

Metformin for Gestational Diabetes: Is it effective?



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ABSTRACT

Gestational Diabetes Mellitus is a pathology related to increased insulin resistance and glucose intolerance, with changes in blood glucose detected

for the first time during the gestational period. Faced with these situations, several therapies are considered, insulin being considered the gold standard, but with recognition of new options involving oral drugs, such as metformin. The objective was to discuss the effectiveness of the use of metformin against gestational diabetes. This is an integrative literature review, through a search in the MEDLINE, LILACS databases, via the VHL and SciELO, using the Health Sciences Descriptors: Pregnancy, Diabetes and Metformin, in association with the Boolean operator “AND”. A total of 16 studies were reached to compose the review. The use of metformin generated positive results, such as lower total cholesterol, uric acid and microalbuminuria, lower risks of premature birth and the development of congenital anomalies, helped with postprandial blood glucose, lower maternal weight gain and avoided maternal hypoglycemia. and neonatal. The general effectiveness is proven, however it is still a topic that needs further studies, as it also presents negative results and can lead to maternal and fetal complications, since metformin is a medication that crosses the placenta, which can lead to fetal harm.

Keywords: Gestation, Diabetes, Metformin.

1 INTRODUCTION

Pregnancy is a process that involves many adaptations and complexities that can generate the triggering of diseases. One of the most commonly presented complexities among women is the increase in blood glucose during the gestational period, which can generate the emergence of several related pathologies, such as gestational diabetes (Leal, Silva & Oliveira, 2022).

Gestational Diabetes Mellitus (GDM) is a pathology related to increased insulin resistance and a glucose intolerance, with changes in blood glucose first detected during the gestational period, diagnostic through an initial screening, followed by confirmation with tests: fasting or postprandial glucose, glycated hemoglobin and the oral test of tolerance to glucose, these tests should be redone throughout pregnancy for diagnostic confirmation and/or follow-up of health status evolution (Silva et al., 2021).



This type of diabetes has an incidence of more than 7% in Brazil, being then considered as a major problem for public health, mainly because it is a situation that classifies pregnancy as high risk, a factor that requires greater care and complete monitoring (Junqueira et al., 2021).

This factor is considered problematic when understanding that GDM can cause several maternal and fetal complications, such as arterial hypertension, urinary tract infections, preterm labor and consequently prematurity, maternal and fetal hypoglycemia, fetal macrosomia or inadequate birth weight, respiratory distress syndrome, congenital malformations, increased fetal bilirubin, risk of premature rupture of the limbs, increase in the number of deliveries by cesarean section, in addition to the risk of causing the death of the fetus, which configures GDM as a risk pregnancy (Junqueira et al., 2021 & Laginestra et al., 2020).

Because of this, several approaches and therapies are prescribed to avoid such complications. According to the guidelines of the Brazilian Society of Diabetes (2019), among the available treatments, non-pharmacological treatments are mentioned, involving nutritional therapies and appropriate changes in lifestyle; and pharmacological drugs, including insulin and oral medications. It is considered that the most used prescription is insulin therapy, being the first-line agent.

However, although insulin is extremely beneficial for pregnant women and is the gold standard for treatment, it presents some negative factors during its use, such as a higher cost, difficulty in accepting women, the need for a certain knowledge for application, greater pain and irritation, the possibility of developing lipodystrophy and other complications (Fernandes & Bezerra, 2020).

The existence of these negative factors led to prescriptions of a second therapeutic option, the oral drugs: Metformin and Glibenclamide. "Considering that the data regarding glibenclamide showed a tendency to inferiority in efficacy and safety parameters when compared to those of insulin and metformin" (Pan American Health Organization, 2019, p. 42), metformin began to gain prominence as a treatment option for pregnant women (Caldas et al., 2021).

