REVIEW

# Эффективность и безопасность применения препаратов метформина при беременности для лечения гестационного сахарного диабета: современный взгляд на проблему

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*Исторически лечение гестационного сахарного диабета проводилось лишь двумя методами: немедикаментозным — изменение образа жизни (диетотерапия и физические нагрузки), и инсулинотерапия в случае неэффективности первого. Однако в последние годы во всем мире активно обсуждается возможность применения альтернативных способов терапии, а именно — пероральных сахароснижающих препаратов. Из всех имеющихся в арсенале эндокринологов прероральных сахароснижающих препаратов наибольший интерес представляет метформин. Метформин является препаратом, снижающим инсулинорезистентность, которая является характерной для гестационного периода и считается одним из основных механизмов развития нарушений углеводного обмена во время беременности. Наибольшие опасения при применении метформина во время беременности вызывает тот факт, что он практически в неизмененном виде проходит через плаценту в кровь плода. Это является главной причиной того, что во многих странах мира и в России, в соответствии с консенсусом по ведению гестационного сахарного диабета (2012), применение сахароснижающих препаратов относят к запрещенному во время беременности методу лечения.*

***Ключевые слова:*** *метформин; гестационный сахарный диабет; беременность*

## Efficacy and safety of metformin for the treatment of gestational diabetes: a new approach to the problem

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*Historically, the following two methods were used to treat gestational diabetes mellitus: non-medical life-style interventions (diet and increased physical activity) and insulin treatment when other interventions were not effective. The possibility of alternative types of treatment such as oral anti-diabetic drugs has been the source of debate in recent years. Metformin is an oral anti-diabetic drug that reduces insulin resistance, which is common during gestation and is considered one of the main pathways of glucose metabolism alteration during pregnancy.*

*The main concern is that metformin can cross the placenta and is found unchanged in foetal blood. This is the reason why oral anti-diabetic drugs are contraindicated during pregnancy in many countries, including Russia (according to the 2012 Russian recommendations for gestational diabetes treatment).*

*In recent years, many studies investigating the safety and efficacy of metformin for maternal and foetal health have been published. We will review recent randomized clinical trials and discuss new international clinical recommendations (FIGO, 2015) and new opportunities for gestational diabetes mellitus treatment.*

***Keywords****: metformin; gestational diabetes mellitus; pregnancy*



The choice of drug therapy during pregnancy is always difficult, mainly due to ethical issues. However, in recent decades, there has been an increase in the number of medical conditions which allow pregnancy to occur and prolong. Hyperglycaemia is one of the most prevalent endocrine diseases during pregnancy. According to the International Diabetes Federation (IDF), in 2015 one in every six newborns (16.8%) was born to a woman with hyperglycaemia during pregnancy. Type 1 or 2 diabetes mellitus (DM) precede the onset of pregnancy in only 16% of these cases, whereas gestational diabetes mellitus (GDM) is present in most of the cases. The incidence of GDM correlates with the increase in the worldwide prevalence, including women of the reproductive age, of obesity,


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impaired glucose tolerance and type 2 diabetes mellitus (T2DM). Moreover, while the age of onset of impaired glucose tolerance is decreasing, the age at which women are getting pregnant is increasing. All these aspects lead to the fact that there is an increasing predisposition to gestational hyperglycemia among women who get pregnant [1].

Taking into account the obtained results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [2], the criteria for diagnosis of GDM have been revised and considerably decreased in the last decade in many countries and in Russia [3]. This led to an increase in the number of previously undiagnosed cases of GDM. A number of researchers, as listed in the latest recommendations of National Institute of Clinical Excellence UK (NICE) [4], proposed to deliberately overstate the diagnostic criteria for GDM due to the economic unpreparedness of healthcare authorities to cope with the influx of patients diagnosed according to more stringent criteria.

Such high prevalence of GDM requires careful analysis of not only diagnostic methods but also available and safe treatment methods for this disease. Until now, the only studied method of GDM treatment has been insulin therapy in addition to dietary measures. This was mainly based on the ratio of efficacy and safety of insulin therapy as well as the lack of well-studied alternatives.

