencing both maternal and fetus glucose levels. A well-balanced diet should provide essential nutrients for the proper development of pregnancy and at the same time should keep GDM well controlled. The difference in calories uptake between patients suffering from GDM and patients without GDM has not been demonstrated. [13] The daily amount of calories depends on body weight, height, physical activity and age - the average calorie requirement is approximately 30 kcal per kg of ideal body weight, which gives 1,500-2,400 kcal per day. [23] In overweight patients a diet with a calorie content of 25-30 kcal per kg of body weight is recommended. [23] Carbohydrates are the main macronutrient in the diet [45] and should cover approximately 40-50% of energy need (minimum 175 g of carbohydrate per day). [23] They should mainly come from starchy foods with a naturally high content of dietary

fiber, such as vegetables, legumes, fruits, and whole grains. Due to restrictive glycemic target values, pregnant women should consume constant amounts of carbohydrates at relatively regular times in order to optimally adjust insulin doses and avoid hyperglycemia and hypoglycemia. [13] Complex carbohydrates with a low glycemic index distributed in small portions throughout the day are highly recommended in order to avoid sudden spikes in postprandial glycemia. Although some research suggests a positive effect of a low-carb diet, with carbohydrates intake below the daily requirement, there is currently little evidence on this topic. Moreover, some studies claim that replacing carbohydrates with fats may lead to increased lipolysis, an increase in the level of free fatty acids and deepening maternal insulin resistance. [13] Protein should provide about 30% of daily energy requirement and the minimum amount is 71 g per day. Valuable sources of protein are lean meat and fish, as well as protein of plant origin. By eating such products and at the same time limiting the intake of red, processed meat, it is possible to increase insulin sensitivity and thus improve GDM management. [46] Fats should constitute approximately 25-30% of the daily energy requirement, with the amount of saturated fats less than 10%. A sufficient intake of n-3 fatty acids, which can be found in sea fish, walnuts, linseed, is essential. [13]

The recommended weight gain during pregnancy for patients with GDM is the same as for people without this condition. Recommended weight gain during pregnancy for overweight people is 15–25 lb (6.8–11.3 kg) and for those with obesity is 10–20 lb (4.5–9.1 kg). [51] Excessive weight gain during pregnancy may be associated with fetal macrosomia and maintaining maternal excess body weight during postpartum and later on. [2]

PHYSICAL ACTIVITY

Many studies have shown that regular physical activity of moderate intensity for at least 30 min daily or 150 min weekly reduces the risk of developing gestational diabetes, especially among obese and overweight women [3,28, 34] However, it is important to implement regular exercises in the early stage of gestation, in the first trimester or even more recommended, before conception. [5] It is related to the fact that various metabolic changes in pregnant women organisms including an increased production of hormones antagonistic to insulin i.e. placental lactogen, estrogens, progesterone and prolactin starts from the very beginning of the pregnancy. Physical activity implemented in the first trimester of pregnancy has a positive effect on carbohydrate metabolism, while physical activity implemented in the

later stage of pregnancy does not result in a reduced development of gestational diabetes due to the fact that metabolic and endocrine functions of the placenta have been already programmed. [5] This systematic review demonstrated that the exercise intervention delayed the moment of including insulin into GDM management, reduced insulin dose requirements and had a positive impact on glycemia targets. [18]. Regular aerobic physical activity with an emphasis on warm-up and resting afterwards has shown the reduction in both fasting and postprandial blood glucose levels in individuals previously leading a sedentary lifestyle. Even light activity such as brisk walking or arm exercises right after a meal contributes to achieving metabolic goals. [22] Regular physical activity has also been proved to reduce gestational weight gain measured in the mid-second trimester among overweight or obese women. What is more, at the same time, there were no side effects of carefully selected physical activity and no increased incidence of premature births and other complications related to pregnancy and childbirth. [5]

GLUCOSE MONITORING AND GLYCEMIC TARGETS

Pregnancy in people without preexisting diabetes is characterized by lower fasting glucose levels than before pregnancy due to physiological changes such as increased glucose uptake by the fetus and placenta, as well as mild postprandial hyperglycemia and carbohydrate intolerance, related to increased production of insulin antagonist hormones by the placenta. [50]

Among patients with preexisting gestational diabetes, treatment should include insulin therapy and dietary recommendations. The key is to establish a diet plan, determine the number of insulin units per amount of carbohydrates and state the expected weight gain according to the recommended standards. [13] Regardless of the type of diabetes (pre-pregnancy or GDM) glycemic goals are similar.