Metformin is a drug that seeks to control glucose levels in the bloodstream, preventing hyperglycemia, by reducing insulin resistance. It has been gaining prominence as a prescription for cases of GDM, however there are still many debates about its efficiency, when compared to insulin, evidencing the need for the development of research that addresses the positive and negative points of the use of metformin in situations of diabetes in pregnant women (Pan American Health Organization, 2019).

The present study aimed to discuss the efficacy of metformin use against gestational diabetes.

2 METHODOLOGY

The present work is an integrative literature review. This type of methodology is applied through the execution of steps, starting with the definition of the theme, guiding question and general



objective, followed by the choice of criteria to be used at the time of the search and selection of the published documents, in order to be able to perform the grouping of the documents and analysis of the results, and then, the finalization of the review (Ercole, Melo & Alcoforado, 2014).

Considering the theme addressed, we arrived at the definition of the following guiding question for follow-up of the review: "What is the efficacy of the use of metformin by women with gestational diabetes? ". This research problem was defined through the PICo strategy, described by Santos, Pimenta & Nobre (2007), it is understood that (P) population: women with gestational diabetes; (I) intervention: evidence on the efficacy of metformin; (CO) context: refers to the scientific evidence identified on the effectiveness of the use of metformin in gestational diabetes.

For the development of the work, the research was carried out in the databases Medical Literature Analysis and Retrieval System Online (MEDLINE), Latin American and Caribbean Literature in Health Sciences (LILACS), via the Virtual Health Library (VHL) and the Scientific Electronic Library Online (SciELO). For the search in the referred databases, we used the Descriptors in Health Sciences (DeCS): "Pregnancy", "Diabetes" and "Metformin", in association with the Boolean operator "AND".

For the selection of studies, some inclusion criteria were established to be considered when searching, reading and choosing the documents that would compose the results: research that was fully available, published between the years 2017 to 2022, in Portuguese, English or Spanish and that answered the guiding question.

Regarding the exclusion criteria, paid studies, simple or expanded abstracts published in annals of events, incomplete or inconclusive works that were duplicated in different databases, other review research and documents that did not address the central theme were excluded.

3 RESULTS AND DISCUSSION

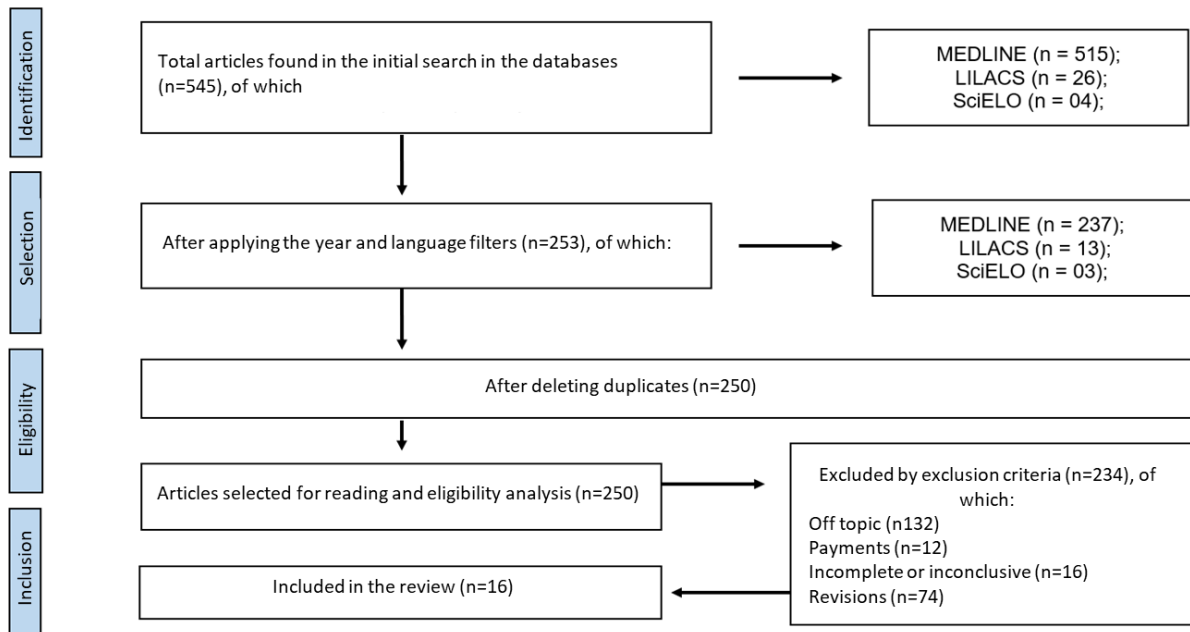
The initial search of the descriptors in the databases described, obtained the number of 545 documents. After applying the filters of year of publication and language, based on the previously selected criteria, 253 documents were obtained.

