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Utilização do cloridrato de metformina no diabetes gestacional: uma revisão sistemática

Use of metformin hydrochloride in gestational diabetes: a systematic review

Uso de clorhidrato de metformina en diabetes gestacional: una revisión sistemática

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Resumo

O Diabetes Mellitus Gestacional é uma condição caracterizada pelo aumento dos níveis de glicose no sangue, que pode ser iniciada ou diagnosticada durante a gestação. Esse processo ocorre devido à produção de altos níveis de hormônios pela placenta, sendo a maioria prejudicial à ação da insulina nas células, aumentando o nível de açúcar no sangue podendo afetar o crescimento e o bem-estar do feto. Dentre os medicamentos aplicados, o Cloridrato de Metformina é um hipoglicemiante oral usado no tratamento do Diabetes Mellitus. O presente

trabalho teve como objetivo a elaboração de uma revisão sistemática sobre o uso do cloridrato de metformina no tratamento do diabetes mellitus gestacional. As buscas foram realizadas nas bases de dados SciElo e Google Acadêmico. Foram encontrados 763 artigos na pesquisa inicial e após as análises das fases pré-analíticas, apenas 6 foram selecionados, uma vez que atendiam aos critérios de inclusão. Após a extração dos dados, fez-se uma relação entre o uso da metformina com as diversas formas de terapia utilizadas nos estudos e evidenciou-se que a metformina é um fármaco bem aplicado como monoterapia chegando a ser utilizado por 40 % dos indivíduos em um dos estudos analisados, sendo também bem aceito em terapia combinada com insulina em pacientes que possuem resistência à mesma, devido a metformina ser um fármaco de fácil acesso e de fácil posologia. Conclui-se então que a metformina é um fármaco seguro, eficaz, de baixo custo e de muita aceitação pelas gestantes que o usam no tratamento do Diabetes Mellitus gestacional.

Palavras-chave: Diabetes gestacional; Metformina; Gestantes; Revisão sistemática.

Abstract

Gestational Diabetes Mellitus is a condition characterized by an increase in blood glucose levels, which can be initiated or diagnosed during pregnancy. This process occurs due to the production of high levels of hormones by the placenta, most of which are harmful to the action of insulin in the cells increasing the blood sugar level and can affect the growth and well-being of the fetus. Among the drugs used, Metformin Hydrochloride is an oral hypoglycemic drug used to treat Diabetes Mellitus. The present study aimed to elaborate a systematic review on the use of metformin hydrochloride in the treatment of gestational diabetes mellitus. The searches were carried out in the SciElo and Google Acadêmico databases. 763 articles were found in the initial research and after the analysis of the pre-analytical phases, only 6 were selected, since they met the inclusion criteria. After extracting the data, a relationship was made between the use of metformin with the various forms of therapy used in the studies and it was shown that metformin is a drug well applied as monotherapy, being used by 40 % of individuals in one of the studies analyzed and it is also well accepted in combination therapy with insulin in patients who have resistance to it, due to metformin being a drug with easy access and easy dosage. It is concluded that metformin is a safe, effective, low-cost and widely accepted drug for pregnant women who use it in the treatment of gestational Diabetes Mellitus.

Keywords: Gestational diabetes; Metformin; Pregnant women; Systematic review.

