

# Effects of Metformin Among Type 2 Diabetes Pregnant Women: A Preliminary Study

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## Abstract

Diabetes mellitus (DM) is a chronic but non-contagious metabolic disease that is characterized by elevated levels of blood sugar. In pregnancy it increases various risk factors, such as adverse maternal, fetal, obstetric, and neonatal consequences. Gestational diabetes (GD) is associated with abnormalities in placental development including impairments in trophoblastic differentiation. Insulin therapy is the best treatment for both mother and fetus. On the other hand, Metformin is an oral anti-hyperglycaemia agent that is commonly used to treat type 2 diabetes (T2D) pregnant and non-pregnant women worldwide. But its role in gestational diabetes management remains controversial. It prevents the production of hepatic glucose, increases fatty acid oxidation, enhances insulin sensitivity, decreases lipid synthesis, and impedes gluconeogenesis. From the scientific researches of scientists obtained that hypoglycaemia is not a concern of Metformin. In this review article the benefits and possible negative impacts of Metformin use during pregnancy are discussed in briefly.

**Keywords:** Type 2 diabetes, Metformin, pregnancy, gestational diabetes

## 1. Introduction

Diabetes in pregnant women is the most common medical complication. About half of the global pregnancies are unplanned due to risky or non-family planning. Diabetes is associated with a risk of preeclampsia four-times higher than in non-diabetic women (Ballas et al., 2012). Among gestational diabetic women, hyperglycaemia can have adverse effects on fetus and progression of pregnancy, such as on congenital anomalies, miscarriage, preterm delivery, preeclampsia, operative deliveries, hypertensive disorders of pregnancy, intrauterine death, and birth trauma (Schaefer-Graf et al., 2018). Their babies are at increased risk of congenital malformations, birth injury, macrosomia, neonatal hypoglycaemia, and perinatal mortality compared to babies of non-diabetic mothers (Kirkpatrick et al., 2020).

Usually, the pregnant women with T2D chose insulin to control glucose. However, due to ease of administration, lower cost, and comparable efficacy, oral hypoglycaemic agents are using to treat T2D (Liao et al., 2020). Most of the T2D women use Metformin as a continuous oral treatment, and they continue it during early pregnancy. Some T2D women are not confirmed about their initial pregnancy and they use Metformin as usual (Nguyen et al., 2018). If GD cannot be controlled by lifestyle changes; insulin or Metformin may be used to achieve euglycaemia. In this situation, most of the T2D pregnant women like to use Metformin during whole period of the pregnancy (ADA, 2019).

The Metformin is associated with reduced adverse pregnancy outcomes and had no effect on birth weight. The long-term implications of Metformin on the health of offspring remain unknown (Panagiotopoulou et al., 2020). Initially, the use of Metformin during pregnancy was limited due to the evidence of safety. The use of Metformin

is increasing before and during pregnancy for its safety and efficacy due to its relatively lower cost and ease of administration (Coetzee & Jackson, 1984).

## 2. Literature Review

Literature review is an introductory section in social science, health science, and natural science, where works of previous researchers are highlighted (Polit & Hungler, 2013). It helps the new researchers to understand the subject, and it serves as an indicator of the subject that has been carried out previously (Creswell, 2007). Linh Nguyen and her coworkers have examined the settings in which Metformin can be passed on from mother to child during pregnancy and address the current controversies relating to the cellular and molecular mechanisms of Metformin. Their efforts highlight the need for more data on the effects of Metformin on general offspring health as well as further scrutiny into fetal development upon exposure to Metformin (Nguyen et al., 2018). William M. Hague has shown that Metformin reduces hyperandrogenaemia, and it allows more effective ovulation to occur, it is now widely used in the management of infertility. Moreover, Metformin is being used in the management of women with polycystic ovary syndrome (Hague, 2007).

Michael Z. Liao and his coauthors have studied the pharmacokinetics of Metformin among pregnant women with GD as compared with non-pregnant women with T2D. They have noticed that the patients receiving Metformin 1000 mg, changes in estimated bioavailability during pregnancy offset the changes in clearance leading to no significant change in higher Metformin apparent oral clearance with the higher dose (Liao et al., 2020). Hannah Lewis and her coworkers have observed that diabetes in pregnancy increases the risk of adverse maternal, obstetric, fetal, and neonatal outcomes (Lewis et al., 2018). Gagan Priya and Sanjay Kalra have explored the current place of Metformin in the management of GD and T2D during pregnancy and lactation (Priya & Kalra, 2018).