From this, it occurred from the initial reading of the titles and abstracts, and when necessary, the complete reading of the documents, excluding 3 for being repeated in more than one database, 132 documents for not answering the guiding question, 12 for being paid, 16 for being incomplete or being inconclusive and 74 for being revisions, leaving 16 studies to compose the review.

This whole search process is exemplified through a flowchart (Figure 1), for better visualization and understanding. This flowchart was based on the PRISMA protocol, which despite having been developed for systematic reviews, it is also possible to adapt it for integrative reviews, with the aim of describing the selection of studies that will compose the work (Galvão, Pansani + Harrad, 2015).



Figure 1 – Flowchart of the search and selection process, 2022.



Source: self-authored, 2022.

These 16 studies were organized in a table (Chart 1), including number of the finding, author(s), year of publication, language in which the study was published, objective and main results.

Table 1 – Selected studies, 2022.

No.	AUTHOR(S) AND YEAR	TONGUE	GOAL	MAIN RESULTS
01	BRAND <i>et al.</i> , 2022.	English	To investigate whether maternal exposure to metformin in pregnancy is associated with increased risk of long- and short-term adverse outcomes.	In women who were taking metformin, alone or in combination with insulin, no events of hypertension or polycystic ovary syndrome were observed, but they were at increased risk for babies small for gestational age.
02	CHAVES <i>et al.</i> , 2021.	English	To study whether combination treatment was associated with better obstetric or neonatal outcomes compared with insulin alone.	Comparing the use of insulin vs insulin associated with metformin, pregnant women who used the association had more obstetric complications and greater weight gain.
03	HERRERA <i>et al.</i> , 2021.	English	To estimate the failure rate of metformin in women with gestational diabetes.	Despite starting metformin early in pregnancy in women with gestational diabetes, there was still a 15% failure rate, resulting in average glucose levels.
04	HUFNAGEL <i>et al.</i> , 2022.	English	To analyze the efficacy of metformin as a glucose reducer, considering its effects on maternal and fetal health.	Metformin has shown efficacy in improving glucose tolerance, reducing weight and restoring uterine artery function, however, its use can bring complications to the fetus, especially in growth.



