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CLINICAL VIGNETTE

Obesity — a still underestimated risk factor during antenatal corticosteroids therapy

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ABSTRACT

Pregnant obese patients are at a greater risk of developing gestational diabetes (GDM). We present a case of an obese patient who developed GDM G2 and periventricular leukomalacia in the neonate after antenatal corticosteroids (ACS) treatment. We suggest that routine blood glucose monitoring should be considered during a course of prenatal steroid therapy in all patients in a higher risk group for glucose intolerance. In cases of hyperglycemia, intensive insulin therapy should be advised. More research and new recommendations are needed on antenatal glucocorticoids (GCS), obesity, and GDM.

Key words: gestational diabetes mellitus; corticosteroids; obesity; pregnancy; insulin therapy

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders that share a common feature of hyperglycemia as a result of absolute or relative insulin deficiency. In Poland, due to the new criteria for the diagnosis of hyperglycemia in pregnancy as well as the greater prevalence of risk factors, the prevalence of glucose metabolism complications almost doubled in last 20 years [1]. Obesity is abnormal or excessive fat accumulation that may impair health. Pregnant obese patients with body mass index (BMI) over 30 kg/m^2 are at increased risk of developing gestational diabetes (GDM). Adequately early diagnosis of GDM in obese pregnant women and initiation of treatment (dietary recommendations, glycemic control, and, if necessary, oral hypoglycemic medication *e.g.*, metformin or insulin injection) significantly reduce the risk of complications such as fetal macrosomia and shoulder dystocia. All obese pregnant women should undergo a glucose loading test of 75 g at the first visit in pregnancy after prior fasting blood glucose control. In women at risk of preterm labor between 24 + 0 and 34 + 6 weeks of pregnancy (wks.), a single course of GCS therapy should be used, *i.e.*, two doses of betamethasone, a drug with proven properties that reduce carbohydrate tolerance. It has been confirmed that their use in pregnancy significantly reduces the mortality of newborns and the incidence of RDS and IVH. Antenatal corticosteroids (ACS) is not associated with any benefit nor risk to the pregnant woman, nor any direct adverse effects on the fetus. Data on the long-term effects of a single course of steroid therapy do not indicate that it is associated with adverse effects in terms of neurological or cognitive functions. On the other hand, insufficient data have been obtained on the long-term effects of multiple cycles of steroid therapy.

CASE STUDY

Pregnant, 29-year-old GII, PI, admitted to the Department of Obstetrics and Pathology of Pregnancy, the Medical University of Lublin at the 31 wks. due to the suspicion of oligohydramnios and symptoms of impending preterm labor: uterine contractions every eight minutes and shortening of the cervix about 30%, dilation 1.5 cm. In the history: spontaneous miscarriage at wks., obesity in pregnancy — body weight 118 kg and BMI > 35 kg/m^2, fasting blood glucose level at 10 wks. were determined, and oral glucose tolerance test (OGTT) 75 g was performed at 26 wks. — normal test result, COVID in the 1st trimester. Intravenous tocolytic treatment (atosiban) and a course of ACS of 2 × 12 mg of betamethasone were applied and anticoagulant prophylaxis with 40 mg of enoksaparin daily. During treatment, due to risk factors and glucosuria, blood glucose measurements were

ordered 5 times a day. The results showed hyperglycemia that did not resolve after two days of observation and a modification of the diet according to Polish Diabetic Society. After a diabetic consultation, long-acting insulin, 6 units per night, was introduced. On the following days, Polhumin was increased to 12 units per night and Novorapid was added as four units to main meals. Ketonuria was observed, in addition, the patient reported malaise, mainly at night. The US-scan confirmed the well-being of the fetus but large for gestational age (LGA), with estimated fetal weight above 90%. Insulin therapy was actively modified, finally with the following doses of drugs: Levemir 16 units for the night and 4 units of Novorapid with each meal. After achieving normal blood glucose values, the patient was discharged home at 34 wks. with recommendations for the assessment. In 37 w1d the patient was admitted to the Department due to increased glycaemia despite insulin therapy. Due to the estimated LGA, disproportion in the measurements of HC/AC < 0.88 of the fetus and oligohydramnios she was qualified for cesarean section. A 3880 g — baby boy was born with an Apgar score of 7–8–8. The transcranial ultrasound revealed mild periventricular leukomalacia (PVL). Three months after giving birth, the patient lost 16 kg but still did not perform the OGTT. The study was observational in nature and was based on patients' responses to different kinds of caregiving and did not involve medical experiment. The authors had obtained informed consent from the patient.

