LETTER TO THE EDITOR

About the article "Metformin, a therapeutic reality in the treatment of gestational diabetes mellitus"

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Mr. Editor:

Gestational diabetes mellitus (GDM) is one of the most common complications in pregnancy and affects between 9% and 26% of the obstetric population(1) so it is considered very timely the article by Hernandez Paret and other researchers where the use of metformin is advocated as a valid alternative in the medical management of this entity, when healthy lifestyles do not achieve adequate metabolic control, with the aim of reducing maternal-fetal complications.

In this article, the author proposes to address some considerations in this regard, from the perspective of molecular biology and epigenetics.

Folic acid (FA) is a biochemically inactive compound, precursor of tetrahydrofolic and methyltetrahydrofolic acid, essential for the de novo synthesis of nucleotide precursors, and also has the purpose of achieving adequate levels of deoxyribonucleic acid (DNA) methylation, which is essential for the dynamics of chromatin conformational changes and consequent gene expression.

Decreased PA levels result in decreased levels of S adenosyl methionine (SAM) leading to insufficient DNA methylation, which is an important epigenetic mechanism regulating genomic programming during embryogenesis.

It has been clearly demonstrated that FA plays a crucial role in the epigenetic regulation of the embryofetal developmental program, and maternal deficiency of this micronutrient implies, in addition to hematological consequences, the appearance of different congenital defects (CD) in the offspring.

The first epigenetic mechanism described was precisely DNA methylation, which is catalyzed by DNA methyltransferase enzymes that transfer methyl groups (CH3) from the SAM to carbon 5` of cytosines present in sites called CPG islands. Along with DNA methylation, acetylation and histone methylation, as well as chromatin modifications are the best characterized epigenetic mechanisms.

The cascade of reactions occurring in the monocarbon metabolic pathway ensures that methyl groups, essential for homocysteine methylation, and the

formation of methionine and SAMe, the major intracellular donor of methyl groups, are donated.[2,3]

Metformin is known to have an effect on the monocarbon metabolic pathway similar to that of PA antagonist drugs, by inhibiting the activity of the enzyme dihydrofolate reductase and thus the synthesis of the metabolically active form of folate: tetrahydrofolate.[4]

There are separate, but not redundant, cytosolic and mitochondrial metabolic pathways that give rise to metabolites for monocarbon metabolism that can be inhibited by metformin, which can lead to methionine deprivation, hyperhomocysteinemia, and decreased de novo synthesis of purines and pyrimidines necessary for DNA replication.

In addition, inhibition of monocarbon metabolism decreases SAM levels and increases S adenosyl homocysteine concentrations, which could have epigenetic effects on gene expression, due to decreased levels of DNA methylation and histone methylation.[4,5]

Hyperhomocysteinemia induces apoptosis leading to trophoblastic dysfunction. Recent studies have found an association between maternal hyperhomocysteinemia and numerous obstetric complications such as recurrent pregnancy losses, preeclampsia, preterm delivery, abruptio placentae, among others.[6]

Shi and colleagues[7] found an association between maternal hyperhomocysteinemia and the presence of congenital heart disease in the offspring.

Although the period of early organogenesis occurs during the third to eighth week of gestation, the administration of metformin for the treatment of hyperglycemia associated with GDM occurs after the end of this critical window of embryonic development, which could explain the fact referred to by the researchers in their article that experimental studies have not shown the presence of DC related to doses of metformin that stimulate maternal AMP-activated protein kinase,[8] a fact supported by the results of large cohort studies.[9]

However, compared to embryonic cells, fetal and placental cells are more differentiated and more dependent on oxidative metabolism and mitochondrial activity. Metformin inhibits complex 1 of the respiratory chain and, as stated in the aforementioned article, causes an increase in the AMP-ATP ratio that stimulates the activity of AMP-activated protein kinase (AMPK).[8] AMPK is involved in the regulation of different processes, including gene expression and protein synthesis, among them some that are key for proper neurological and cognitive functioning.[4] The epigenetic effects of metformin, as a drug capable of crossing the blood-placental barrier, could have a long-term effect if the chromatin modifications are passed on to daughter cells during mitosis, as epimutations. Therefore, the author agrees with the criterion of the authors of the article that: "research on the subject is suggested because few studies on long-term safety are available..."[8]