05	HUHTALA <i>et al.</i> , 2021.	English	To study the effects of metformin treatment compared with insulin or diet on serum umbilical cord metabolome.	Treatment with metformin led to an increase in triglyceride levels in pregnant women and an increase in serious umbilical cord alanine. Serum HDL cholesterol of the umbilical cord is related to the growth of the fetus.
06	HUHTALA <i>et al.</i> , 2022.	English	They studied whether long-term incidences of type 2 diabetes, prediabetes, and metabolic syndrome differed among women who were treated with metformin or insulin.	When comparing the use and efficacy of insulin and metformin, it was noticed that no difference in results was perceived, the two therapies have similar effects.
07	JIAO <i>et al.</i> , 2022.	English	To investigate the combined effects of metformin hydrochloride and insulin during gestational diabetes mellitus.	The inclusion of metformin in insulin treatments promotes a decrease in the levels of total cholesterol, uric acid and microalbuminuria, as well as a lower incidence of hypertension and premature birth, but a higher level of bilirubin.
08	MAN <i>et al.</i> , 2021.	English	Develop a risk prediction model specifically for women with previous GDM.	When comparing metformin with a placebo, it has been shown to be more effective than no treatment at all. Its use decreased from 37.4% to 20% in the development of diabetes in future pregnancies.
09	MOLINA-VEGA <i>et al.</i> , 2022.	English	Elucidate the differences in the composition and function of the gut microbiota in women with GDM treated with metformin compared to those treated with insulin.	The use of metformin promoted an efficacy of lower postprandial glycemia and less increase in weight and BMI of pregnant women, but increased the number of proteobacteria and enterobacteria, affecting the intestinal microbiota.
10	PAZZAGLI <i>et al.</i> , 2020.	English	To determine the association between metformin and CS use and delivery of a large baby for gestational age (GIG) compared to insulin use for GDM.	The number of prescriptions for metformin increased from 2.5% in 2012 to 30% in 2016. There was no evidence that metformin increased the number of cesarean sections, but when combined with insulin, women were more likely to have a cesarean section.
11	PICON-CÉSAR <i>et al.</i> , 2021.	English	To test whether metformin could achieve the same glycemic control as insulin and similar obstetric and perinatal outcomes, with a good safety profile, in women with gestational diabetes.	The use of metformin showed better effectiveness in: maternal hypoglycemia, postprandial glycemia and weight gain when compared to insulin. In addition to having a low failure rate.
12	RAMALHO <i>et al.</i> , 2022.	English	To evaluate the impact of the increasing use of metformin on cesarean and large rates for gestational age, when compared to insulin.	Metformin and insulin alone were not associated with higher numbers of cesarean sections, but these values increased when the medications were used in combination.



13	SCHOONEJANS <i>et al.</i> , 2021.	English	To investigate the effect of maternal intervention with metformin during obese pregnancy with glucose intolerance on gonadal white adipose tissue (BAD).	Metformin caused a decrease in the fat mass of those who were obese. Obesity led to a decrease in the size of the fetuses and this reduction was not prevented by the medication.
14	TEW <i>et al.</i> , 2022.	English	To evaluate the impact of preemptive metformin on the level of glycosylated hemoglobin at 36 weeks of pregnancy in women with gestational diabetes mellitus controlled by diet change.	When comparing the use of metformin with placebo, it was found that the medication did not prevent the increase in glycosylated hemoglobin and still generated a lower birth weight for the fetus.
15	VENKATEASH <i>et al.</i> , 2022.	English	Define prescribing standards and factors associated with the choice of pharmacotherapy for gestational diabetes mellitus (GDM), namely metformin, glyburide and insulin, during a period of evolution of professional guidelines.	Between 2015 and 2018, the use of metformin increased considerably in gestational diabetes, being increasingly likely to be prescribed to pregnant women, however its efficacy and safety remains relative, when compared to insulin.
16	YU <i>et al.</i> , 2021.	English	To evaluate the comparative efficiency and safety of the use of glyburide, metformin and insulin in gestational diabetes mellitus (GDM).	The main results evidenced with the use of metformin in gestational diabetes were: reduction of postprandial glycemia, had better effects on neonatal hypoglycemia and preeclampsia, but worse on low birth weight and maternal weight gain.

Source: Self-authored, 2022.

When analyzing the results, it is evident that 100% of the studies were published in English, this generates a certain limitation and presents an absence of documents in Portuguese, which may be a result of the lack of stimuli or may mean that metformin is an option more commonly used outside the country, which in Brazil is not yet seen as a 100% validated option. Of these, 100% were also present in the same database, MEDLINE.

It also found that of the 16 documents, 8 (50%) were published in 2022, 7 (43.75%) in 2021 and 1 (6.25%) in 2020. These results may mean that the theme has become increasingly debated within the scientific world.