DISCUSSION

Gestational diabetes mellitus usually develops in the second half of pregnancy and has significantly increased in prevalence over the last 20 years. The current incidence rates are 1.7 to 15.7%, depending on the ethnic origin, maternal age, and diagnostic criteria [2]. The likelihood of GDM increases with increasing BMI which is significant for all racial/ethnic groups. One of the classic side effects of steroid therapy is the induction of hyperglycemia in people not burdened with other diseases. Considering all the above currently, there are no clear recommendations regarding the monitoring of blood glucose levels in any pregnant women undergoing steroid therapy.

In one observational, longitudinal study Rahmi et al. [3] performed continuous glucose monitoring in obese pregnant women (OG) with normal OGTT between the 24th and the 28th wks. The control group (CG) consisted of pregnant women with normal weight. The 24-hour, daytime, and nighttime glucose values were higher in the OG when compared with

the CG. They proved that obesity in pregnancy was associated with higher glycemic values even in the presence of normal findings on OGTT.

Glucocorticoids are necessary for fetal development, but on early stages of pregnancy can negatively influent the embryogenesis (organ development and miscarriage). Long-term corticosteroid therapy may be associated with the development of diabetes in pregnant women.

In 2000 Star et al. [4] studied the degree and timing of maternal hyperglycemia following betamethasone therapy in nondiabetic patients to establish a prophylactic dose of insulin. Eighty-five percent of patients who did not receive insulin exhibited hyperglycemia at levels previously associated with fetal acidosis. Significant differences in mean postprandial plasma glucose levels were found between the no-treatment and insulin groups on Days 1 and 2. No significant differences were noted between groups on Day 3. They concluded that maternal hyperglycemia can be limited by insulin treatment. In our case the hyperglycemia continued long after corticosteroid withdrawal probably due to obesity of the patient.

The use of oral antidiabetic agents was not recommended in any guidelines because of the lack of safety and efficacy studies in the inpatient setting. However, in recent years, metformin has gained acceptance as a safe, effective, and rational option for reducing insulin resistance in pregnant women with type 2 diabetes, GDM, or PCOS. It may also provide benefits to obese non-diabetic women during pregnancy. In our case, the patient benefits the most from multiple insulin daily injections (MDI). The other method of insulin therapy is continuous subcutaneous insulin infusion (CSII) with a personal insulin pump. The goal of the treatment is to achieve ‘time in range’ (TIR).

Maternal obesity is also an independent risk factor for PVL in the neonate [5]. Periventricular leukomalacia (PVL) is a cerebral white matter injury, both focal and diffuse. It is characterized by deep necrosis or a decrease in premyelinating oligodendrocytes and subplate neurons. The nutrient excess associated with obesity activates innate immune response leading to chronic, sterile low-grade inflammation affecting the liver, adipose tissue, muscle, hypothalamus, pancreas, and blood vessels. Besides obesity, our patient had no other risk factors of PVL, like prematurity, chorioamnionitis nor intrauterine infection.