Resumen

La Diabetes Mellitus gestacional es una afección caracterizada por un aumento en los niveles de glucosa en sangre, que puede iniciarse o diagnosticarse durante el embarazo. Este proceso ocurre debido a la producción de altos niveles de hormonas por la placenta, la mayoría de los cuales son perjudiciales para la acción de la insulina en las células, lo que aumenta el nivel de azúcar en la sangre y puede afectar el crecimiento y el bienestar del feto. Entre los medicamentos utilizados, el clorhidrato de metformina es un agente hipoglucemiante oral que se usa para tratar la Diabetes Mellitus. El presente estudio tuvo como objetivo elaborar una revisión sistemática sobre el uso de clorhidrato de metformina en el tratamiento de la diabetes mellitus gestacional. Las búsquedas se llevaron a cabo en las bases de datos SciElo y Google Acadêmico. Se encontraron 763 artículos en la investigación inicial y después del análisis de las fases preanalíticas, solo se seleccionaron 6, ya que cumplían con los criterios de inclusión. Después de extraer los datos, se estableció una relación entre el uso de metformina con las diversas formas de terapia utilizadas en los estudios y se demostró que la metformina es un fármaco bien aplicado como monoterapia, siendo utilizado por el 40 % de las personas en un de los estudios analizados y también es bien aceptado en la terapia de combinación con insulina en pacientes que tienen resistencia a ella, debido a que la metformina es un medicamento con fácil acceso y dosificación fácil. Se concluye que la metformina es un medicamento seguro, efectivo, de bajo costo y ampliamente aceptado para mujeres embarazadas que lo usan en el tratamiento de la Diabetes Mellitus gestacional.

Palabras clave: Diabetes gestacional; Metformina; Mujeres embarazadas; Revisión sistemática.

1. Introduction

Diabetes Mellitus (DM) is a metabolic syndrome of multiple origin that affects about 8.8 %, about 424.9 million people in the world population, between 20 and 79 years of age (SBD, 2019). It is a chronic disease that has its related etiology due to deficiency in the production of insulin by the pancreas or in its action, or in both mechanisms. This disorder is due to the destruction or inefficiency of β-pancreatic cells, and the character of the disease may be autoimmune or be associated with problems with insulin receptors, in addition to insufficient secretion of the hormone, which in turn, contributes to the installation of the disease (Oliveira; Melo, Pereira, 2016).

Gestational Diabetes Mellitus (GDM) is a condition characterized by an increase in blood glucose levels, which can be initiated or diagnosed during pregnancy. The etiology of the disease is due to the production of high levels of hormones by the placenta, the majority of which are harmful to the action of insulin in the cells, increasing the level of sugar in the blood, which can affect the growth and well-being of the fetus. (Oliveira et al., 2019). There are factors that influence a higher incidence in the occurrence of GDM, among them: age over 25 years, obesity or excessive weight gain, family history of diabetes in first-degree relatives, excessive fetal growth, excess amniotic fluid, hypertension or pre-eclampsia, obstetric history of fetal or neonatal death and macrosomia (Lucena, 2007).

The treatment of GDM aims to reduce the incidence of complications, both maternal and fetal, especially macrosomia, pre-eclampsia, the occurrence of cesarean section and neonatal adiposity. The main conducts to be taken are: appropriate diet associated with physical activity, administration of oral medications (hypoglycemic agents) or insulin (Amaral et al., 2015).

Metformin Hydrochloride (MH), popularly known in Brazil as GLIFAGE®, was first marketed in 1957. It is a hypoglycemic agent, where its main therapeutic indication is the treatment of Type 2 Diabetes Mellitus, which can act as monotherapy or as an adjunct, taking into account the patient's glucose imbalance. This medication works by reducing both glucose absorption and hepatic neoglycogenesis, as well as increasing the use of peripheral glucose (Silva; Souza; Silva, 2013). Unlike other oral hypoglycemic agents, MH is a category B drug (has no teratogenic effects in animals) according to the *US Food and Drug Administration*, and although no adverse fetal effects have been reported with its use, metformin crosses the placenta, however it does not have a teratogenic effect on the fetus (Peixoto & Ramalho, 2016).

It is known that there are countless therapies for the control of blood glucose, whether for patients with Type 1, Type 2 Diabetes Mellitus or GDM, but not all respond to a particular therapy in the desired way, especially if this patient is a pregnant woman. In this context, the present study aimed to evaluate the use of Metformin Hydrochloride in the treatment of Gestational Diabetes Mellitus through a systematic review.

2. Methodology

Systematic review used for methodology is a type of study considered as a secondary research, because it uses primary studies to interpret data, evaluate the quality of evidence and

expand knowledge in references on a specific topic, being a critical study of the literature that uses methodological and systematized search criteria (Linares-Espinóis et al., 2018). The systematic review carried out in this study was a qualitative methodology, with interpretation and description by the authors in relation to the data collected in the studies that answered the guiding question on the theme (Pereira et al., 2018).