Researching on the theme addressed, it was noticed that from the end of the year 2015 to the year 2018, the prescription of metformin as a treatment of GDM increased considerably, becoming increasingly considered by medical professionals, despite this, when comparing its efficacy and safety with insulin therapy, which is the gold standard treatment, there are still many doubts (Venkatesh *et al.*, 2022). This increase in prescription, which in 2016 was greater than 27%, is related to the restrictions that exist in the use of insulin, such as the high costs and difficulties presented at the time



of application (Pazzagli et al., 2020).

"In summary, insulin therapy is effective in reducing macrosomia in some women; however, it is currently unclear whether insulin reduces the risk of neonatal hypoglycemia", generating the need to seek, study, develop and include new treatments that complement or match the results of insulin, without bringing risks to the woman or the fetus (Bastian et al., 2022, p. 454).

Even with the increase in prescription, there are controversies about its use, since it is a therapy that is not recommended by Anvisa, and its package leaflet includes metformin in pregnancy receives a categorization of B, meaning that there are no controlled studies in pregnant women, only that the animals that participated in the research did not have any type of fetal risk or teratogenic effects. In disagreement, the Brazilian Diabetes Society recognizes metformin as a therapy option in gestational diabetes, however it may fail, requiring further studies to address its effectiveness (Moreira et al., 2020 & Zajdenverg et al., 2022).

When seeking such efficacy, Huhtala et al. (2022) stated that comparing the two therapies, there were no different effects, in both there was improvement in anthropometric measurements and insulin resistance.

It was identified that the inclusion of metformin in insulin treatments, making the association or using metformin alone, generated positive results: lower level of total cholesterol, uric acid and microalbuminuria, lower risks of premature birth and the development of congenital anomalies (Brand et al., 2022; Jiao et al., 2022), aided in postprandial blood glucose, lower maternal weight gain, and prevented maternal and neonatal hypoglycemia (MOLINA-VEJA et al., 2022; Picón-César et al., 2021 & Yu et al., 2021), so the association was considered as a combination with significant effect.

Based on Calixto (2017, p. 54):

Metformin is safe in pregnancy for the mother and has proven intrauterine safety for the fetus and in the baby up to two years of life. There are no reports of changes in offspring after this period of life. Metformin has been shown to be equally effective with insulin in glycemic control during pregnancy. This oral hypoglycemic agent does not need to prove to be better than insulin. By presenting greater safety and greater patient satisfaction in use, greater ease of transportation and storage and being able to reduce costs with hospital admissions, metformin gains strength as a choice to be strongly considered in the services of assistance to diabetic pregnant women, including seeking the role as the first choice.

In contrast to these results, there are also negative points and harms of this association or its isolated use: higher bilirubin levels (Jiao et al., 2022), maternal weight gain (Chaves et al., 2021 & Yu et al., 2021), increased number of triglycerides, increased serum alanine (Huhtala et al., 2021) and higher rates of cesarean delivery, considering that separately the medications were not associated with the increase in the number of cesarean sections in women with GDM, but when associated, the probability increased considerably (Pazzagli et al., 2020; Ramalho et al., 2022).

The study by Chaves et al. (2021, p. 618) reaffirms this information, describing that:



"Metformin may be associated with better outcomes compared to other drugs, but when added to insulin this effect seems to disappear." This condition can be explained by exacerbated insulin resistance, and only one type of treatment is not enough to correct blood glucose levels.

Already analyzing the comparison of the use of metformin and a placebo, Man et al. (2020) states that in relation to placebo, metformin is more effective than not using any treatment. Further, during this comparison with placebo, metformin did not prevent the increase in glycosylated hemoglobin (Tew et al., 2022).

