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Gestational diabetes – is diet and insulin the only solution?

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Abstract

Gestational diabetes (GDM) is a relatively common complication of pregnancy. Maternal hyperglycemia causes many serious side effects for mothers, fetuses and newborns. In 90% of women diagnosed with GDM, a dietary treatment results in satisfactory levels of blood glucose. The remaining 10% require insulin therapy to achieve the recommended glycemic levels. The majority of recent studies show the efficiency of metformin in gestational diabetes and prove that it is not a cause for any harmful side effects to the embryo and/or fetus. Metformin is an effective alternative to insulin in glycemic control in pregnant women. The implementation of metformin, as a routine procedure in gestational diabetes, requires further research, the results of which would unequivocally confirm its efficacy and safety for pregnant women and their offspring.

GESTATIONAL DIABETES

Gestational diabetes (GDM) is a relatively common complication of pregnancy, which prevalence is estimated at 1.9–3.8% of all pregnancies in different regions in Poland. The prevalence varies depending on the population studied, in subjects with multiple diabetes risk factors reaching up to 10% (Cypryk *et al.* 2008).

According to current recommendations (Polish Diabetes Association, 2017), all pregnancies which are not at risk of GDM, should be screened by fasting glucose test during the first prenatal visit, and if the test result is around average, 75.0 g OGTT should be performed between 24–28 weeks of gestation or in case of symptoms which suggest diabetes. In the risk group patients, 75.0 g OGTT should be performed at the first prenatal visit, and again between 24–28 weeks of pregnancy if the initial test proves successful. Gestational diabetes can be diagnosed at any time of pregnancy when at least one of the following criteria are met: fasting plasma glucose 5.1–6.9 mmol/l (92–125 mg/dl), plasma glucose in 60th minute of OGTT ≥10.0 mmol/l (≥180 m/dl) or plasma glucose in 120th minute of OGTT 8.5–11.0 mmol/l (153–199 mg/dl) (American Diabetes Association 2016; Polish Diabetes Association 2017).

Physiologically reduced insulin sensitivity observed in pregnancy aims to provide an opti-

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mal glucose supply to structures of a developing fetus. Placental hormones are responsible for alterations in maternal metabolism and hormone levels, such as human placental lactogen (hPL), oestrogens, progesterone, prolactin and cortisol, which concentrations significantly increase during pregnancy (Kalkhorff *et al.* 1978; Ryan and Enns 1988; Guyton and Hall 2006). Human placental lactogen and cortisol act antagonistically to insulin, and in addition, a lipolytic effect of hPL causes an increase of free fatty acids, inhibiting muscle glucose uptake that potentiates insulin resistance and glucose sparing for the fetus (Yoshino *et al.* 2014). Placental pathologic changes in gestational diabetes have been carefully reviewed by other authors (Jarmuzek *et al.* 2015).

In pregnancies complicated by gestational diabetes, an increase of circulating inflammatory factor TNF-α (Tumor Necrosis Factor-α) involved in pregnancy-associated insulin resistance was observed. Placental TNF-α inhibits autophosphorylation of insulin receptor tyrosine kinase, thereby exacerbating insulin resistance (Friedman *et al.* 2008).

Regulation of glucose uptake in insulin-sensitive tissues depends on the level of IRS-1 (Insulin Receptor Substrate-1) protein, which is decreased in skeletal muscle by 30–50% in GDM patients compared with obese non-pregnant subjects. Therefore, the low level of IRS-1 protein may be indirectly responsible for increasing insulin resistance observed in GDM (Friedman *et al.* 1999). It was shown, additionally, that serine phosphorylation of IRS-1 responsible for reduced translocation of GLUT-4 (GLUcose Transporter type 4) to the plasma membrane and diminished insulin-stimulated glucose uptake to skeletal muscle is more inhibited in women with GDM, compared to normal obese patients suffered from impaired glucose tolerance (Sivalingam *et al.* 2014).