Kerstin M. Brand and her coauthors have wanted to investigate maternal pregnancy exposure if Metformin is associated with increased risk of long-term and short-term adverse outcomes in the child. Their study has found no increased long-term risk related to pregnancy exposure to Metformin, compared with insulin. Increased risk of small for gestational age (SGA) is observed for Metformin; increased risk of large for gestational age, preterm birth and hypoglycemia are observed for combination treatment; no increased risk is observed for neonatal mortality, hyperglycaemia, or major congenital anomalies (Brand et al., 2022).

Devajit Mohajan and Haradhan Kumar Mohajan have discussed the anthropometric tools to measure body fat and body weight that are harmful and may create DM (Mohajan & Mohajan, 2023c-g). They have also discussed severe life-threatening chronic eating disorders that may cause physical and psychosocial morbidity among teenage girls (Mohajan & Mohajan, 2023h, i, l). They have also consulted on the hyperglycaemia, hyperosmolar hyperglycaemic state, hypoglycaemia, and extreme obesity in brief (Mohajan & Mohajan, 2023m, o, q). They have also discussed oral hypoglycaemia agents and their activities (Mohajan & Mohajan, 2023v, w, x). They have discussed aspects of diabetes and its related various complications (Mohajan & Mohajan, 2023 j, k, n, p, r, s, t, u). Milena Skibinska and her coworkers have taken attempt to discuss the use of Metformin during pregnancy and the safety of the treatment in the light of current studies and recommendations. They are in doubt that since Metformin crosses the placenta, the major argument for cautious use of this drug is the potential long-term effects of the treatment for the child and its development in later life (Skibinska et al., 2021).

## 3. Research Methodology

The academicians take the research as an essential and influential work to lead in the academic world (Pandey & Pandey, 2015). A researcher tries to reflect his/her philosophical beliefs and interpretations of the world prior to the starting research (Crotty, 1998). Methodology is the guideline of a research work that follows scientific methods efficiently (Kothari, 2008). It relates nature and power to science, truth, and epistemology (Ramazanoglu & Holland, 2002). It displays the research design and analysis research procedures (Hallberg, 2006). Therefore, a research methodology is a strategy for planning, arranging, designing and conducting a fruitful research confidently (Legesse, 2014).

To prepare this paper we have used secondary data sources that are collected from published and unpublished data sources. We have also taken help from the journal articles, conference papers, published books and handbooks, internet, websites, etc. (Mohajan, 2017, 2018, 2020). We start our research through the discussion of pre-gestational diabetes and gestational diabetes. We have taken attempt to discuss diabetes complication and use of Metformin to treat DM during pregnancy. Then we have highlighted about the pre-concern of Metformin use. Finally, we have discussed the side effects of Metformin.

## 4. Objective of the Study

The focal objective of this study is to discuss the benefits and limitations of Metformin. Other secondary objectives of the study are as follows:

- to focus on pre-gestational and gestational diabetes, and their complications,
- to highlight on the Metformin use with safely, and
- to focus on the side effects of Metformin.

## 5. Pre-Gestational Diabetes

Pre-gestational diabetes exists before pregnancy and can be either type 1 or type 2 (Lewis et al., 2018; Mohajan & Mohajan, 2023t). When  $\beta$ -cells in the pancreas are destructed due to invasion by virus, action of chemical toxins, action of autoimmune antibodies, etc. causes insulin deficiency; and consequently, type 1 diabetes (T1D) is visible in the body (Wang et al., 2011; Mohajan & Mohajan, 2023a, b). Some people carry genes that make them more likely to develop T1D damaging cells in the pancreas through the process “autoimmune” (Ambler et al., 2021; Mohajan & Mohajan, 2023a, b).

Type 2 diabetes (T2D) is also called non-insulin dependent diabetes, and is usually detected after the age of 40. It is developed when the body does not produce enough insulin for proper function (Chatterjee et al., 2017). Some other risk factors to convert pre-gestational diabetes are physical inactivity, hypertension, dyslipidemia, family history of diabetes, and smoking (Alomari & Al Hisnah, 2022; Mohajan & Mohajan, 2023u). Pre-gestational diabetes can be performed through the lifestyle modification, psychological support, and application of pharmacotherapy appropriately (Bell et al., 2020).

## 6. Gestational Diabetes

Gestational diabetes (GD) is diagnosed during the second or third trimester of pregnancy that is not clearly pre-gestational due to uncontrolled blood glucose levels (Mohajan & Mohajan, 2023r, s). The main cause of GD is increasing insulin resistance that is caused by a rise in the level of gestational hormones, such as progesterone, leptin, placental lactogen, and cortisol that are insulin antagonists. Other factors of GD are genetic, and environmental, such as obesity, lack of exercise, excessive food intake, series consumption of fast foods, etc. (Skibinska et al., 2021).