Seeking results from the isolated use of metformin, a lower incidence of Arterial Hypertension in pregnancy or Polycystic Ovary Syndrome was observed (Brand et al., 2022 & Jiao et al., 2022), decreased fat mass in obese women, improved glucose tolerance and assists in the restoration of uterine artery function (Schoonejans et al., 2021).

In addition, the research developed by Man et al. (2020) argues that women who used metformin, decreased by around 17% the possibility of developing diabetes again in future pregnancies. That is, it is a therapeutic practice profitable for women's health, as it can extend and benefit treatment for other pathologies.

Regarding the failure rate, even starting medication since the discovery of pregnancy and previous diagnosis, the failure rate remains 15% (Herera et al., 2021), which can be considered as a low overall failure rate of metformin (Picón-César et al., 2021).

Chaves et al. (2021) refer to data contrary to the previous authors, that the use of metformin in pregnant women with high fasting glucose values, generated a higher risk of failure. Stating that almost 80% of the patients had to subsequently include insulin in the treatment to achieve satisfactory glycemic results.

It is important to highlight the main problems when investigating its efficacy, mainly for the reason that metformin is almost 5% more likely to generate obstetric complications when compared to insulin (Chaves et al., 2021).

The first problem of its use relates to the adverse effects of the medication itself, since metformin acts in the intestine, modifying the intestinal flora and may cause gastrointestinal effects in pregnant women. Molina-Vega et al. (2022) confirms this information, by addressing in their study that women who made use of the drug, showed an increase in the amount of proteobacteria and enterobacteria, which are related to the intestinal microbiota.

Another element to be considered when deciding which would be the best prescription is the fact that metformin crosses the placenta, which generates a greater possibility of triggering problems for the fetus, especially when considering that serum HDL cholesterol of the umbilical cord is directly related to fetal size and development, this means that metformin can cause complications in the baby's growth (Huhtala et al., 2021).



This same result was also evidenced in the studies of Ramalho et al. (2022), Brand et al. (2022), Hufnagel et al. (2022), Tew et al. (2022) and Yu et al. (2021), that is, it was the most prevalent result among the selected studies, being cited by 37.5% of the documents.

4 FINAL CONSIDERATIONS

It was found that metformin has a good efficacy, with positive results in glycemic control in cases of gestational diabetes mellitus, preventing complications that are linked to the pathology. It was also observed that including the prescription of metformin in insulin therapy treatments generates better efficiency in the control of diabetes, intensifying the therapy.

The general efficacy is proven, however it is still a topic that needs further studies, because it also has negative results and can cause maternal and fetal complications, since metformin is a medication that crosses the placenta, which can lead to damage to the fetus.

Among the complications related to metformin, fetuses with growth and development problems, being small for gestational age, were more prevalent among the studies. All these factors indicate that metformin is a viable therapeutic option that has been growing within prescriptions, but that still requires more studies that address its quality and overall safety.

As recommendations for future studies, we cite the study of other medications in the face of Gestational Diabetes, and later, comparative research between all other drug options available and which among them, was considered the one with the greatest results and efficacy against Gestational Diabetes.



