

Insulin resistance in pregnancy complicated by type 1 diabetes mellitus. Do we know enough?

Insulinooporność w ciąży powikłanej cukrzycą typu 1.
Czy wiemy na jej temat dostatecznie dużo?

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Abstract

Insulin resistance (IR) is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization. In recent years the increasing role of IR in the pathogenesis of type 1 diabetes mellitus (T1DM) related complications has been taken into account.

The aim of this article is to discuss the possible role of IR in pregnancy complicated by T1DM.

At the moment, there is no doubt that IR is not only frequently observed in T1DM patients, but also is a separate risk factor of several complications in non- pregnant patients. The role of IR in pregnancy complicated by T1DM has not been widely studied yet. However, data from the studies on different populations showed that IR may predispose to such conditions as miscarriage, preeclampsia and macrosomia. Interestingly, all of these are more frequently diagnosed in women with T1DM in comparison to healthy subjects.

The literature on the role of IR in human pregnancy is relatively rich. However, despite its significance in pathophysiology of T1DM and its complications in general population, there is a lack of understanding of how it affects maternal and fetal health in pregnancy complicated by this disease. Nonetheless, based on the available literature, IR may be proposed as an additional factor modifying pregnancy outcome in woman with T1DM. Therefore, measures that might reduce IR such as good glycemic control and control of weight gain should be recommended for every woman with T1DM, optimally when planning but also throughout the pregnancy.

Key words: **type 1 diabetes mellitus / insulin resistance / pregnancy /
/ metabolic syndrome / preeclampsia / macrosomia /**

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Streszczenie

Insulinooporność definiuje się jako zmniejszenie wrażliwości tkanek obwodowych na insulinę zarówno endogenną jak i egzogenną. W ostatnich latach podnosi się rolę insulinooporności w patogenezie powikłań cukrzycy typu 1.

Insulinooporność jest nie tylko częstym zjawiskiem u pacjentów z cukrzycą typu 1 ale również stanowi izolowany czynnik ryzyka szeregu powikłań w populacji kobiet nie będących w ciąży oraz mężczyzn. Rola insulinooporności w ciąży powikłanej cukrzycą typu 1 nie była dotychczas szeroko zbadana. Dane z badań przeprowadzonych w innych populacjach ciężarnych pokazują iż insulinooporność zwiększa ryzyko takich powikłań jak poronienia, stan przedrzucawkowy i makrosomia. Co istotne, wszystkie te powikłania spotyka się istotnie częściej u pacjentek z cukrzycą typu 1. Mimo braku badań dotyczących roli insulinooporności w ciąży powikłanej cukrzycą typu 1, na podstawie danych z innych populacji ciężarnych, insulinooporność może być uznana za dodatkowy czynnik ryzyka powikłań. Stąd też działania, które potencjalnie mogą doprowadzić do zmniejszenia insulinooporności takie jak kontrola glikemii oraz kontrola przyrostu masy ciała powinny być zalecane pacjentkom zarówno w okresie planowania ciąży jak i w trakcie jej trwania.

Słowa kluczowe: **cukrzyca typu 1 / insulinooporność / ciąża / zespół metaboliczny / stan przedrzucawkowy / makrosomia /**

Introduction and objectives

There has been a 50-70% increase in the incidence of T1DM in women of childbearing age over the last 20 years [1]. Despite significant advances in the management of diabetes, professionals continue to be challenged by the goal set at St Vincent's in 1989 of improving pregnancy outcome to approximate that of non-diabetic women [2]. The pathophysiology of complications related to maternal hyperglycemia in the periconceptional period and during pregnancy has been thoroughly studied [3, 4]. However, hyperglycemia is not solely responsible for increased risk of complications in T1DM pregnancies.