2.1 Systematic literature search

This systematic review was carried out in accordance with the guidelines of the preferred reporting items for systematic reviews and meta-analyzes (PRISMA statement) with modifications.

2.2 Search strategy and article selection

The research was carried out between September and October 2019 in the Google Acadêmico and Scientific Electronic Library Online (SciElo) databases, including all articles published in the last five years until the end of October 2019, using the following terms and Medical Subject Headings (MeSH): 'Diabetes', 'Gestational Diabetes' and 'Metformin'. In the tracking of publications the logical operators “AND” and “OR” were used, in order to combine the terms/subjetcs mentioned above.

2.3 Inclusion and exclusion criteria for studies

The selection of articles was carried out according to the search terms found in the titles and abstracts, followed by screening and evaluation of complete documents, in order to identify studies that met the inclusion and exclusion criteria. For that, the following inclusion criteria were considered: a) experimental studies that used the drug of choice Metformin Hydrochloride for the treatment of Gestational Diabetes Mellitus, which may or may not be associated with other hypoglycemic drugs; b) pregnant women who had DM before pregnancy, as well as those who developed diabetes during pregnancy; c) publication period from 2015 to 2019; and d) publications in Portuguese.

The exclusion criteria were articles of meta-analysis, systematic review, literature review, dissertation, theses, abstracts of proceedings, duplicates and any other studies on the treatment of Gestational Diabetes Mellitus that did not use Metformin Hydrochloride. The selection of studies was carried out in three stages: 1st stage - reading the titles; 2nd stage -

reading the abstracts of the articles selected in the 1st stage; 3rd stage - full reading of the articles selected in the 2nd stage.

