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## Metformin monotherapy is an effective alternative for management of gestational diabetes mellitus in patients refusing insulin monotherapy

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# Metformin monotherapy is an effective alternative for management of gestational diabetes mellitus in patients refusing insulin monotherapy

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**ABSTRACT** A clinical decision report using:

Ghomian N, Vahed SHM, Firouz S, Yaghoubi MA, Mohebbi M, Sahebkar A. The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: A randomized clinical trial. *J Cell Physiol.* 2019;234(4):4695-4701. <https://doi.org/10.1002/jcp.27238>

for a patient with gestational diabetes mellitus (GDM) who does not wish to undergo insulin monotherapy.

**Keywords:** *gestational diabetes mellitus, diabetes, insulin, metformin, fetal macrosomia*

## Clinical-Social Context

Linda Johnson (pseudonym) is a 27-year-old, G2P1001 African American woman at 25 and 4/7 weeks gestation, that presented to the high-risk obstetric clinic following a recent diagnosis of gestational diabetes mellitus (GDM) by a positive 75g glucose tolerance test (GTT) at 24 weeks gestation. Her past medical history included a prior cesarean delivery due to poorly controlled GDM as well as severe asthma. Upon talking to Ms. Johnson, she expressed that she was “very disappointed and worried” that she had been diagnosed with GDM for her second pregnancy. She stated that this happened during her first pregnancy and she took insulin to control her sugar but that she had a difficult time injecting the insulin due to pain and a fear of needles. She said that “taking insulin was the worst thing in the world” and she eventually stopped, leading to fetal macrosomia, prompting a cesarean delivery which was particularly “traumatizing.” Following Mrs. Johnson’s positive GTT test, her low-risk obstetrician recommended a diet and exercise intervention for one week, but she had been unable to make necessary changes. She said that she improved her diet but cannot exercise due to her severe asthma that has worsened during pregnancy. At her clinic visit, she had a fasting glucose of 103.5 mg/dl, indicating her glucose was still not well controlled. She asked, “I know metformin is for regular diabetes, but can I use it for pregnancy diabetes too?” She emphasized the fact that she would refuse to use insulin again but also did not want to undergo another cesarean delivery.

Of note, Mrs. Johnson said that she has ample access to healthy food options at the local store and has a driver’s license and car for transportation. She does not currently work but her husband has a secure job at Ford Motor Company and can support the family’s financial needs. She lives in a single-story townhouse with her husband and 3-year-old son and feels very safe at home and in the community.

TYLER RUSSETH is a fourth-year medical student at the Wayne State University School of Medicine.



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## Clinical Question

Is metformin monotherapy as efficacious as insulin monotherapy (gold standard) for management of gestational diabetes mellitus (GDM) for prevention of fetal macrosomia and risk of cesarean delivery?

## Research Article

Ghomian N, Vahed SHM, Firouz S, Yaghoubi MA, Mohebby M, Sahebkar A. The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: A randomized clinical trial. *J Cell Physiol.* 2019;234(4):4695-4701. <https://doi.org/10.1002/jcp.27238><sup>1</sup>

## Description of Related Literature

Collection of related information began with searching “gestational diabetes management” on The American College of Obstetrics and Gynecology (ACOG) to view current guidelines. At present, ACOG recommends pharmacologic treatment when target glucose levels cannot be achieved through nutrition and exercise. First line pharmacologic treatment is insulin with second line being oral antidiabetic medications (metformin and glyburide).<sup>2</sup> One randomized control trial (RCT) was mentioned that directly compared insulin versus metformin with primary outcome measures being neonatal hypoglycemia and maternal glucose levels.<sup>3</sup> The study demonstrated equivalent efficacy of metformin to insulin but did not measure fetal macrosomia and risk for cesarian delivery which is Mrs. Johnson’s main concern.

Additional literature review was performed on PubMed with an initial search using the key words “gestational diabetes [title] and metformin and insulin” which yielded 239 results and after filtering for RCTs, 35 articles remained. Seventeen of these articles were removed due to being unrelated to the question in focus. Two studies were removed due to comparing metformin to placebo rather than insulin.<sup>4-5</sup> A number of studies focused on the direct comparison of metformin versus insulin therapy for GDM. However, many were removed due to measuring unrelated outcomes such as markers of metabolic status (triglycerides, lipids, and A1c levels),<sup>6-8</sup> inflammatory markers,<sup>9</sup> and B12 levels<sup>10</sup>. Several RCTs had primary outcomes focusing on fetal macrosomia and cesarian delivery but were not chosen for clinical use because upwards of 46.3% of study participants in the metformin group received supplemental insulin to achieve euglycemia.<sup>11-17</sup> Mrs. Johnson has attempted and failed insulin therapy in the past and refuses to consider insulin use for this pregnancy.