However, despite all the positive properties, insulin therapy has several limitations, such as the economic aspect, the necessity of patient education and frequent follow-up visits, low patient compliance due to the need for repeated injections and blood glucose measurements and risk of hypoglycaemia. The possibility of oral administration of antidiabetic drugs would be the perfect solution to these limitations. Because the main underlying pathogenesis of GDM is insulin resistance, insulin-sensitizing agents, particularly metformin, come to the forefront when considering oral antidiabetic therapy. Until recently, pregnancy and lactation were contraindications to metformin administration. Currently, however, many studies on the efficacy and safety of metformin during pregnancy have been conducted. An experience with the drug in the early gestation period was reported in women with polycystic ovary syndrome (PCOS) in case of a late drug withdrawal. The first data on the health status of children aged 1–8 years and exposed to metformin in utero were also reported.

In the near future, can we actually expect a breakthrough in diabetology and revision of the existing guidelines? Or is it still untimely to talk about the safety of oral therapy for GDM during pregnancy? Discussion of these issues is the exact focus of this literature review.

## Historical data on use of metformin

### Metformin discovery and Description of the molecule

The history of metformin (dimethylbiguanide) use for DM treatment can be traced back to the middle ages, when extracts of the plant *Galega officinalis* (goat's rue) were used as a medicine for the treatment of 'polyuria mellitus'. Studies performed in the late 1800s showed that *G. officinalis* contains large amounts of guanidine and galegine—substances that were proven in 1918 by Watanabe to have antihyperglycaemic efficacy in animals. The first biguanides were less toxic guanidine analogues that were synthesized in 1929. In 1956, the French scientist Sterne selected dimethylbiguanide (metformin) as the most effective biguanide and named it as 'Glucophage' (Glucophage—'glucose eater'). A little later, between 1957 and 1958, phenformin and buformin, which have even greater antihyperglycaemic activity, were also described. However, due to the greater toxicity and propensity to cause lactic acidosis, these two drugs are no longer used at present [5].

Metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK), which is a liver enzyme that plays an important role in insulin signal pathways and glucose and fat metabolism [6]. AMPK activation leads to the suppression of gluconeogenesis in the liver, increase in tissue sensitivity to insulin, enhanced peripheral and skeletal muscle glucose uptake by the phosphorylation factor GLUT-4, increase in fatty acid oxidation and reduced glucose absorption from the gastrointestinal tract [6].

A metformin molecule is small and positively-charged and can freely penetrate through the placenta via organic cationic transporters [7]. The high permeability of the placental barrier to metformin is the exact major source of concerns related to foetal drug toxicity.

### Concerns related to metformin use

The first historical data on metformin use in pregnancy were released in 70s–80s in South Africa, where perinatal mortality was lower in pregnant women with GDM and type 2 diabetes who were under oral antidiabetic treatment than in those without any treatment at all, but was higher than that in the general population [8]. Further studies were not conducted until 1994, when a study on animals showed high embryotoxicity of phenformin, the precursor of metformin, as well as a negative effect of metformin on late closure of the neural tube [9].

In 2000, the results of an observational study conducted by E. Hellmuth et al. supported the risks of metformin therapy; they showed a much higher prevalence of pre-eclampsia ($p < 0.001$) and perinatal mortality ($p < 0.02$) with the use of metformin in women with GDM and pre-existing diabetes than in those on insulin therapy [10]. Despite the obvious limitations of that study, including a mixed sample of DM patients and with an incomplete control group, all of these data led to particular concerns about metformin administration during pregnancy.

## Randomized controlled trials and meta-analyses

### Randomized controlled trials on the safety and efficacy of metformin

Since 2002, there have been contradicting data in the literature that showed not only the absence of teratogenicity