Insulin resistance (IR) is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in individuals as much as it does in a normal population. Several mechanisms have been proposed as possible causes underlying the development of IR, including genetic abnormalities of one or more proteins of the insulin action cascade, increase in visceral adiposity and the role of selected adipokines [5,6]. Pregnancy itself significantly induces insulin resistance. However, a marked increase of IR occurs mainly in the second part of gestation. During early gestation insulin secretion increases with unchanged or even decreased IR. These changes facilitate the accretion of adipose tissue. In late pregnancy these mechanisms are reversed. Adipose tissue depots decline, and the ability of insulin to inhibit lipolysis is markedly limited, which results in an increased level of free fatty acids. This further stimulates hepatic gluconeogenesis and IR.

Insulin resistance is an important component of cardiovascular-metabolic abnormalities, commonly referred to as "The Insulin Resistance Syndrome" or "The Metabolic Syndrome" [7]. In recent years the increasing role of IR in the pathogenesis of T1DM-related complications has been taken into account. At the moment, there is no doubt that IR is not only frequently observed in type 1 diabetic patients, but also is a separate risk factor of several complications in non-pregnant patients [8, 9, 10, 11, 12]. However, data concerning the influence of IR on the course of pregnancy in type 1 diabetic patients is scarce [13].

Therefore, the aim of this article is to discuss the possible role of insulin resistance (IR) in pregnancy complicated by T1DM.

Early pregnancy

T1DM is an important risk factor for early pregnancy complications. It significantly increases the risk of spontaneous miscarriages and development of fetal defects [14, 15]. Maternal hyperglycemia is suggested to be an important factor for these complications, however, the overall mechanism is not fully understood.

The effect of IR on early pregnancy development was studied in women with polycystic ovary syndrome (PCOS). The presence of IR in PCOS patients seems to impair pregnancy rate after in-vitro fertilization (IVF). Importantly, this effect is not related to altered embryo development [16]. This suggests that hyperinsulinemia (as a consequence of IR) alters endometrial function and implantation process. The insulin-sensitizing agent metformin reduces miscarriage rates in PCOS patients, which further supports the role of IR/hyperinsulinemia in early pregnancy loss [17, 18].

The effect of IR on early pregnancy loss in patients with T1DM has not yet been studied.

Women with poorly controlled diabetes (high glycated hemoglobin values-HbA1c) are at increased risk of miscarriage and birth defects [4, 19]. These women have higher IR, because this parameter positively correlates with HbA1c [20]. Regardless of the influence of hyperglycemia, chronic inflammation and oxidative stress may exert further deleterious effects on early pregnancy development. Some degree of uterine inflammation is necessary for the implantation and subsequent maternal immune tolerance of a semi-allogeneic fetus. However, in diabetes, the inflammation seems to be excessive which may lead to embryo maldevelopment. The association between inflammation and miscarriage was examined by many authors, however only a small number of studies focused on T1DM women [21]. Wender-Ozegowska et al., showed that inflammation and resultant oxidative stress may contribute to unfavorable outcome in this group of patients [22]. Moreover, the same authors found that substantial changes in the first-trimester serum chemokine concentrations (RANTES, MCP-1) occur in T1DM women who miscarried [23]. There is strong evidence, that both oxidative stress and altered chemokine levels are involved in IR induction. However, the mechanism of

how inflammation-induced IR may affect early pregnancy development remains unknown and needs further research.

Visceral adiposity is strongly linked with IR [24]. Obese T1DM patients have higher insulin requirements, which suggests increased IR. Some studies found a positive association between obesity and the risk of miscarriage [25, 26]. However, none of these focused on T1DM patients.

Birth defects are among the complications of early pregnancy associated with increased pre-pregnancy BMI. The strongest association has been found for neural tube defects (NTD's) [27, 28]. Higher incidence of NTD's in obese women might be at least partly explained by lower serum folate concentrations found in this group [29]. However, more recent studies indicate that pre-pregnancy obesity increases the risk of other birth defects, such as congenital heart defects (CHD's), which suggests the involvement of other mechanisms [30].

Both, obesity and diabetes induce several metabolic alterations in which IR plays important role. Other factors such as abnormalities in lipid metabolism and action of adipocyte hormones may be also involved. Thus, the mechanism of early pregnancy complications in T1DM women is rather complex and not only confined to hyperglycemia. The role of IR as an isolated teratogenic factor in T1DM requires further investigation.