REFERENCES

- Bastian, B., Smithers, L. G., Davis, W., Pape, A., & Francois, M. E. (2022). 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. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 62(3), 453-456.
- Brand, K. M., Saarelainen, L., Sonajalg, J., Boutmy, E., Foch, C., Väärasmäki, M., ... & CLUE Study Group. (2022). Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study. *BMJ Open Diabetes Research and Care*, 10(1), 1-14.
- Caldas, G. R. F., dos Santos, M. G., Areia, P. S., Rocha, S. A., Costa, E. N. F., Branco, F. M., ... & Luz, D. C. R. P. (2021). Por que amamentar?: Uma revisão de literatura. *Research, Society and Development*, 10(4), 1-11.
- Calixto, A. C. (2017). *Metformina na Gestação: Reflexão à Luz da Literatura e seu Uso no Hospital das Clínicas da UFMG*. 61f. Dissertação (Mestrado em Perinatologi) – Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte, 2017.
- Chaves, C., Cunha, F., Martinho, M., Garrido, S., Silva-Vieira, M., Estevinho, C., ... & Almeida, M. (2021). Metformin combined with insulin in women with gestational diabetes mellitus: A propensity score-matched study. *Acta Diabetologica*, 58, 615-621.
- Ercole, F. F., Melo, L. S. D., & Alcoforado, C. L. G. C. (2014). Revisão integrativa versus revisão sistemática. *Reme: Revista Mineira de Enfermagem*, 18(1), 09-11.
- Fernandes, C. N., & Bezerra, M. M. M. (2020). O Diabetes Mellitus Gestacional: Causa e Tratamento/The Managemental Diabetes Mellitus: Cause And Treatment. *ID on line. Revista de psicologia*, 14(49), 127-139.
- Galvão, T. F., Pansani, T. D. S. A., & Harrad, D. (2015). Principais itens para relatar Revisões sistemáticas e Meta-análises: A recomendação PRISMA. *Epidemiologia e serviços de saúde*, 24, 335-342.
- Herrera, K. M., Ou, J. P., Persad, M. D., Bernasko, J., Garretto, D., & Garry, D. (2021). Risk of metformin failure in the treatment of women with gestational diabetes. *Journal of Perinatal Medicine*, 49(9), 1084-1088.
- Hufnagel, A., Fernandez-Twinn, D. S., Blackmore, H. L., Ashmore, T. J., Heaton, R. A., Jenkins, B., ... & Ozanne, S. E. (2022). Maternal but not fetoplacental health can be improved by metformin in a murine diet-induced model of maternal obesity and glucose intolerance. *The Journal of physiology*, 600(4), 903-919.
- Huhtala, M. S., Rönnemaa, T., Pellonperä, O., & Tertti, K. (2021). Cord serum metabolome and birth weight in patients with gestational diabetes treated with metformin, insulin, or diet alone. *BMJ Open Diabetes Research and Care*, 9(1), 1-9.
- Huhtala, M., Nikkinen, H., Paavilainen, E., Niinikoski, H., Väärasmäki, M., Loo, B. M., ... & Tertti, K. (2022). Comparison of glucose metabolism and anthropometry in women with previous gestational diabetes treated with metformin vs. insulin: 9-year follow-up of two randomized trials. *Acta Obstetrica et Gynecologica Scandinavica*, 101(5), 514-523.