Table 1

The results of the comparison between metformin and insulin in GDM according to the results of the largest RCT [24, adapted and expanded]

| Author | Year | Region | Number of patients | Results of the comparison of metformin and insulin groups |
|---|---|---|---|---|
| Rowan J. A., et al. | 2008 | Australia, N. Zealand | 733 | In metformin group less hypoglycemia (p=0.008), but more often premature birth (p=0.04). Metformin as monotherapy was ineffective in 46%, it requires additional insulin |
| Ijas H., et al. | 2011 | Finland | 97 | No difference in outcomes |
| Niromanesh S., et al. | 2012 | Iran | 160 | In metformin group there is less maternal weight gain and lower anthropometric parameters of newborns |
| Hassan J. A., et al. | 2012 | Pakistan | 150 | Birth weight is similar, but in metformin group somatomegaly less often occurred (p<0.05), resuscitation is less often required |
| Tertti K., et al. | 2013 | Finland | 217 | No difference in outcomes. Metformin as monotherapy was ineffective in 20.9%, additional insulin is required |
| Spaulonci C. P., et al. | 2013 | Brazil | 94 | In the Metformin group: lower basal (p=0.042) and postprandial glycemia (p=0.02); weight gain in mother is smaller (p=0.002); neonatal hypoglycemia less often occurred (p=0.032). Metformin as monotherapy is ineffective in 26.8%, additional insulin is required |
| Ruholamin S., et al. | 2014 | Iran | 119 | No difference in outcomes |
| Ainuddin J., et al. | 2015 | Pakistan | 150 | In the Metformin group there is smaller weight gain in the mother (p<0.000), less common preeclampsia, lower body weight at birth (p<0.01), and better neonatal prognosis. Metformin as monotherapy is ineffective in 42.7%, additional insulin is required |
| Beyuo T., et al. | 2015 | Africa | 104 | In metformin group there is a lower level of postprandial glycemia (p=0.004) |

of the drug but also its positive effect on reducing the risk of congenital malformations [11, 12]. Until 2008, there were only two small randomized clinical trials (RCTs) that showed favourable effects of metformin on maternal and neonatal outcomes in cases with GDM [13, 14].

Up to the present time, the prospective randomized trial by A.J. Rowan et al—the metformin versus insulin for the treatment of gestational diabetes (MIG, 2008) (n = 733)—has been the study that unsurpassed the others in the scale and obtained results [15]. MIG was designed primarily to clarify the neonatal risks of metformin administration during pregnancy, which could not fail to alarm clinicians due to previous reports. Therefore, neonatal and not maternal outcomes were the main purpose of the study, although the latter was highly detailed in the results. Data from the study clearly indicated the absence of increased risk for neonatal complications after metformin administration for GDM treatment. Also, a lower percentage of severe neonatal hypoglycaemia was observed with metformin treatment than that with insulin, although the frequencies of overall neonatal hypoglycaemia were the same. The expected result was a greater compliance in the metformin group (76% vs. 27%, p < 0.001). However, a slightly higher frequency of premature births (before 37 weeks) in the metformin group than in the insulin group (p = 0.04) was an unexpected and negative result. Although the association between preterm birth and iatrogenic effect was not proven, no deterioration was obtained regarding neonatal outcomes; this factor remains to be clarified.

Another unfavourable result was the insufficient efficacy of metformin monotherapy even at a high dose of 2000 mg/day in 46%, which led to additional insulin requirement to achieve the target glucose levels. Those who needed additional insulin usually had higher baseline blood glucose, greater body mass index and/or a pre-existing history of GDM. However, compared with the group that received insulin therapy alone, the insulin + metformin group received lower daily doses of insulin (median dose of 42 U/day vs. 50 U/day) and had less weight gain during pregnancy. Overall, this study significantly proved the equivalence of metformin and insulin in terms of safety as well as maternal and neonatal short-term prognosis.

After MIG study, many RCTs comparing metformin with insulin were published, and most of them confirmed the MIG results [16-23]. The only key difference was the lack of the tendency for premature delivery in the group of patients who received metformin, which has been shown in the MIG study. One of the studies by J. Ainuddin et al [22] demonstrated a reduced risk of pre-eclampsia, which contradicted the previously reported results of E. Hellmuth et al.; this remains a contentious issue for many clinicians (Table 1).