Glycemic goals for pregnant individuals with preexisting DM1 or DM2 according to ADA:

- fasting glucose 70–95 mg/dL (3.9–5.3 mmol/L) and either
- one-hour postprandial glucose 110–140 mg/dL (6.1–7.8 mmol/L)
- two-hour postprandial glucose 100–120 mg/dL (5.6–6.7 mmol/L)

Achieving these glycemic levels is recommended, but treatment should be monitored in order to avoid adverse effects such as clinically significant hypoglycemia. People with preexisting type 1 diabetes are at increased risk of hypoglycemia, especially if they have a history of recurrent hypoglycemia and an unawareness of hypoglycemia. [52] If significant hypoglycemia occurs, therapy should be modified and individualized based on clinical experience. The measurement of glycated hemoglobin level (HbA1c) which reflects the average blood glucose levels over the last two or three months, may be a prognostic factor for pregnancy complications prevalence. Some observational studies have shown that maintaining HbA1c<6-6.5% was associated with lower fetal adverse outcomes. Clinical trials have not evaluated this issue, however it is recommended to maintain the HbA1c level <6-7% while carefully monitoring the risk of hypoglycemia. [22,52] HbA1c measurement does not fully indicate the phenomenon of postprandial hyperglycemia, which is a risk factor for macrosomia.. Moreover, due to physiological phenomena related to pregnancy, such as changes in blood and red blood cells, HbA1c levels decrease during pregnancy. Taking all this into account, HbA1c measurement may be useful although it should be treated as a secondary method of measuring glycemia, after blood glucose monitoring. [13] Another way to monitor glycemia in patients using continuous subcutaneous insulin infusion (CSII) is continuous glycemia monitoring systems (CGM). This study [20] showed that the use of CGM in a pregnancy complicated by DM1 had a positive effect on maintaining HbA1c values within the normal range and had a significant effect on maternal glucose time in range (TIR). The effect was a reduction in the incidence of large-for-gestational-age births, length of infant hospital stays, and severe neonatal hypoglycemia. Data from this research [21] indicates that the use of the CGM-reported mean glucose is superior to the use of estimated HbA1c in the matter of glycemia measurement.

After diagnosis, the GDM treatment is based on medical nutrition therapy, regular physical activity and weight control. The glycemic goals for GDM maintain the same as for individuals with preexisting DM1 or DM2.

Glycemic levels recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus [22]:

- Fasting glucose <95 mg/dL (<5.3 mmol/L) and either
- One-hour postprandial glucose <140 mg/dL (<7.8 mmol/L) or

- Two-hour postprandial glucose <120 mg/dL (<6.7 mmol/L)

The lower glycemic goals for patients with GDM are determined when it is necessary to implement insulin therapy and are the same as for pregnant individuals with preexisting DM1 or DM2. [13]

POSTPARTUM GLYCEMIA MONITORING AND SCREENING FOR DM

Gestational diabetes is often correlated with previously undiagnosed impaired glucose tolerance, DM2 and even DM1, which is why postpartum glycemia monitoring is particularly significant. The recommended method of measurement is fasting 75g-OGTT, using nonpregnancy criteria of diabetes recognition, in the 4-12 week of delivery. [13] This study showed that GDM increases the maternal risk of future diabetes by up to tenfold compared to individuals with normal glycemia during pregnancy [25], therefore patients with a history of gestational diabetes should undergo annual screening for prediabetes or DM2 with any recommended glycemic test i.e. HbA1C, fasting blood glucose or every three years with 75-g OGTT using thresholds for nonpregnant individuals. Taking into consideration fact that the lifetime risk of developing diabetes increases linearly with time, from 20% 10 years after delivery to even 60% 50 years after pregnancy, [26] leading a healthy lifestyle and obesity prevention are essential in order to reduce the risk of diabetes mellitus. [27] Many large RCTs have proven that implementing healthy lifestyle patterns not only reduces the risk of diabetes mellitus development but also minimizes cardiovascular risk factors. [29]. Among individuals with pre-existing DM1, the demand for insulin decreases rapidly immediately after delivery and insulin requirements may decrease by slightly over 30% compared to the pre-pregnancy period. Patients on insulin therapy should pay attention to the prevention of hypoglycemia by carefully adjusting the dosage of insulin and planning well-balanced meals. [31]