- Jiao, Y., Qiao, Z., Han, R., Du, J., Zhang, J., & Zhang, S. (2022). Effects of metformin and insulin on gestational diabetes mellitus: A dual drugs therapy approach. *Pakistan Journal of Pharmaceutical Sciences*, 35(1), 161-64.
- Junqueira, J. M. O., Nascimento, S., Marques, S. R., & Fontes, J. F. (2021). Diabetes mellitus gestacional e suas complicações—Artigo de revisão Gestational diabetes mellitus and its complications—Review article. *Brazilian Journal of Development*, 7(12), 116574-116589.
- Laginestra, A. J. C., de Souza, D. F., da Rocha Oliveira, E., da Rosa Morelli, F. M., Jardim, M. B., & de Carvalho, L. L. (2020). Diabetes mellitus gestacional e complicações fetais e neonatais. *Cadernos da Medicina-UNIFESO*, 2(3), 40-47.
- Leal, A. C. S., Silva, L. B. V. & Oliveira, P. S. D. (2022). Conhecimentos de gestantes sobre diabetes gestacional. *Bionorte*, 11(1), 190-198.
- Molina-Vega, M., Picon-Cesar, M. J., Gutierrez-Repiso, C., Fernandez-Valero, A., Lima-Rubio, F., Gonzalez-Romero, S., ... & Tinahones, F. J. (2022). Metformin action over gut microbiota is related to weight and glycemic control in gestational diabetes mellitus: a randomized trial. *Biomedicine & Pharmacotherapy*, 145(112465), 1-9.
- Moreira, N. A., Rezende, C. O., Pereira, N. S., & Neto, E. E. M. (2020). O uso de metformina no controle do Diabetes Gestacional. *Brazilian Journal of Health Review*, 3(3), 5959-5962.
- Organização Pan-Americana da Saúde. Ministério da Saúde. Federação Brasileira das Associações de Ginecologia e Obstetrícia. Sociedade Brasileira de Diabetes. (2019). Tratamento do diabetes mellitus gestacional no Brasil. Brasília, DF: OPAS, 57 p.
- Pazzagli, L., Abdi, L., Kieler, H., & Cesta, C. E. (2020). Metformin versus insulin use for treatment of gestational diabetes and delivery by caesarean section: A nationwide Swedish cohort study. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 254, 271-276.
- Picón-César, M. J., Molina-Vega, M., Suárez-Arana, M., González-Mesa, E., Sola-Moyano, A. P., Roldan-López, R., ... & González-Romero, S. (2021). Metformin for gestational diabetes study: metformin vs insulin in gestational diabetes: glycemic control and obstetrical and perinatal outcomes: randomized prospective trial. *American Journal of Obstetrics and Gynecology*, 225(5), 517-527.
- Ramalho, D., Correia, S., Realista, R., Rocha, G., Alves, H., Almeida, L., ... & Diabetes and Pregnancy Study Group of the Portuguese Society of Diabetology. (2022). Impact of pharmacological treatment of gestational diabetes on the mode of delivery and birth weight: a nationwide population-based study on a subset of singleton pregnant Portuguese women. *Acta Diabetologica*, 59(10), 1361-1368.
- Santos, C. M. D. C., Pimenta, C. A. D. M., & Nobre, M. R. C. (2007). A estratégia PICO para a construção da pergunta de pesquisa e busca de evidências. *Revista latino-americana de enfermagem*, 15, 508-511.
- Schoonejans, J. M., Blackmore, H. L., Ashmore, T. J., Aiken, C. E., Fernandez-Twinn, D. S., & Ozanne, S. E. (2021). Maternal metformin intervention during obese glucose-intolerant pregnancy affects adiposity in young adult mouse offspring in a sex-specific manner. *International Journal of Molecular Sciences*, 22(15), 81-94.
- Silva, A. L. A. da et al. (2021). Diabetes Mellitus Gestacional com ênfase nas Gestantes de Alto Risco. *Revista de psicologia*, 15(58), 278-291.



Sociedade Brasileira de Diabetes. (2019). Diretrizes 2019-2020. São Paulo: Clannad Editora Científica.

Tew, M. P., Tan, P. C., Saaid, R., Hong, J. G., & Omar, S. Z. (2022). Metformin in gestational diabetes mellitus: a double-blind placebo-controlled randomized trial. *International Journal of Gynecology & Obstetrics*, 156(3), 508-515.

Venkatesh, K. K., Chiang, C. W., Castillo, W. C., Battarbee, A. N., Donneyong, M., Harper, L. M., ... & Landon, M. B. (2022). Changing patterns in medication prescription for gestational diabetes during a time of guideline change in the USA: a cross-sectional study. *BJOG: An International Journal of Obstetrics & Gynaecology*, 129(3), 473-483.

Yu, D. Q., Xu, G. X., Teng, X. Y., Xu, J. W., Tang, L. F., Feng, C., ... & Wang, L. Q. (2021). Glycemic control and neonatal outcomes in women with gestational diabetes mellitus treated using glyburide, metformin, or insulin: a pairwise and network meta-analysis. *BMC Endocrine Disorders*, 21(1), 1-15.

Zajdenverg, Lenita. *Tratamento farmacológico do diabetes na gestação*. Diretriz Oficial da Sociedade Brasileira de Diabetes, 2022.