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## OPINION

# Metformin: A promising option for the management of gestational diabetes mellitus – Exploring the benefits, challenges and clinical needs in the current management of gestational diabetes mellitus

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*Conflict of Interest:* The authors report no conflicts of interest.

Received: 31 August 2021;  
Accepted: 13 February 2022

The incidence of gestational diabetes mellitus (GDM) is increasing. One in three women require insulin to achieve glycaemic targets in GDM. However, it is unclear whether insulin therapy alone is the most effective treatment for all women in achieving glycaemic control and preventing adverse pregnancy outcomes. Although no oral hypoglycaemic agents are approved for pregnancy in Australia, recent research indicates that metformin is effective in preventing adverse perinatal outcomes and may even have possible benefits in the long term. Furthermore, there appears to be a specific role for both metformin and insulin among the GDM population. Metformin provides an option to offer an individualised approach to treat GDM.

## KEYWORDS

gestational diabetes mellitus, insulin, metformin, pregnancy, pregnancy complication

Gestational diabetes mellitus (GDM) is the fastest-growing type of diabetes in Australia and the most common pregnancy complication.<sup>1,2</sup> The number of women diagnosed with GDM has doubled over the past decade.<sup>1</sup> The increased incidence of GDM is related to changes in the diagnostic criteria of GDM and changing demographics of women such as advancing age, being overweight or obese and diverse ethnicity.<sup>2,3</sup> GDM is a heterogeneous condition characterised by increased insulin resistance or reduced insulin secretion or both.<sup>4</sup> Women who have had GDM are also at an increased risk of developing type 2 diabetes and cardiovascular

disease.<sup>1,5</sup> In addition, GDM is associated with many adverse pregnancy outcomes, including gestational hypertension, pre-eclampsia and polyhydramnios in women and macrosomia, shoulder dystocia, neonatal hypoglycaemia, jaundice and respiratory distress in the newborn.<sup>6</sup> Women with GDM are more likely to have longer hospital stays, and their babies are twice as likely to be admitted to special care nurseries (SCNs) compared to those without GDM.<sup>7</sup> Therefore, the aim of GDM treatment is to manage maternal hyperglycaemia and reduce the adverse perinatal outcomes to that of background population without GDM.<sup>8</sup>

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Approximately one-third of women with GDM use insulin to manage hyperglycaemia in pregnancy.<sup>1</sup> There is strong evidence to show that hyperglycaemia in pregnancy can lead to adverse outcomes,<sup>9</sup> and strict blood glucose control through lifestyle modifications in pregnancy can improve outcomes.<sup>6</sup> Insulin is considered the gold standard for treatment and is prescribed when medical nutrition therapy (MNT) is insufficient to achieve glycaemic targets. Currently there are no hypoglycaemic agents approved in pregnancy in Australia. Moreover, there is a dearth of evidence-based exercise prescription in GDM. Women requiring insulin therapy commonly have a higher metabolic risk profile, lower insulin sensitivity and impaired beta cell function compared to women who are diet managed in pregnancy.<sup>10</sup> However, the aim of insulin treatment is to attenuate the risk of adverse outcomes. Insulin treatment warrants additional education, training and frequent reviews for women on top of their regular antenatal visits. Women who require insulin often undergo induction of labour<sup>11</sup> based on local policies and have high rates of birth interventions such as caesarean section (CS)<sup>10</sup> or instrumental delivery. In essence, women requiring insulin in pregnancy have a higher metabolic risk and require more intensive treatment and surveillance.

Despite intensive insulin treatment, some women fail to achieve optimal glycaemic control. The Atlantic DIP study<sup>8</sup> showed that women with GDM who had high pre-pregnancy body mass index (BMI) and/or gestational weight gain (GWG) had higher birthweight babies, macrosomia, higher rate of elective CS, polyhydramnios and higher rate of admission to SCN despite insulin therapy. A trial in Belgium identified that insulin-treated GDM women still had large babies and more CS even after adjusting for BMI, GWG and age compared to diet-managed women.<sup>10</sup> It is purported by the Pedersen hypothesis that maternal hyperglycaemia leads to fetal hyperinsulinaemia and neonatal hypoglycaemia<sup>12</sup>; however, whether exogenous insulin therapy improves these outcomes, specifically, neonatal hypoglycaemia, remains disputable. Research in women treated with insulin in pregnancy still shows higher rates of neonatal hypoglycaemia requiring intravenous glucose treatment and neonatal nursery admission.<sup>6,8</sup> Thus, it can be argued that while insulin therapy with MNT reduces the risk of serious consequences due to macrosomia such as shoulder injury or perinatal death,<sup>6,13</sup> the risks of neonatal hypoglycaemia, SCN admission, respiratory distress and hyperbilirubinaemia remain high.<sup>9,13</sup> In summary, insulin therapy is effective in reducing macrosomia in some women; however, it is currently unclear whether insulin reduces the risk of neonatal hypoglycaemia, or GWG, the latter potentially leading to other medical problems especially in women with high BMI or severe insulin resistance. Even though there is a dearth of evidence on diagnosis or treatment targets for early GDM (fewer than 24 weeks), women are treated similarly with insulin regardless of their weeks of gestation, BMI or level of insulin resistance. Further research and evidence are needed to establish the benefits of insulin therapy in all population subgroups.