Facilitated diffusion allows the transportation of glucose across the placenta; when maternal hyperglycemia occurs, the abundance of plasma glucose reaches the fetus stimulating insulin secretion, which can result in hypertrophy of insulin-sensitive fetal tissues. That, in turn, induces accelerated fetal growth and/or macrosomia. The replication of β cells, which occurs as a result of islets Langerhans hypertrophy, additionally increases fetal insulin secretion, as well as the levels of some metabolic fuels, e.g. aminoacids, free fatty acids, increase. An increased metabolic rate, which is caused by fetal hyperinsulinemia, results in excessive oxygen consumption at the cellular level (Sermer *et al.* 1995; Metzger *et al.* 2008; Freinkel 1980; Di Cianni *et al.* 2003). When combined with altered oxygen transport, it may cause fetal hypoxia and even may result in stillbirth (Garcia Carrapato 2003).

Fetal hyperinsulinemia can also be responsible for respiratory distress or hyaline membrane disease, as is delays pulmonary maturation associated with a decreased production of surfactant (Kjos *et al.* 1990).

METFORMIN

Metformin is an orally administrated insulin sensitizer, which is classified as a biguanide antidiabetes drug. Currently, it is the mostly used as a first-line pharmacological therapy for type 2 diabetes (Nathan *et al.* 2009). Metformin exerts a hypoglycemic effect mainly by the inhibition of hepatic glucose output (Song 2016). Hepatic mechanisms of metformin include: 1) the activation of AMPK (5'AMP-activated Protein Kinase) through liver kinase B1 and decreased energy charge (Shaw *et al.* 2005; Zhou *et al.* 2001), 2) the inhibition of glucagon-induced cAMP production by blocking adenylyl cyclase (Milleret *et al.* 2013), 3) the increase of the AMP/ATP ratio by restricting NADH-coenzyme Q oxidoreductase (complex I) in the mitochondrial electron transport chain (El-Mir *et al.* 2000), however the last effect only at high metformin concentrations (~5 mmol/L). Next mechanisms comprise augmentation of GLUT-4 transporter amount and activity (Klip and Leiter 1990) and, more recently reported – the reduction of lactate and glycerol metabolism to glucose through a redox change by inhibiting mitochondrial glycerophosphate dehydrogenase (Madiraju *et al.* 2014). Biguanides have been shown to reduce fatty acid oxidation (Muntoni 1999). Metformin treatment is often associated with a reduction of circulating triglycerides as a consequence of decreased synthesis and increased clearance of VLDL lipoproteins (Zavaroni *et al.* 1984; Jeppesen *et al.* 1994). Reduction of FFA (Free Fatty Acids) supply to the liver, lower triglyceride synthesis, and increased insulin sensitivity may all contribute in reducing fat accumulation in the liver (Hookman and Barkin 2003). The reduction in concentration and oxidation of plasma FFA can contribute to the improvement in insulin action that follows metformin treatment in obese type 2 diabetes. In these patients, the common elevation in plasma FFA levels promotes hepatic glucose production and peripheral insulin resistance (Boden and Shulman 2002). In skeletal muscle, FFA can inhibit pyruvate dehydrogenase (Randle's cycle) but they can also impair glucose transport and/or phosphorylation (Boden and Shulman 2002). Increased plasma FFA concentration exerts a lipotoxic effect on the β-cell, as well (Poitout and Robertson 2002). Thus, by decreasing FFA levels, metformin not only improves insulin sensitivity but may also help to correct impaired insulin secretion by β-cells (Patane *et al.* 2000). It is considered that insulin action may also be involved in the regulation of the secretory insulin function. The increase in AMPK activity is associated with translocation of GLUT-4 to the plasma membrane, stimulation of glucose uptake in muscle and liver, fatty acid oxidation in muscle and liver, and suppression of hepatic glucose output, triglyceride and cholesterol synthesis and lipogenesis (Winder and Hardie 1999). Activation of AMPK by metformin was reported to be required for the decrease in glucose formation and the increase in fatty acid oxidation in

hepatocytes and for the increase in glucose uptake in skeletal muscle (Zhou *et al.* 2001). The mechanism of action of metformin in the liver involves insulin receptor activation *via* increasing insulin receptor tyrosine phosphorylation, followed by IRS-1 activation and increased GLUT-2 translocation from microsomal fraction to the plasma membranes of hepatic cells (Ashton Acton 2013).