COMPLICATIONS RELATED WITH GESTATIONAL DIABETES MELLITUS

The complications of different types of diabetes include maternal and neonatal adverse outcomes and they may appear shortly after delivery or later on during lifetime. [32] Short-term complications include macrosomia, respiratory distress syndrome (RDS), neonatal hypoglycaemia, neonatal intensive care unit admission, congenital anomalies, preterm birth,

pre-eclampsia, cesarean section and preterm birth while in the long-term both mothers and their offspring have an increased risk of cardiovascular and metabolic disorders. [32,33] The results of this systematic review confirm that pregestational diabetes is associated with a higher incidence of pregnancy complications compared to GDM. Poor glycemic control before conception and at the beginning of pregnancy exposes the fetus to high intrauterine glucose concentration and increases the risk of congenital defects, since the first trimester of pregnancy is crucial for organogenesis. [4, 32] Macrosomia (infant body mass > 4-4,5 kg) is one of the main complications affecting the fetus and is caused by increased glucose levels in the mother's blood. Although, apart from the intrauterine maternal environment, many factors ultimately influence birth weight, including fetal genes and maternal prepregnancy BMI which may be a predictor of high birth weight as well. Therefore, obesity prevention and excess weight loss may be beneficial not only for minimizing the long-term risk of obesity but also diabetes in the offspring. [22]

Individuals with GDM have an up to tenfold increased risk of developing diabetes and the American Diabetes Association (ADA) recommends screening at least every three years. In addition to non-modifiable risk factors for the progression of GDM to DM2, including maternal age, family history of diabetes and genetic predisposition, modifiable ones have been identified. Regular physical activity, well-balanced diet and postpartum weight loss improve insulin sensitivity and decrease the risk of DM2 development. [37] Identifiable risk factors for the development of metabolic syndrome including insulin resistance, central obesity, hypertension and dyslipidemia are also associated with the development of GDM and cardiovascular diseass (CVD). Glycemia monitoring during pregnancy complicated by impaired glucose tolerance may contribute to the detection of previously undiagnosed metabolic syndrome or one of its components leading to the development of CVD. This study showed that the 3 month postpartum prevalence of the metabolic syndrome increases progressively from 10% in pregnant women with normoglycemia to 17.6% in women with gestational impaired glucose tolerance and to even 20% in women with previous GDM. [38] Taking all this into consideration, gestational diabetes may be associated with an increased risk of metabolic syndrome and cardiovascular disease in the long-term perspective and therefore lifestyle modifications including well-balanced diet and regular physical activity may be beneficial. [37]

CONCLUSIONS

Gestational diabetes is a type of diabetes which pathogenesis is closely related to metabolic and hormonal changes during pregnancy. [44] It develops around the second trimester of pregnancy and usually resolves after delivery. There are many risk factors for its development, including overweight or obesity, macrosomic births in the past, advanced maternal age or diagnosis of gestational diabetes in previous pregnancies. Gestational diabetes has separate diagnostic values for laboratory tests, and the recommended tests are fasting plasma glucose levels and oral glucose tolerance tests. Both people with risk factors for developing GDM and those previously diagnosed with DM1 or DM2 should be informed about the necessity to lose excess body weight, modify their diet and implement regular physical activity. In most cases, treatment of gestational diabetes is based on nutritional interventions and a healthy lifestyle, insulin therapy is relatively rarely necessary. People with DM1 should regularly adjust their insulin dosage to changing requirements in order to meet glycemic goals. People with DM2 planning a pregnancy should replace metformin with insulin or discontinue it in the first trimester at the latest. Gestational diabetes as well as pregestational diabetes increase the risk of perinatal complications and have an impact on the long-term risk of developing type 2 diabetes, obesity and cardiovascular diseases in both the mother and the offspring, therefore effective treatment, repeated glycemic measurements and regular screening are essential.

Disclosure

Supplementary materials

Not applicable.

Authors contribution:

Conceptualization, Adrianna Skóra and Katarzyna Hajduk-Maślak; methodology, Beniamin Michalik and Aleksandra Szypuła; software, Iwona Galasińska; check, Iwona Galasińska and Aleksandra Szypuła; formal analysis, Michał Sęk and Beniamin Michalik; investigation, Adrianna Skóra; resources, Michał Sęk; data curation, Aleksandra Szypuła; writing - rough preparation, Iwona Galasińska and Beniamin Michalik, writing - review and editing; Adrianna Skóra, Katarzyna Hajduk-Maślak; visualization, Katarzyna Hajduk-Maślak; supervision, Michał Sęk; project administration, Adrianna Skóra All authors have read and agreed with the published version of the manuscript.

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The data presented in this study are available upon request from the correspondent author.

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