Second half of pregnancy

Rapidly growing fetal energy needs induce profound metabolic changes in the mother during the second half of pregnancy. In contrast to early gestation, which is an anabolic state with decreased IR, late gestation is characterized by gradually increasing catabolism and IR. In physiological conditions, these processes are well-balanced and maintain maternal homeostasis and thus, proper fetal development. Diabetes, especially when uncontrolled, leads to distortion of the metabolic equilibrium, which places pregnant women at high risk of developing several maternal and perinatal complications.

Pregnant women with T1DM are at especially high risk of developing PE, with the incidence estimated as 15-20% [31,32]. There are many factors involved in the pathophysiology of PE, however, abnormal development of the placenta is considered to play a crucial role in this disease. Nonetheless, placental dysfunction in PE is complex and might have its origin in numerous genetic, immunological, and inflammatory processes [33]. Importantly, all of these seem to be modified by pre-existing maternal medical conditions, as well as the environmental triggers [34]. It was shown in several studies that patients who develop PE tend to have elevated IR [35, 36]. It is further confirmed by the fact that the incidence of PE is significantly higher in overweight and obese women. Moreover, it positively correlates with increasing adiposity [37]. The other components of the metabolic syndrome, such as hypertension and hypertriglyceridemia, are also independent risk factors for PE [38, 39]. It is well-known that patients with the metabolic syndrome develop profound insulin resistance, which might be an important explanation for higher incidence of PE in this group. In addition to IR, women who develop PE have signs of altered angiogenesis, marked by significant changes in the expression of substances such as placental growth factor (PlGF), placental soluble fms-like tyrosine kinase 1 (sFlt-1) and endoglin (sEng). Importantly, low PlGF, high sFlt-1, as well as high eEng precede the onset of PE by several months,

which shows similar relation to that observed for IR, which was also found to be useful in prediction of PE [33]. Altered angiogenesis and vascular dysfunction are typical features of T1DM, especially when the disease is longstanding, uncontrolled and complicated by vasculopathy. Whereas the placenta is almost entirely the vascular structure, it is especially prone to be affected by the diabetic environment, from the onset of placentation until the end of pregnancy. Furthermore, several studies showed that long duration of diabetes and the presence of vascular complications were strongly associated with PE. It is important to note that patients with vascular complications tend to have higher IR, which may also contribute to alterations in placental function. Nonetheless, the exact role of IR in the pathogenesis of placental dysfunction in PE among type 1 diabetic subjects remains to be fully elucidated and there is a need for further research in this area.

Hormonally and metabolically active adipose tissue is a source of several adipokines, some of which have been found to play a role in PE. In a study performed in a non-diabetic group of patients (PE vs. healthy subjects) third-trimester serum levels of adiponectin, resistin and leptin were higher in PE [40]. It is important to note that some of these adipokines (adiponectin and resistin) have been found to be elevated in patients with T1DM [41, 42]. It may suggest the involvement of altered adipokines as well as resultant IR in the pathophysiology of PE in T1DM, however, it also needs further study.

Fetal macrosomia is one of the major complications of diabetic pregnancy. Large for gestational age (LGA) fetuses are at increased risk for several complications. There are significantly higher rates of intrauterine fetal deaths (IUFD), birth injuries, cesarean sections as well as early neonatal complications among LGA offspring [43]. Moreover, these children are a high-risk population for metabolic disorders such as obesity, metabolic syndrome and type 2 diabetes in the future [44]. Etiology of macrosomia is multifactorial, however some maternal characteristics predispose to abnormal fetal growth. Instead of diabetes, maternal obesity as well as excessive gestational weight gain together with IR was found to be independent risk factors for macrosomia. These associations have been studied mainly in healthy and GDM subjects, however, the mechanisms are probably similar in T1DM [45]. Excess of maternal adipose tissue creates an abnormal environment for the developing fetus. Obese patients have higher IR, and thus exhibit tendency for hyperglycemia and other metabolic disturbances, including changes in lipid metabolism. All of these lead to fetal overnutrition and increased fat deposition. Glucose transport across the placenta depends on maternal-fetal concentration gradient. Maternal hyperglycemia elevates this gradient, leading to increased glucose flux to the fetus. Concurrently, the healthy fetal pancreas starts to produce more insulin. Fetal hyperinsulinemia results in pro-anabolic state with increased insulin-stimulated glucose utilization, which further elevates maternal-fetal glucose concentration gradient. Maternal IR as a factor that predispose to hyperglycemia may also contribute to increased transplacental glucose flux with its consequences to the fetus. However, the origin of macrosomia is rather complex and not only confined to maternal hyperglycemia. Maternal dyslipidemia was found to be involved in fetal macrosomia. Knopp et al. in their study on GDM patients, found that maternal triglyceride concentrations had a higher correlation to fetal weight