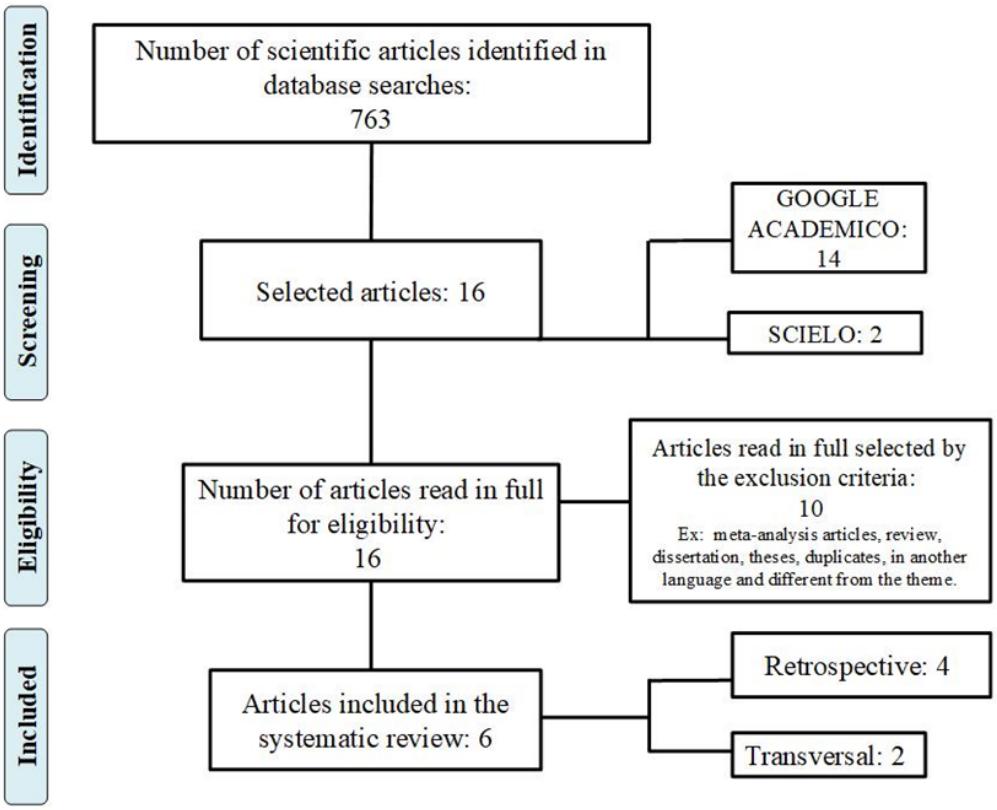
2.4. Data extraction and analysis

The data were extracted manually and separated in a standardized form in the Microsoft Office Excel® 2010 software, in which descriptive and quantitative analyzes were performed. The variables extracted from each article and included in the review were: authors and year of publication; number of pregnant women treated with metformin; metformin hydrochloride in combination with insulin; comparison between the indication of metformin hydrochloride and insulin; and comparative between pharmacological therapy.

3. Results and Discussion

About 763 articles obtained in the initial search in the two databases, 16 were selected after reading the titles (1st stage) and among these, 10 were excluded after reading the abstracts (2nd stage) as they did not meet the inclusion criteria. The flowchart below (Figure 1) outlines the stages for selecting the studies and the final number of those eligible for review, as well as the number and justification of excluded articles.

Figure 1. Flowchart of search results, selection and inclusion of studies.



Source: The authors (2020).

The data and information extracted from the six selected and analyzed studies are shown in Table 1. The studies were published in the years 2015 to 2019, but no study was found in 2017 that met the research requirements. Only four studies analyzed both the treatment of patients with GDM with MH, as well as the association of MH with another therapy, while the other two studies divided patients into two groups: patients treated with metformin and patients treated with insulin.

Table 1. Characteristics of the articles analyzed in the systematic review on the use of Metformin in Gestational Diabetes Mellitus.

Author (Year)	Type of study	Amount	Pregnant women treated only with MH	Pregnant women treated only with Insulin	Pregnant women treated with MH in combination with Insulin	Pregnant women treated only with diet and physical activity
Oliveira et al. (2019)	Transversal	893	366 (40.9%)	112 (12.5 %)	109	306
Silva et al. (2019)	Transversal	663	276 (41.6%)	75 (11.3 %)	92	220
Rodrigues et al. (2019)	Retrospective	323	88 (27.2%)	34 (10.5 %)	-	-
Silveira-Filho et al. (2018)	Retrospective	705	249 (35.3%)	163 (23.1 %)	-	292
Silva et al. (2016)	Retrospective	367	128 (34.9%)	68 (18.5 %)	34	137
Amaral et al. (2015)	Retrospective	255	80 (31.37%)	92 (36.0 %)	32	51

MH: Metformin Hydrochloride. Source: The authors (2020).

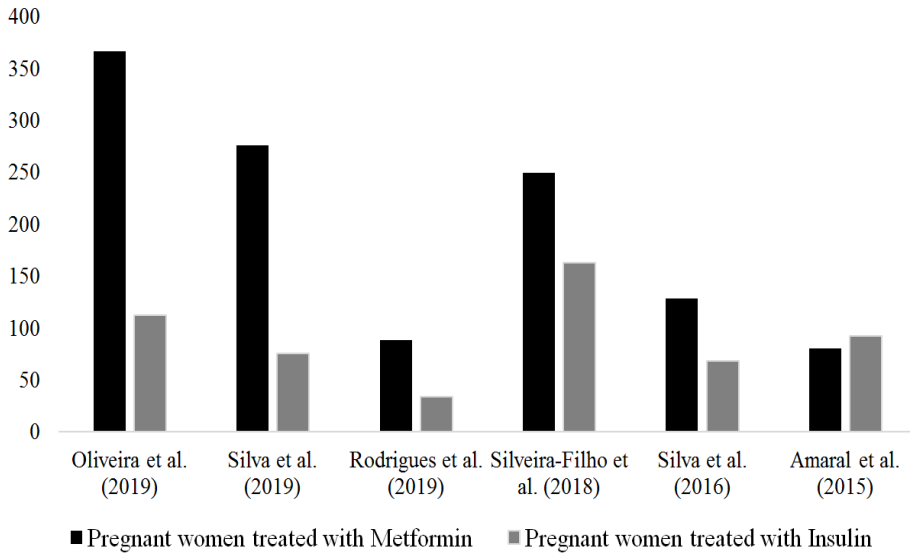
According to Table 1, variations were found in the indication of MH in the studies analyzed, where in two of them, Oliveira et al. (2019) and Silva et al. (2019), there is a percentage greater than 40% in the indication of the drug, while in the other study of the same year by Rodrigues et al. (2019) we have a decrease in indication, below 30%. It was also observed that in the studies by Amaral et al. (2015), Silva et al. (2016) and Silveira-Filho et al. (2018) the indication of the MH was in a range above 30%.