Moore et al.<sup>18</sup> published their preliminary results for a prospective randomized control trial investigating metformin and insulin as therapeutic options for GDM. 63 participants were randomly placed in either intervention group following a positive 75g GTT test and that failed a 2-week trial of diet and lifestyle interventions. No participants in the metformin group required supplemental insulin. Preliminary results demonstrated no statistical difference in rate of cesarian delivery or neonate birth weight, suggesting metformin is a promising option. This study was ultimately not chosen due to the limited sample size, availability of only preliminary results, and two-week trial of diet and lifestyle rather than a one-week trial like Mrs. Johnson.

The randomized control trial chosen for appraisal was a study conducted by Ghomian et al.<sup>1</sup> The study randomly assigned 286 pregnant women that were diagnosed with GDM following a 75g GTT and failed a 1-week trial of diet and exercise, to either insulin or metformin monotherapy. Of note, patients with a prior history of overt diabetes mellitus were not included in the study. If a patient in the metformin group required supplemental insulin, they were removed from the study and replaced with another study participant. The study concluded that there was no statistical difference between the two groups for birth weight, birth trauma, and rate of cesarean delivery. The article’s findings are similar to the findings of the previously reviewed papers and best captures the efficacy of metformin alone in management of GDM. This study was selected because it is the only available paper that examines metformin therapy without the use of supplemental insulin, best correlating to Mrs. Johnson’s desire for therapeutic options that do not include insulin.

According to the strength of recommendation taxonomy (SORT), this study achieves a category B grade Strength of Recommendation due to the lack of at least two other good quality RCTs with consistent findings.<sup>19</sup> Currently, Moore et al.<sup>18</sup> is the only other paper that examines metformin monotherapy without use of supplemental insulin.

## Critical Appraisal

The study by Ghomian et al.<sup>1</sup> is a multicenter, randomized clinical trial that recruited patients from three academic hospitals affiliated with Mashad University of Medical Sciences in Iran. A total of 286 participants aged 18 to 40 (mean = 28.36 years) with a gestational age over 24 weeks and recently diagnosed with GDM via a positive 75g GTT were recruited (mean = 24.95 weeks gestation at diagnosis). Additional inclusion criteria included singleton pregnancy, failure to achieve glycemic control with diet and exercise, absence of diabetes mellitus and other medical diseases. Exclusion criteria included refusal to follow up and not responding to the maximal dose of 1500mg metformin to better evaluate the effects of metformin by itself. Once selected, patients were randomly assigned to receive insulin (gold standard) or metformin. Both study groups were similar in age, body mass index, previous history of GDM, and gestational age at treatment onset. Glycemic control goals were fasting plasma glucose <95 mg/dl and 2hr postprandial glucose <120mg/dl. All patients followed up every 2 weeks to receive a fasting and 2hr postprandial plasma glucose (FPG and 2-hr PG) measurement and subsequent dosage adjustment if necessary, to meet goal glucose values. Patients were followed until delivery. The study was not blinded due to the nature of administration of the two therapies, oral pill versus injection; however, the outcome assessor and data analyst were blinded to treatment groups. According to SORT criteria, this would be considered level 1 evidence.<sup>19</sup>

The primary outcomes assessed in the study were FPG, 2-hr PG, preterm birth, Apgar score, birth weight, birth trauma, admission to NICU, and mode of delivery (vaginal or cesarean). Inferential analysis (student's t test and the  $\chi^2$  test) found no statistical difference between the two groups (insulin vs. metformin) in any of the measured primary outcomes. Average neonate birth weight was 3450  $\pm$  548g and 3544  $\pm$  57g for the metformin and insulin group, respectively ( $p = 0.15$ ). 25 (42.9%) and 24 (38.5%) of the patients from the metformin and insulin groups, respectively, underwent cesarean delivery ( $X^2 = 0.887$ ;  $p=0.642$ ).

Mrs. Johnson is well represented in the sampled participants because she has a similar age, gestational age at GDM diagnosis, and baseline glucose values and meets all inclusion criteria for this study. Additionally, 34% of the metformin group had a prior history of GDM. The primary outcomes evaluated address her concerns of neonate weight and necessity of cesarian delivery for metformin therapy.