METFORMIN IN PCOS

In gynecology, metformin is the most widely used in the treatment of PCOS (Misso *et al.* 2013). Several studies have suggested that metformin has an influence on the steroidogenesis in granulosa cell and oocyte maturation (Tosca *et al.* 2007). It has been shown that metformin impacts the gene expression of proteins involved in steroid production (CYP11A1, 3bHSD, aromatase) (Diamanti-Kandarakis and Papavasiliou 2006).

Within the ovary, metformin reduces androgens synthesis in theca cells, by inducing the growth of AMPK activity and a reduction in proliferation of theca cells, which decreases the systemic androgen in women suffering from PCOS (Tosca *et al.* 2007; Palomba *et al.* 2010; Kocak and Ustün 2006). As the amount of aromatizable androgens decreases, their availability to granulosa cells is diminished, which consequently leads to a reduced estrogen synthesis (Kayampilly and Menon 2012; Kayampilly and Menon 2009). Additionally, by stimulating the activity of AMPK, metformin indirectly increases the expression of granulosa cells visfatin, which is responsible for IGF-1 induced steroid secretion (Reverchon *et al.* 2013; Lewandowski *et al.* 2007). Metformin-induced AMPK activation may also intensify antioxidant defenses at the ovarian tissue level. By reducing insulin levels, metformin may inhibit LH receptor expression. This, together with above-mentioned mechanisms of action, may lead to lower overproduction of sex steroids and reduce premature luteinization. As a consequence, the attenuation of androgen excess and ovulation improvement occur (Dimanti-Kandarakis *et al.* 2010).

METFORMIN IN GESTATIONAL DIABETES

For women diagnosed with gestational diabetes, in 90% of the cases, satisfactory levels of blood glucose are possible to obtain by diet modification. The remaining 10% require insulin therapy to achieve the recommended glycemic levels. Currently, the treatment of gestational diabetes includes: human insulin, insulin analogues: lispro, glulisine, aspart, glargine and detemir. For years, there have been many attempts of using metformin in gestational diabetes' treatment. The first available data from PubMed, which refers to gestational diabetes oral therapy, dates back to 1979. Coetzee and Jackson (1979) were the first ones to confirm the safety and effectiveness of the method. Metformin, as classified by FDA, is a category B drug The majority of recent studies shows the efficiency of metformin in gestational diabetes, and proves that it is not a cause for any harmful side effects to the embryo and/or fetuses (Lautatzis *et al.* 2013). In 2008, Rowan *et al.* published the results of a randomized trial (MiG), which compared maternal glycemic and neonatal results in women treated with insulin and metformin. The study consisted of 751 female patients with gestational diabetes, between 20 and 33 weeks of pregnancy. 373 women had undergone a metformin treatment, and the remaining 378 were treated with insulin. In the cases of metformin patients with insufficient glycemic control, insulin was added to therapy. Assessed were the results of fetal blood sugar level, incidence of respiratory disorder, perinatal injuries, need for phototherapy and premature deliveries. There were no statistically significant differences in the cumulative rate of neonatal complications between these two studied groups. In metformin group, the incidence of severe fetal hypoglycemia (<1.8 mmol/L) was lower than in insulin group (3.3% vs. 8.1% p=0.008). The frequency of premature deliveries in metformin group was higher, however the incidence of iatrogenic premature deliveries was similar in both groups. There were no statistically significant differences in the results of anthropometric measurement of newborns. The studies suggest that the satisfactory maternal blood glucose level has been achieved faster in metformin group. The positive influence of metformin on weight gain in pregnancy and after delivery was also observed. Metformin treatment did not cause any serious side effects for mothers and newborns. In metformin group, 76.6% of women declared that they would undergo the treatment again, compared to only 27.2% in insulin group (statistical significance p<0.001). The study was continued in the form of MiG-TOFU research, and the results were published in 2011 (Rowan *et al.* 2011). Subjects were 2-year old children, whose mothers suffering from gestational diabetes, were treated either with metformin or insulin. Estimated were anthropometric measurements, bioimpedance and the amount of fat. The results obtained did not show any spectacular differences between newborns of these groups. However, in children, whose mothers were treated with metformin, bigger arm circumference and thicker skin folds – subvane and brachial – were observed, when compared to measurements of children born to mothers treated with insulin. It may suggest that the body fat metabolic distribution is more favorable in children from metformin group. Spaulonci *et al.* (2013) reported the outcomes of the next randomized comparative study. That time, results of the metformin group showed a statistically lower maternal weight gain from the moment of diagnosis to the time of delivery (0.53±2.52 kg vs. 2.3±2.77 kg; p=0.002) and from the beginning of the treatment to the time of delivery. There were no significant differences between groups, referring to the incidence of preeclampsia, prematurity and cesarean