**Meta-analyses**

According to the recent results of several meta-analyses of RCTs [25-28] that compared the maternal and neonatal outcomes between metformin and insulin (Table 2), maternal outcomes were comparable regarding achievement of glycaemic control; however, patients who received metformin therapy had smaller weight gain and lower risk of gestational hypertension. The risk of pre-eclampsia was similar between the two groups. Among the neonatal outcomes, the children from metformin group had a slightly lower risk of hypoglycaemia in the first few

Table 2

Comparison of outcomes with metformin administration compared with insulin according to meta-analyses [24, adapted, completed]

| | Maternal outcomes | Neonatal outcomes | | | |
|---|---|---|---|---|---|
| Meta-analysis | Weight gain | Gestational arterial hypertension (GAH) | Neonatal hypoglycemia | Preterm delivery | Weight, somatomegaly |
| Gui J., et al., 5 RCTs | Lower with metformin therapy, p=0.003 | GAG less often with metformin therapy, p=0.02 | Comparable | More often with metformin therapy, p=0.01 | Comparable |
| Su D. F., et al., 6 RCTs | Lower with metformin therapy, p=0.01 | Comparable | Less often with metformin therapy | More often with metformin therapy | Comparable |
| Li G., et al., 2015, 11 RCTs | Lower with metformin therapy, p=0.0001 | GAG less often with metformin therapy, p=0.02 | Less often with metformin therapy, p=0.001 | More often with metformin therapy, p=0.03 | Lower with metformin therapy, p=0.04 |
| Zhao L., et al., 2015, 8 RCTs | Comparable | GAG less often with metformin therapy (relative risk 0.54) | Comparable | Comparable | Comparable |

days after birth, but the risk of preterm birth was slightly higher; apparently, these results may have been due to the inclusion of large study, such as MIG, whose results were conflicting to those of the other studies included in the meta-analyses.

Metformin is not the only oral antidiabetic drug offered as a part of GDM treatment. Therefore, there are a number of studies that compared not only metformin with insulin but also sulfonylureas (glibenclamide/glyburide). Meta-analyses of RCTs that compared insulin therapy with oral antidiabetic agents (metformin, glibenclamide and glyburide) in GDM showed that metformin was the best alternative to insulin therapy in terms of efficacy and safety [29-35]. Compared with sulfonylureas, metformin rarely led to neonatal hypoglycaemia. Therefore, there was a tendency for a lower risk of hypertensive disorders during pregnancy and lower weight gain with metformin.

## Planned trials and first changes in the guidelines

### Study on long-term prognosis in children

While the impact of metformin on immediate neonatal outcomes is well established, and it has showed no adverse effects, the question on long-term prognosis in older children remains open and requires further studies.

To the present time, the largest study has been the Metformin in gestational diabetes: the offspring follow-up (MIG TOFU) [36], which was an extension of the MIG study, but focused on the assessment of long-term prognosis in children exposed to metformin in utero, compared with the insulin therapy group. According to this study, children exposed to metformin in utero had thicker skin fold in the shoulder and scapula region at the age of 2 years than those whose mothers received insulin therapy during pregnancy. The total content of fatty tissue was similar in both groups, which indirectly indicated a favourable distribution of adipose tissue—subcutaneous, but not visceral type. The authors concluded that further follow-up is required to assess whether these changes persist for a lifetime and whether these children would have higher insulin sensitivity. If so, metformin use during pregnancy can have a significant impact on the current pandemic of obesity and T2DM.

Another large prospective study involving 126 children from mothers with PCOS who took metformin since early pregnancy also showed no adverse effects on anthropometric parameters, physical activity and behavioural responses in children at the age of 18 months [37].

However, not all prognoses were equally favourable, and a number of studies showed slight adverse effects of metformin on the offspring. For example, in a study on the anthropometric parameters in the first year of life in children exposed to metformin in early gestational age and from mothers with PCOS, Carlsen et al. showed greater weight gain in these children than in those in the control group (10.2 ± 1.2 kg vs. 9.7±1.1 kg, p = 0.003) [38]. Another small study by the same authors showed higher fasting glucose levels (4.93 vs. 4.6 mmol/l, p = 0.04) at the age of 8 years in children born to the group of women treated with metformin [39]. However, it should be noted that despite a statistical difference in the compared groups of children, no clinically significant abnormalities were identified in either group.