Metformin is considered a drug of low teratogenic risk, being included by the US Food and Drug Administration (FDA) in risk category B, which refers to the fact that "animal reproduction studies have not demonstrated a risk to the fetus and there are no adequate well-controlled studies in pregnant women."[4]

For the use in pregnant women of drugs with low teratogenic risk (included in groups A and B of the FDA) it is not necessary to evaluate the risk-benefit, so we agree with what the authors referred to in their article regarding that "a pharmacological repositioning for metformin should be considered within the therapeutics of GDM and other associated obstetric conditions..."[8]

The recommended dose of FA in pregnant women and women of reproductive age, for the prevention of CD is 400 micrograms daily, in Cuba the usual dose indicated is one milligram (1 mg) per day. However, when there is a history of previous folate-sensitive CD or consumption of PA antagonist drugs, such as certain antineoplastic and anticonvulsant drugs, it is recommended to increase the dose up to 4 mg daily.[2]

Therefore, taking into account the considerations made in this article, the author is of the opinion that, together with the insertion of metformin in the pharmacological treatment of GDM, as the authors state "not only with the aim of achieving optimal glycemic goals, but also to reduce maternal-fetal morbidity and mortality", it would be advisable to associate it with the use of PA, both from the preconception stage in women with type 2 diabetes mellitus or polycystic ovary syndrome, as well as in those with GDM.

BIBLIOGRAPHIC REFERENCES

1. Zhang TN, Huang XM, Zhao XY, Wang W, Wen R, Gao SY. Risks of specific congenital anomalies in offspring of women with diabetes: A systematic review and meta-analysis of population-based studies including over 80 million births. PLoS Med [Internet]. 2022 [cited 06/03/2022];19(2):e1003900. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8806075/. https://doi.org/10.1371/journal.pmed.1003900
2. Taboada Lugo N. Papel del ácido fólico, zinc y cobre en la prevención primaria de los defectos congénitos. Rev Cubana Med Gen Integr [Internet]. 2016 [cited 06/03/2022];32(4):[aprox. 9 p.]. Available at: https://revmgi.sld.cu/index.php/mgi/article/view/167/110
3. Taboada Lugo N, Herrera Martinez M. Mecanismos epigenéticos y vía de señalización Notch en el origen de diferentes defectos congénitos. Medicentro Electrónica [Internet]. 2018 [cited 06/03/2022];22(3):197-207 Available at: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1029-30432018000300002
4. Lindsay RS, Loeken MR. Metformin use in pregnancy: promises and uncertainties. Diabetologia [Internet]. 2017 [cited 06/03/2022];60:1612-1619. Available at: https://link.springer.com/content/pdf/10.1007/s00125-017-4351-y.pdf. https://doi.org/10.1007/s00125-017-4351-y
5. Taboada Lugo N. Factores epigenéticos involucrados en el origen de defectos congénitos relacionados con la deficiencia materna de ácido fólico y otros micronutrientes. Acta Méd Centro [Internet]. 2019 [cited 06/03/2022];13(3):439-454. Available at: https://revactamedicacentro.sld.cu/index.php/amc/article/view/937/1295
6. Dai C, Fei Y, Li J, Shi Y, Yang X. A novel review of homocysteine and pregnancy complications. BioMed Res Int [Internet]. 2021 [cited 06/03/2022]:2021:6652231. Available at: https://www.hindawi.com/journals/bmri/2021/6652231/. https://doi.org/10.1155/2021/6652231
7. Shi H, Yang S, Lin N, Huang P, Yu R, Chen M, et al. Study on maternal SNPs of MTHFR gene and HCY level related to congenital heart diseases. Pediatric Cardiol

[Internet]. 2021 [cited 06/03/2022];42(1):42-46. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7864808/. https://doi.org/10.1007/s00246-020-02449-1

8. Hernández Parets M, Brito Ferrer Y, Zayas González M. Metformina, una realidad terapéutica en el tratamiento de la diabetes mellitus gestacional. Acta Méd Centro [Internet]. 2022 [cited 06/03/2022];16(2):374-377. Available at: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S2709-79272022000200374
9. Brand KMG, Saarelainen L, Sonajalg J, Boutmy E, Foch C, Vääräsmäki M, et al. Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study. BMJ Open Diabetes Res Care [Internet]. 2022 [cited 06/03/2022];10(1):e002363. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8734020/. https://doi.org/10.1136/bmjdrc-2021-002363

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.