deliveries. In metformin group, the frequency of neonatal hypoglycemia was lower and there was no neonatal macrosomia. In insulin group macrosomia was recognized in three newborns. Furthermore, in women treated with insulin, higher fasting and postprandial plasma glucose were observed, when compared to women treated with metforminat. It has been shown that gestational age at the moment of diagnosis, and blood glucose level before the treatment are predictive factors of additional insulin therapy in women treated with metformin. The earlier gestational diabetes is recognized, the higher is the probability of additional insulin therapy. In a follow-up study, published in 2014 by Ijas *et al.* weight, height, motoric, social and lingual development were assessed for 6, 12 and 18 months old infants, born to mothers treated with metformin or insulin during pregnancy. It was shown that infants from metformin groups were significantly heavier in the 12th month of life, whereas in the 18th month of life they were both heavier and taller than those born to mother treated with insulin. There were no significant differences between studies groups regarding motoric, social and lingual development in the 18th month of life (Ijas *et al.* 2015). Similarly, the comparative study performed by Tertti *et al.* published in 2015, which assessed cognitive, lingual and motoric skills of 2 year old children born to mothers treated with insulin or metformin during pregnancy, did not show any statistically significant differences between the examined groups (Tertti *et al.* 2015). Farrar *et al.* (2017) have published network meta-analyses which suggest that metformin is probably the most effective treatment compared with insulin or glibenclamide, when outcomes are taken into account.

Based on the results of the mentioned studies, it can be concluded that metformin is an effective alternative to insulin in glycemic control in pregnant women. Considering the pathological mechanism of gestational diabetes, in which insulin resistance plays a key role, it seems that metformin as a medication, effectively increases insulin sensitivity, thus, it should find a permanent place in the treatment of women with gestational diabetes. Its advantages include: being well accepted by patients, not increasing the risk of hypoglycemia, which makes it safer than insulin, and being cheaper and easier to use.

CONCLUSIONS

The use of metformin does not rule out joining insulin for the treatment gestational diabetes at any stage in the absence of blood glucose stability. Furthermore, metformin may intensify insulin action, which can lead to the decrease in insulin doses. The results of research substantiate the argument that metformin does not have a harmful influence on physical and mental development of children born to mothers who were taking metformin during pregnancy. Moreover, the use of metformin in pregnant women, does not increase the frequency of obstetric complications. However, the implementation of metformin, as a routine procedure in gestational diabetes, requires further research on the issue, the results of which would unequivocally confirm its efficiency and safety for pregnant women and their offspring.

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