Pharmacotherapeutic treatment is only started when glycemic control is not achieved only with diet and physical activity, so this data proves a still low indication of MH in the study by Rodrigues et al. (2019). MH is indicated as a drug of first choice because it is a safe oral hypoglycemic for pregnant women, where almost always the administration of a single pill a day is already able to control glucose levels, in addition to being a drug distributed free by the Unified System of Health (Pontes et al., 2010). Other benefits of initial treatment with metformin include fewer prematurity and cesarean deliveries, reduced maternal weight gain

and unfavorable neonatal outcomes such as macrosomia and admission to special neonatal care services (Oliveira et al., 2019).

In Graph 1, we have the comparison between oral therapy with MH and insulin therapy. It is observed that only in the study by Amaral et al. (2015) insulin therapy was superior to MH therapy, because insulin has long been the gold standard in the treatment of GDM, as it does not cross the placental barrier, therefore safe for therapeutic use in pregnant women, however adherence it is still low (Oliveira et al., 2019).

Graph 1. Comparison between insulin therapy vs. oral therapy with Metformin Hydrochloride.



Source: The authors (2020).

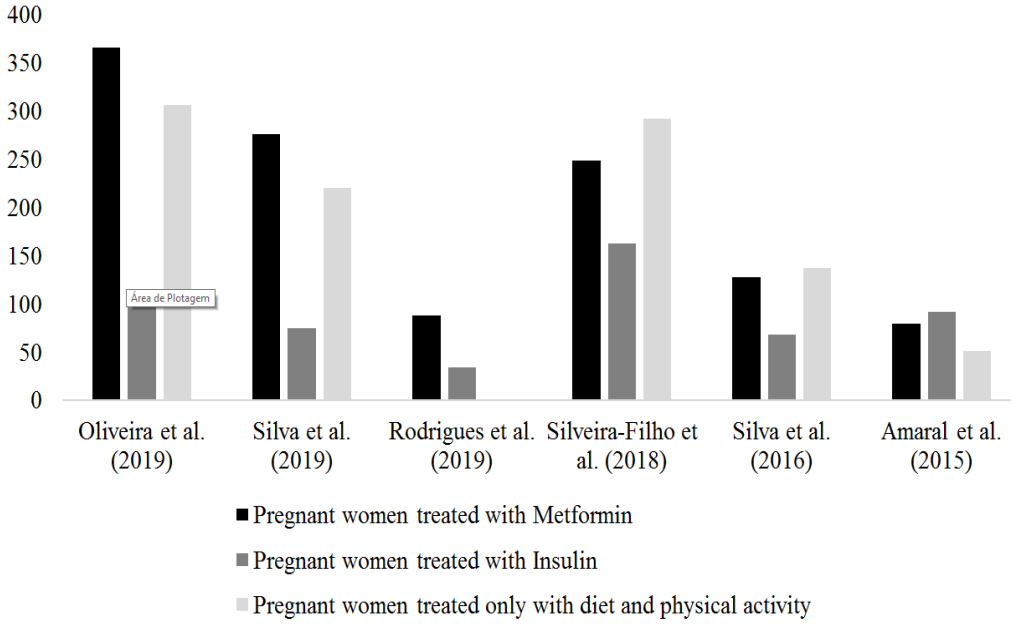
In the studies analyzed in the subsequent years (2016-2019), we can notice an increase in the indication of oral drugs, such as MH, as they demonstrate safety, effectiveness, simple administration and favorable glycemic control, being recommended due to the ease of application, storage and low cost, when compared to insulin (Silva et al., 2019).