On the contrary, metformin, an oral hypoglycaemic agent, is commonly used in pregnancy overseas. Recent research has

highlighted the advantages of metformin over insulin in terms of perinatal outcomes and ease of care. Several studies have reported on the benefits of metformin on perinatal outcomes compared to insulin in terms of prevention of macrosomia, severe neonatal hypoglycaemia,<sup>14</sup> maternal hypoglycaemia, lower postprandial readings,<sup>15,16</sup> GWG,<sup>14-16</sup> pre-eclampsia and gestational hypertension<sup>14</sup>; however, no differences were found in primary outcomes such as respiratory distress, hyperbilirubinaemia and birth trauma.<sup>14,17</sup> Furthermore, metformin also requires less monitoring in pregnancy and has patient preference over insulin,<sup>14</sup> even though a small portion of women may experience gastrointestinal side effects and up to 20–50% women may need some supplemental insulin.<sup>18,19</sup> Although some may view the use of supplemental insulin as a failure of metformin, it will still be beneficial in reducing total insulin requirements in pregnancy, thus potentially preventing additional weight gain and reducing the risk of maternal and neonatal hypoglycaemia. Another concern of clinicians when treating women with metformin is growth restriction or small for gestational age (SGA) infants. However, the risk of SGA babies was noted only in studies of women with type 2 diabetes exposed to metformin and not in women with polycystic ovary syndrome or GDM<sup>15,20</sup> or obese pregnant women. As a precautionary approach, the risk of growth restriction with metformin can be monitored through fetal growth surveillance.

Recent data from preliminary studies show metformin is safe for use in pregnancy and in some cases may have benefits on the offspring's metabolic risks in the future.<sup>14,18</sup> This is particularly important given the risk of future metabolic disease in GDM women and offspring<sup>21</sup> as well as the steady increase in the incidence of type 2 diabetes in the general population. The cautionary approach to the use of metformin in pregnancy and clinician inertia in Australia,<sup>22</sup> despite its common use in pregnancy overseas, is due to cross-placental transfer and lack of long-term safety data. Children born to women with GDM, 18–24 months post intrauterine metformin exposure, showed no changes in BMI<sup>17,18</sup> but a redistribution of fat from visceral to subcutaneous, which could be a protective effect.<sup>18</sup> Paavilainen *et al.*<sup>23</sup> demonstrated that at nine years after in utero exposure, children of insulin-treated ( $n = 90$ ) and metformin-treated ( $n = 82$ ) mothers had no differences in anthropometric measures, but boys exposed to metformin had a higher high-density lipoprotein compared to the insulin group. Rowan *et al.*<sup>14</sup> showed that there were no marked adverse effects at age seven years ( $n = 109$ ) and nine years ( $n = 99$ ) after in utero exposure to metformin with similar metabolic and fat measures, including total abdominal fat, body fat, HbA1c, lipids, glucose and insulin levels in offspring despite having larger BMI and waist circumference measures when compared to the insulin subgroup.<sup>14</sup> Paavilainen *et al.*<sup>23</sup> attributes the differences in anthropometric measures between the aforementioned two studies to higher maternal BMI and heterogeneity at enrolment in the metformin group in the study by Rowan *et al.*<sup>14</sup> We believe it is time for the safety of metformin to be reassessed by the Therapeutic Goods



Administration as a matter of priority with a view to providing other treatments for GDM that can reduce poor obstetric and neonatal outcomes. The current category C rating in pregnancy, which implies that the drug may be suspected of causing harmful effects on the human fetus or neonate without causing malformations, makes its prescription more difficult.

In our view, metformin is an underutilised treatment option for GDM in Australia, and including metformin along with insulin in the treatment of GDM for women unresponsive to MNT provides an option for individualised care. Though insulin is currently first line as the only approved pharmacological intervention in pregnancy in Australia, metformin could play an important role in improving care and treatment outcomes for women with GDM. An individualised approach towards treatment of GDM is recommended considering its heterogeneity. For an individualised treatment approach in GDM, women with higher pre-pregnancy BMI or excessive GWG may benefit from a combination of metformin and supplemental insulin to alleviate insulin resistance and further weight gain, whereas women with normal BMI and GWG may benefit from focusing on diet and insulin therapy to reduce adverse pregnancy outcomes. In our opinion, the choice of metformin and insulin to treat GDM could be based on the assessment of variables such as maternal BMI, fetal growth measurements, GWG in addition to cost effectiveness, tolerance to the medication and patient preference. The clinician inertia for treatment intensification can be addressed through more evidence-based resources and education. Patients should also be encouraged to make informed choices about their treatment options for managing GDM to enhance acceptance, compliance and empowerment, which may in turn positively impact their outlook on health, quality of life and future risk of diabetes.

## ACKNOWLEDGEMENTS

We would like to thank Illawarra Shoalhaven Local Health District and Illawarra Health and Medical Research Institute for their support and grants provided. Open access publishing facilitated by The University of Queensland, as part of the Wiley - The University of Queensland agreement via the Council of Australian University Librarians.

## FUNDING INFORMATION

M.E.F. is supported by an NHMRC Investigator grant.

## AUTHOR CONTRIBUTIONS

B.B. drafted the manuscript; B.B., W.D., A.P., L.G.S. and M.E.F. revised and edited the manuscript and approved the final version.

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