GD usually disappears after the baby is born, but has a risk of developing T2D later on (White, 1949). During pregnancy placenta makes more hormones that may be insulin resistance, and lead to high blood sugar, and cause diabetes (WHO, 1999). GD can damage the health of the fetus, and can create various complications, such as growth abnormalities, preeclampsia, placental abruption, miscarriage, intrapartum hypoxia, accelerated growth, hypocalcemia and hypomagnesemia, jaundice, polycythemia, etc. (WHO, 2002; García, 2017). Untreated GD results either large or small for gestational age, and increased the susceptibility of the fetus to intrapartum hypoxia (Setji et al., 2005).

## 7. Diabetes Complication During Pregnancy

Uncontrolled diabetes pregnancy is the increased risk for maternal infections, traumatic deliveries, hypertensive disorders, and preeclampsia as well as neonatal hypoglycemia, respiratory distress syndrome, macrosomia, polyhydramnios, shoulder dystocia, and kernicterus (Reece, 2010). More common problems of diabetes women during pregnancy are miscarriage, preeclampsia, pre-term labor, and operative deliveries. After born babies of these women are at the increased risk of congenital malformations, macrosomia, birth injury, neonatal hypoglycaemia and perinatal mortality compared to babies of non-diabetic mothers (Wang et al., 2013). Proper management of gestational diabetes can reduce the incidence of all these complications. Planned pregnancy with controlled diabetes is an important factor to reduce the risk of complications in pregnancy (Priya & Kalra, 2018).

## 8. Metformin Use in Pregnancy

From the historical view, the use of Metformin in pregnant women came from 1975 reports of Aberdeen International Colloquia on Sulphonylureas, Biguanides and insulin in pregnancy (Lindsay & Loeken, 2017). Metformin is one of the safest and most effective first-line glucose-lowering oral drug therapies for overweight and obese type T2D patients, and those with normal kidney function (Mohajan & Mohajan, 2023v, w). It seems to be attractive especially for the patients who wish to avoid insulin injections. It improves glucose levels, supports weight loss, and reduces cardiovascular morbidity (Maruthur et al., 2016). It has become one of the most successful drugs for the treatment of T2D worldwide. It is absorbed mainly in the small intestine through organic cation transporters (OCTs). It is commonly prescribed off-label to improve anovulation and conception. It is also used to treat polycystic ovary syndrome (PCOS), obesity-associated insulin resistance, and cancer during pregnancy (Johnson, 2014).

For about 50 years, Metformin has been used before and during pregnancy. From the various studies it is well-established that Metformin can cross the placenta and circulate during the development of fetus (Nguyen et al., 2018; Mohajan & Mohajan, 2023w). Metformin treatment reduces maternal weight gain during pregnancy. Although, the maternal food intake and the weight of pups at birth are not affected, suggesting that Metformin do not have anorexic effect (Daniella et al., 2020; Mohajan & Mohajan, 2023x).

## 9. Pre-Concern of Metformin

Metformin has anti-cell growth and pro-apoptotic effects; there are persistent concerns over the use of Metformin in early pregnancy (Sutherland & Stowers, 1979). It is safe in pregnancy, but crosses the placenta and may have comparable plasma concentrations in the mother and child at birth. Metformin and combination treatment of Metformin and insulin during pregnancy is not associated with long-term increased risk of obesity, hypoglycemia, and hyperglycemia. In some studies, it is seen that Metformin use is sometimes associated with higher offspring weight (de Oliveira Baraldi et al., 2011).

## 10. Side Effects of Metformin

After use of Metformin the patients may face acute liver failure, cardiac failure, hypotension/sepsis, and active vitamin B<sub>12</sub> deficiency for long-term use (Tahrani et al., 2007). It is observed that the mothers who use Metformin have an anti-growth, nutritionally-restrictive and energetically-restrictive action of it in fetus. As a result, reconsideration is needed to use it during early pregnancy (Pedersen, 1968). Sometimes, Metformin may cause a metallic taste in the mouth, nausea, vomiting, diarrhea, and abdominal pain among about 5% patients (Salpeter et al., 2010).

## 11. Conclusions

Since the 1970s Metformin has been used worldwide for the treatment of diabetes in pregnancy. At present the use of Metformin during pregnancy becomes popular and more common in globally due to its beneficial effects. Cause of this familiarity of Metformin is; it is relatively inexpensive and easy to administer in pregnancy. It is effective in reducing macrosomia, large-for-gestational-age infants, and reduces maternal weight gain. But we have not acquired complete knowledge how it can affect embryonic and fetal development. Various research analyses support that Metformin may improve insulin sensitivity during pregnancy, and also can be used by breastfeeding women. Long-term follow-up studies are essential to ensure the treatment options are secure or not for the long-term health of those treated during their pregnancy. During pregnancy pregnant women should use Metformin very carefully to avoid probable side effects and possible risks.

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