There is growing evidence that GDM significantly increases the risk of a number of short- and long-term adverse consequences for the fetus and mother. Acute, severe

hyperglycemia can result in decrease in fetal blood pH (acidosis) and diabetic ketoacidosis which has been reported to be associated with a risk of stillbirth in up to 30% [6]. In research of Myszkowski et al. [7] in twin pregnancies with GDM G1 in group of LGA fetuses a higher incidence of RDS, second-degree intracranial bleeding and grade II of preterm retinopathy were observed [7]. In the group of smaller infants (FGR) in twin pregnancies, anemia was more frequent. Long-term negative impact causes obesity, metabolic syndrome, type 2 diabetes and cardiovascular disease and is called ‘fetal programming’. Therefore, it should not be a great deal of controversy to recommend screening for hyperglycemia in patients receiving GKS and having risk factors for GDM.

CONCLUSIONS

In conclusion, in pregnant women with risk factors for gestational diabetes such as obesity, routine blood glucose monitoring should be considered during a course of prenatal steroid therapy. In the case of hyperglycemia, intensive insulin therapy should be advised. Adequate prenatal care during pregnancy has a great impact in prevention on the occurrence of serious neonatal complications.

More research is needed to open a discussion on changing the policies and recommendations on ACS, obesity, and GDM. An optimal strategy to achieve maternal glycemic control after ACS is needed. Therefore a “Glycemic Control After Antenatal Corticosteroids in Women with Pregestational and Gestational Diabetes (Close the GAP)” trail has started in February 2022.

Our team is starting a longitudinal, prospective observational/experimental study on benefits on daily glucose monitoring in high-risk pregnant patients during ACS. This study was approved by the Bioethical Commission at the Medical University of Lublin (Res No. KE-0254/98/04/2022). The results will be a part of a thesis and will be published in peer-reviewed journals and presented at international conferences.

Conflict of interest

The authors report no conflicts of interest.

REFERENCES

1. Bomba-Opoń DA, Godek B, Czekaj L, et al. Hyperglycemia in pregnancy - prevalence and perinatal outcomes. A retrospective multicenter cohort study in Poland. Ginekol Pol. 2022 [Epub ahead of print], doi: 10.5603/GP.a2021.0257, indexed in Pubmed: 35315020.

2. Ornoy A, Becker M, Weinstein-Fudim L, et al. Diabetes during pregnancy: a maternal disease complicating the course of pregnancy with long-term deleterious effects on the offspring. A clinical review. Int J Mol Sci. 2021; 22(6), doi: 10.3390/ijms22062965, indexed in Pubmed: 33803995.

3. Rahmi RM, de Oliveira P, Selistre L, et al. Continuous glucose monitoring in obese pregnant women with no hyperglycemia on glucose tolerance test. PLoS One. 2021; 16(6): e0253047, doi: 10.1371/journal.pone.0253047, indexed in Pubmed: 34111215.

4. Star J, Hogan J, Sosa ME, et al. Glucocorticoid-associated maternal hyperglycemia: a randomized trial of insulin prophylaxis. J Matern Fetal Med. 2000; 9(5): 273–277, doi: 10.1002/1520-6661(200009/10)9:5<273::AID-MFM3>3.0.CO;2-N, indexed in Pubmed: 11132581.

5. Herzog M, Cerar LK, Sršen TP, et al. Impact of risk factors other than prematurity on periventricular leukomalacia. A population-based matched case control study. Eur J Obstet Gynecol Reprod Biol. 2015; 187: 57–59, doi: 10.1016/j.ejogrb.2015.02.008, indexed in Pubmed: 25748489.

6. Dalfrà MG, Burlina S, Sartore G, et al. Ketoacidosis in diabetic pregnancy. J Matern Fetal Neonatal Med. 2016; 29(17): 2889–2895, doi: 10.3109/14767058.2015.1107903, indexed in Pubmed: 26461169.

7. Myszkowski B, Stawska A, Glogiewicz M, et al. Influence of gestational diabetes in twin pregnancy on the condition of newborns and early neonatal complications. Ginekol Pol. 2022 [Epub ahead of print], doi: 10.5603/GP.a2022.0037, indexed in Pubmed: 35894496.