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gain than maternal glucose concentrations [46]. Placental lipase is able to hydrolyse triglycerides, producing non-esterified fatty acids (NEFAs) that cross the placental barrier easily, again depending on the maternal-fetal gradient [47]. Excess of NEFAs, together with fetal hyperinsulinemia, may stimulate fat storage and fetal weight gain. It is important to mention that raised triglycerides is one of the clinical components of the metabolic syndrome and closely correlates with IR [48]. Therefore, maternal IR might be suggested as an additional risk factor for LGA in type 1 diabetic women by promoting increased transfer of glucose and NEFAs to the fetus. However, due to lack of studies in this group of patients, there is a clear need for further research in this area.

Summary

The incidence of T1DM has doubled over last 20 years and continues to rise. T1DM epidemic is parallel to a growing incidence of childhood obesity. Based on the accelerator hypothesis, IR is not only the consequence of long-standing diabetes, but it might be one of the causes of beta-cell dysfunction in T1DM together with autoimmunity [49].

Obesity, long duration of diabetes, poor metabolic control, as well as exogenous hyperinsulinism, have been found to exaggerate IR. However, even lean and well-controlled subjects with uncomplicated T1DM have decreased insulin sensitivity in comparison to healthy controls matched for age, gender and BMI. Importantly, IR in these patients involves several metabolic pathways such as lipolysis, hepatic and peripheral glucose metabolism [50]. Therefore, it indicates that IR may be a prominent feature of every T1DM subject.

The role of IR in non-pregnant patients with T1DM seems to be relatively well-defined in the literature. Elevated IR predisposes to diabetic microvascular complications and cardiovascular disease. However, much less is known on how IR affects pregnancy in T1DM women. For ethical reasons, the gold standard for the measurement of insulin sensitivity in T1DM- hyperinsulinemic euglycemic clamp method- is of very limited use in pregnancy, due to its complexity and invasiveness. However, estimated glucose disposal rate (eGDR)- a non-invasive tool of IR assessment, was found to correlate closely with clamp method. This is a formula based on such clinical parameters like glycated hemoglobin (HbA_{1c}), hypertension and waist to hip ratio (WHR). Its major limitation is that it might be used only in early pregnancy, when WHR is not yet affected by an enlarging uterus. At this moment, there are no standardized methods of IR assessment in the second part of pregnancy complicated by T1DM and there is a necessity for research in this area. Currently available data on the role of IR in the pathophysiology of human pregnancy mainly comes from studies on healthy, PCOS, GDM, as well as preeclamptic women. The majority of these studies used simple methods of IR assessment, such as homeostasis model assessment (HOMA), quantitative insulin sensitivity check index (QUICKI), and C-peptide-to-glucose ratio (CGR) during oral glucose tolerance test. All of these methods are inadequate for the measurement of IR in patients with severely impaired or absent beta-cell function as in T1DM.

To summarize, the literature on the role of IR in human pregnancy is relatively rich. However, despite its significance in the pathophysiology of T1DM and its complications in the general population, there is a lack of understanding of how it affects ma-

ternal and fetal health in pregnancy complicated by this disease. Nonetheless, based on the available literature, IR may be proposed as an additional factor modifying pregnancy outcome in women with T1DM. Therefore, measures that might reduce IR, such as good glycemic control and control of the weight gain should be recommended for every woman with T1DM, optimally when planning but also throughout the pregnancy.

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