

# Metformin in the gestational diabetes

## Editorial

Gestational Diabetes Mellitus (GDM), defined as any degree of glucose intolerance with onset or initially detected during pregnancy, is increasing worldwide and currently complicates up to 10% of the pregnancies. GDM is associated with poorer pregnancy outcomes and might have long-term implications for both mother and child. Therefore, it must be recognized precociously and appropriately managed.<sup>1</sup>

The pharmaceutical approaches for the management of GDM are still evolving. Traditionally, the insulin is considered the gold standard of pharmacotherapy for GDM, as it has proven effectiveness and safety. Several disadvantages of insulin are recognized, such as multiple daily injections, risk of hypoglycemia, maternal weight gain and higher frequency of medical assessments. Hence, the use of oral antidiabetic agents (ODA) in GDM would be less expensive and more convenient for the patients, possibly enhancing their compliance. There are randomized controlled trials that demonstrated efficacy and safety of some ODA, as glyburide and Metformin, which are increasingly being used in GDM, although most governments and societies still have not widely approved their use in pregnancy.<sup>2</sup>

Metformin is the first line medication for type 2 diabetes mellitus and theoretically occupies the top of the ODA for GDM. Metformin decreases hepatic gluconeogenesis, improves peripheral and hepatic sensitivity to insulin and does not induce hypoglycemia or maternal weight gain. However, as Metformin crosses the placenta and the long-term effects in the offspring are unknown, the use of Metformin in GDM still remains controversial.<sup>3</sup> There are more than 10 studies assessing Metformin safety and efficacy.<sup>4-14</sup> The largest study is known as Metformin in Gestational Diabetes (MiG) study<sup>5</sup> and involved 751 pregnant women with GDM. Some smaller studies have been later performed.<sup>7-14</sup> Globally, the results have been favorable to Metformin. Compared to women taking insulin, those under Metformin have no difference in maternal glycemic control, congenital abnormalities, macrosomy, rates of neonatal hypoglycemia or other maternal or neonatal adverse outcomes. Moreover, it has been reported less maternal hypoglycemia with the use of Metformin in comparison to insulin regimens. However, the exposure to Metformin in the MiG trial was associated with higher frequency of prematurity, raising a concern of an unrecognized effect on the labor process.<sup>5</sup> Later, Balani<sup>7</sup> and Mesdaghinia<sup>13</sup> reported lower rates of prematurity with Metformin in comparison to insulin.

Metformin monotherapy fail in 30-50% of women with GDM, requiring additional insulin. The proportion variance of GDM under Metformin that requires supplementary insulin depends on the features of the population and the glycemic targets to titrate the pharmacological treatment. An adequate and careful selection of the GDM patients may lower the failure rates of Metformin monotherapy. Weight excess, younger patients and mild hyperglycemic profile are features that may indicate better responses to the isolated use of Metformin. Contrarily, women with significant hyperglycemia, such as fasting glucose levels  $\geq 140$ mg/dL and/or 2h-postprandial glucose levels  $\geq 180$ mg/dL, unlikely will achieve glycemic targets with the Metformin monotherapy.

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Classically, the most common side effects of Metformin are gastrointestinal, like nausea, vomiting, diarrhea, which frequently are non-limiting and transitory. Serious adverse effects in pregnant women are rare. The MiG trial<sup>5</sup> and Balani<sup>7</sup> reported interruption rates of Metformin due to intolerable toxicity in 1.9 and 5%, respectively.

To sum up, Metformin, alone or with additional insulin, appears to constitute a safe and effective treatment option for women with GDM who do not have satisfactory glycemic control despite lifestyle interventions. Nevertheless, further randomized controlled trials are required to further establish the role and safety of Metformin in this setting and the subset of these patients who likely benefit more with Metformin. Further follow-up data is also needed to establish the long-term safety in the Metformin groups. Taking in consideration the increasing incidence of GDM, this topic is currently highly relevant. Thus, we hope to have contributors and original research data to expand the knowledge on this matter.

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## Conflict of interest

Author declares that there is no conflict of interest.

## References

1. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358:1991–2002.
2. Blumer I, Hadar E, Hadden DR, et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98(11):4227–4249.
3. Wensel TM. Role of metformin in the treatment of gestational diabetes. *Ann Pharmacother*. 2009;43(5):939–943.
4. Moore LE, Briery CM, Clokey D, et al. Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. *J Reprod Med*. 2007;52(11):1011–1015.
5. Rowan JA, Hague WM, Gao W, et al. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008;358:2003–2015.
6. Terti K, Ekblad U, Vahlberg T, et al. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective, case-control study. *Rev Diabet Stud*. 2008;5(2):95–101.

7. Balani J, Hyer SL, Rodin DA, et al. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case-control study. *Diabet Med.* 2009;26(8):798–802.
8. Rai L, Meenakshi D, Kamath A. Metformin – a convenient alternative to insulin for Indian women with diabetes in pregnancy. *Indian J Med Sci.* 2009;63(11):491–497.
9. Ijas H, Vaarasmaki M, Morin-Papunen L, et al. Metformin should be considered in the treatment of gestational diabetes: a prospective randomized study. *BJOG.* 2011;118(7):880–885.
10. Goh JE, Sadler L, Rowan J. Metformin for gestational diabetes in routine clinical practice. *Diabet Med.* 2011;28(9):1082–1087.
11. Niromanesh S, Alavi A, Sharbaf FR, et al. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. *Diabetes Res Clin Pract.* 2012;98(3):422–429.
12. Tertti K, Ekblad U, Koskinen P, et al. Metformin vs. Insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. *Diabetes Obes Metab.* 2013;15(3):246–251.
13. Mesdaghinia E, Samimi M, Homaei Z, et al. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: a randomized blinded trial. *Int J Prev Med.* 2013;4(3):327–333.
14. Spaulonci CP, Bernardes LS, Trindade TC, et al. Randomized trial of metformin vs insulin in the management of gestational diabetes. *Am J Obstet Gynecol.* 2013;209(1):34.e1–7.