One preclinical study [40] showed that in vitro use of metformin decreased the secretion of testosterone in human and rat testicular cells. During the study, in vivo effects of metformin in pregnant mice showed that the drug reduced the size of the testicles. The number of germ cells remained unchanged, but the number of Sertoli cells was decreased in the foetal and neonatal periods, whereas the number of Leydig cells and testosterone secretion decreased only in the foetal period. Whether a similar pattern would be demonstrated when using physiologic doses of metformin in humans is not yet clear. This would require much more long-term studies on sexual function at puberty in boys treated with metformin in utero. However, the risk of high permeability of the placental barrier to metformin cannot be excluded.

### Planned trials

Currently, there is a global increase in the prevalence of obesity and diabetes. In fact, the term ‘diabesity’ has been coined in literature to emphasize pathogenic relationship

of these conditions. Therefore, it is assumed that the use of metformin will gradually increase. A number of studies investigating the use of metformin during pregnancy not only in GSD but also in several other conditions have been currently planned and initiated.

Currently, a randomized multicentre study on the effect of metformin on body weight in pregnant obese women without diabetes (n = 2178) [Metformin in Obese Non-diabetic Pregnant Women (MOP)] [41] is being conducted. Another large randomized study (n = 500) is being conducted in Canada to examine the efficacy of metformin in addition to insulin in pregnant women with T2DM [Metformin in Women with Type 2 Diabetes in Pregnancy Trial (MiTY)] [42]. As a continuation of this study, the same group of researchers plan to study the decrease in obesity and insulin resistance in children at the age of 2 years whose mothers received metformin in the study MiTY (MiTY Kids Trial) [43].

Among other studies that explored the long-term risks of metformin administration, additional preclinical studies on laboratory animals and their second generation offspring, as well as clinical trials on biometric body composition in children older than 6–9 years and studies on sexual function in adolescents can be considered promising.

**International recommendations**

Until recently, the use of metformin was contraindicated during pregnancy due to concerns regarding possible teratogenicity and suspected side effects. However, after publication of the MIG study, the situation began to change. Currently, different countries have adopted different recommendations on the possibility of metformin administration during pregnancy.

For example, the WHO recommendations, the NICE in the UK (2015), Australian Obstetrics and Gynecological Society (2014), the IDF recommendations (2009) and Canadian guidelines (2013) [24] have allowed limited use of metformin as a second line only in cases when initiation of insulin is associated with certain difficulties or when patients refuse to use insulin.

However, the Russian recommendations (2012) [3], the German Diabetes Association and the German Association for Gynaecology and Obstetrics guidelines (2014) [44] prohibit the use of all oral antidiabetic drugs during pregnancy.

In October 2015 the International Federation of Gynecology and Obstetrics (FIGO) developed a document to address the health burden posed by GDM: Initiative on Gestational Diabetes Mellitus: A Pragmatic Guide for Diagnosis, Management, and Care [1]. In this project, the following recommendations were published for the first time:

1. Insulin, glyburide, and metformin are safe and effective therapies for GDM during the second and third trimesters, and may be initiated as first-line treatment after failing to achieve glucose control with lifestyle modification. Among OADs, metformin may be a better choice than glyburide (strength of recommendation and quality of evidence 2++).
2. Insulin should be considered as the first-line treatment in women with GDM who are at high risk of failing on OAD therapy, including some of the following factors (strength of recommendation and quality of evidence 2++):
   - Diagnosis of diabetes <20 weeks of gestation;
   - Need for pharmacologic therapy >30 weeks;
   - Fasting plasma glucose levels >110 mg/dL (>6.1 mmol/l);
   - 1-hour postprandial glucose >140 mg/dL (>7.8 mmol/l);
   - Pregnancy weight gain >12 kg.

## Conclusion

Currently, in Russia, the use of oral antidiabetic agents during pregnancy is prohibited. However, the results of studies over the last decade have demonstrated the safety and efficacy of metformin administration in pregnancy. Moreover, the 2015 FIGO recommendations have allowed us to take a new look at acceptable methods of GDM treatment including metformin administration as a first-line therapy. Of course, pending the revision of the existing Russian Federation Consensus on GDM management, it is untimely to talk about the possibility of immediate implementation of these recommendations in routine practice. However, it is already clear that in a short time, GDM treatment can vary significantly, both globally and in Russia.

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