Participants were recruited upon diagnosis of GDM. There is small attrition bias as only 8.7% ( $n=20$  metformin and  $n=10$  insulin) of participants were lost at some point during their 2-week follow-ups. There is no indication bias as both treatment groups had a similar BMI, family history of diabetes, history of prior GDM, and baseline glucose levels at treatment onset. Lastly, there was no apparent funding bias. The study was funded by a grant from the university and the authors did not declare any conflicts of interest. Additional strengths of the study include large sample size and consistent treatment protocol for both arms of treatment.

The appraised study is prone to selection bias as participants that failed metformin monotherapy were excluded from the study and replaced with new participants. There may be an underlying reason why this group is unable to maintain target glycemic values on metformin alone, concealing a confounding variable. This is the single biggest methodological flaw of the study. Yet, if this is kept in mind when attempting to counsel Mrs. Johnson, we are able to use the evidence presented to make clinical decisions. We wanted a study evaluating metformin without supplemental insulin and this is the only piece of literature that examines this. Additionally, the study may be prone to performance bias as the study was not double blinded. The performance bias could lead to differences in study participant compliance to therapy or physician interactions during routine checkups. However, the study focuses on objective measures for therapy adjustments (FPG and 2-hr PG) and for mode of delivery (e.g. fetal weight and fetal heart tracings) which can mitigate this source of bias. The outcome assessor, the individual at delivery, was blinded. Another weakness in the paper is the study location. The study was performed in Iran and all participants are presumptively from surrounding areas and are not African American. The ethnicity and diet and lifestyle of the study participants differ from Mrs. Johnson living in a metropolitan area. The difference in culture or surrounding food options might contribute to varying difficulty in managing GDM on metformin alone.

## Clinical Application

Mrs. Johnson wanted to know if metformin rather than standard insulin therapy would be a good option for managing her GDM, especially in prevention of fetal macrosomia and cesarean delivery. Her preference stems from her bad experience during her first pregnancy and refusal to continue insulin. Based on the findings of the appraised article, Mrs. Johnson was informed that metformin is a good alternative to insulin therapy and that either therapy, when followed correctly, can manage her GDM and prevent fetal complications and risk for



cesarian delivery. However, she was informed that a small percentage of patients still cannot adequately control their GDM through metformin alone and that insulin therapy might need to be reconsidered in the future. It was emphasized that she needs to regularly follow up with the clinic every 2 weeks to check her glucose levels and adjust metformin dosages as needed. Mrs. Johnson was happy that we were willing to try metformin therapy and understood that she cannot miss any future doctor appointments and that the therapy may not work for her for unknown reasons.

## New Knowledge Related to Clinical Decision Science

Mrs. Johnson's reluctance of insulin therapy for management of her GDM led to the clinical team exploring other therapeutic options that could achieve euglycemia and prevent maternal and fetal complications. While not first line therapy, metformin is a great alternative for Mrs. Johnson. This clinical scenario illustrates the interplay between the patient and physician when making clinical decisions. The healthcare team needs to listen and fully understand the patient's healthcare wishes, especially when choosing treatment plans. If the patient is ignored, they may not be willing to adhere with any treatment, possibly leading to further complications down the road. In fact, Mrs. Johnson told us that is exactly what happened with her previous pregnancy.

Mrs. Johnson's preferences originate from a poor experience with insulin therapy due to the nature of frequent injections with needles. In her case, why not try a second line therapy if it demonstrates equivalent efficacy and avoids the use of needles? She is willing to be compliant and has the necessary transportation resources for frequent checkups. Worst case she fails metformin therapy, and her physicians must sit down and reassess her ability to adhere to insulin therapy. But at least another therapy was attempted. Other efficacious therapeutic options should always be explored based on the patient's distinct social context or personal experience.

The question that Clinical Decision Science needs to explore is situations where the recommendations of the physician and the willingness of the patient to accept those recommendations are at odds. How far are physicians willing to support "poor decisions" of patients by participating in sub-optimal treatment plans. This issue frequently occurs when doctors must face whether to provide treatment to patients who leave the hospital against medical advice. Do physicians become "co-dependent" to unhealthy behavior or are they honoring the agency of the patient to choose treatment for themselves. These types of decisions also occur frequently in end-of-life decisions. Understanding the various contributing factors in how such decision are made is the task for Clinical Decision Science.

In this Decision Report, the doctors took the time and effort to find evidence to support the patient's decision, convincing themselves it was an appropriate management plan—one that worked for both the patient and the treatment team.

## Conflict Of Interest Statement

The author declares no conflicts of interest.

## References

1. Ghomian N, Vahed SHM, Firouz S, Yaghoubi MA, Mohebbi M, Sahebkar A. The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: A randomized clinical trial. *J Cell Physiol.* 2019;234(4):4695-4701. <https://doi.org/10.1002/jcp.27238>
2. Caughy AB, Turrentine M, American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. *Obstet Gynecol.* 2018;131(2):e49-e64. <https://doi.org/10.1097/AOG.0000000000002501>
3. Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RPV. Randomized trial of metformin vs insulin in the management of gestational diabetes. *Am J Obstet Gynecol.* 2013;209(1):34.e1-7. <https://doi.org/10.1016/j.ajog.2013.03.022>
4. Refuerzo JS, Viteri OA, Hutchinson M, et al. The effects of metformin on weight loss in women with gestational diabetes: a pilot randomized, placebo-controlled trial. *Am J Obstet Gynecol.* 2015;212(3):389.e1-9. <https://doi.org/10.1016/j.ajog.2014.12.019>



5. Valdés E, Sepúlveda-Martínez A, Candia P, et al. Metformin as a prophylactic treatment of gestational diabetes in pregnant patients with pregestational insulin resistance: A randomized study. *J Obstet Gynaecol Res.* 2018;44(1):81-86. <https://doi.org/10.1111/jog.13477>
6. Barrett HL, Gatford KL, Houda CM, et al. Maternal and neonatal circulating markers of metabolic and cardiovascular risk in the metformin in gestational diabetes (MiG) trial: responses to maternal metformin versus insulin treatment. *Diabetes Care.* 2013;36(3):529-536. <https://doi.org/10.2337/dc12-1097>
7. Pellonperä O, Rönnemaa T, Ekblad U, Vahlberg T, Tertti K. The effects of metformin treatment of gestational diabetes on maternal weight and glucose tolerance postpartum--a prospective follow-up study. *Acta Obstet Gynecol Scand.* 2016;95(1):79-87. <https://doi.org/10.1111/aogs.12788>
8. Huhtala MS, Tertti K, Rönnemaa T. Serum lipids and their association with birth weight in metformin and insulin treated patients with gestational diabetes. *Diabetes Res Clin Pract.* 2020;170:108456. <https://doi.org/10.1016/j.diabres.2020.108456>
9. Huhtala MS, Tertti K, Juhila J, Sorsa T, Rönnemaa T. Metformin and insulin treatment of gestational diabetes: effects on inflammatory markers and IGF-binding protein-1 - secondary analysis of a randomized controlled trial. *BMC Pregnancy Childbirth.* 2020;20(1):401. <https://doi.org/10.1186/s12884-020-03077-6>
10. Gatford KL, Houda CM, Lu ZX, et al. Vitamin B12 and homocysteine status during pregnancy in the metformin in gestational diabetes trial: responses to maternal metformin compared with insulin treatment. *Diabetes Obes Metab.* 2013;15(7):660-667. <https://doi.org/10.1111/dom.12080>
11. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med.* 2008;358(19):2003-2015. <https://doi.org/10.1056/NEJMoa0707193>
12. Tertti K, Ekblad U, Koskinen P, Vahlberg T, Rönnemaa T. Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. *Diabetes Obes Metab.* 2013;15(3):246-251. <https://doi.org/10.1111/dom.12017>
13. Ijäs H, Väärasmäki M, Morin-Papunen L, et al. Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. *BJOG.* 2011;118(7):880-885. <https://doi.org/10.1111/j.1471-0528.2010.02763.x>
14. Ainuddin J, Karim N, Hasan AA, Naqvi SA. Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country: a randomized control trial. *Diabetes Res Clin Pract.* 2015;107(2):290-299. <https://doi.org/10.1016/j.diabres.2014.10.001>
15. Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus Insulin in the Management of Pre-Gestational Diabetes Mellitus in Pregnancy and Gestational Diabetes Mellitus at the Korle Bu Teaching Hospital: A Randomized Clinical Trial. *PLoS One.* 2015;10(5). <https://doi.org/10.1371/journal.pone.0125712>
16. Ashoush S, El-Said M, Fathi H, Abdelnaby M. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus. *J Obstet Gynaecol Res.* 2016;42(6):640-647. <https://doi.org/10.1111/jog.12950>
17. Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. *Diabetes Res Clin Pract.* 2012;98(3):422-429. <https://doi.org/10.1016/j.diabres.2012.09.031>
18. 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.
19. Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): A Patient-Centered Approach to Grading Evidence in the Medical Literature. *J Am Board Fam Pract.* 2004;17(1):59-67. <https://doi.org/10.3122/jabfm.17.1.59>