Graph 2 shows the comparison between pharmacological therapies with Metformin and Insulin, and non-pharmacological therapies, where pregnant women associated diet with physical activity to control glycemia.

Rodrigues et al. (2019) did not report non-pharmacological treatment, only pharmacological treatment. It was observed that only in the study by Oliveira et al. (2019) the most prescribed pharmacological therapy with MH when compared to non-pharmacological

therapy, justified due to the prevalence of obesity/overweight in most pregnant women. In other studies, non-pharmacological therapy was superior to pharmacological therapy.

Graph 2. Comparison between pharmacological and non-pharmacological therapy.



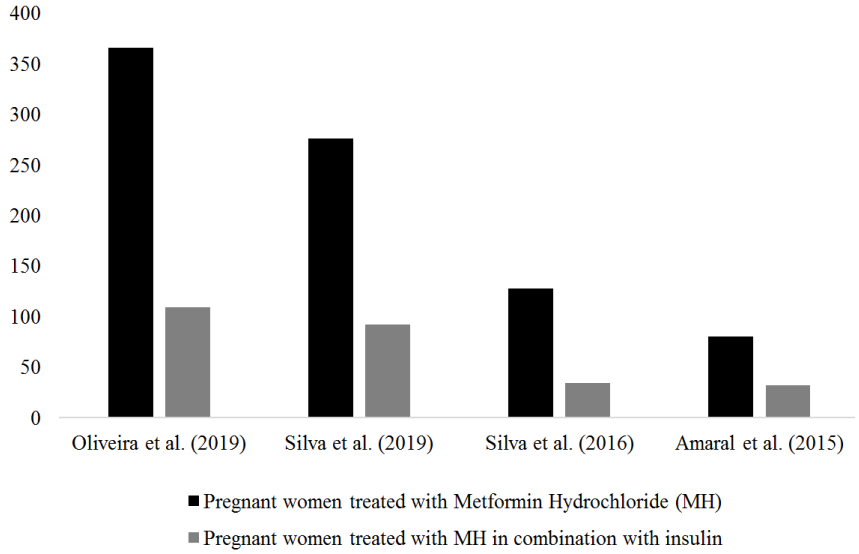
Source: The authors (2020).

Rodrigues et al. (2019) state that the inadequate nutritional status of pregnant women may favor the emergence of pregnancy complications such as diabetes and pre-eclampsia, and its control is relevant, since it is a modifiable risk factor and the risk of developing GDM is linked to the BMI (Body Mass Index) of pregnant women. Silveira-Filho et al. (2018) report that the earlier the diagnosis of GDM, the better the chances of glycemic control with non-pharmacological therapy alone, but pregnant women who had a late diagnosis of the disease had higher risks and, therefore, need for pharmacological therapy.

Graph 3 shows a comparison between treatment with MH alone and MH associated with insulin (parenteral drug), where only in four of the six studies analyzed, MH was in association with insulin.

It was found that in all cases the treatment with MH alone was effective in maintaining blood glucose levels within the standards. As for the association of drugs, studies have shown that it was only necessary when there were cases of insulin resistance, observed in the study by Amaral et al. (2015).

Graph 3. Comparison between pharmacotherapy with Metformin Hydrochloride vs. pharmacotherapy with Metformin Hdrochloride associated with Insulin.



Source: The authors (2020).

Thus, in these studies it was observed that in addition to monotherapy with MH being effective, adherence to pharmacotherapy by most pregnant women was greater when a single drug is administered orally. The MH in addition to being safe for use in pregnant women has a variety of pharmaceutical presentations (500 mg, 550 mg, 750 mg and 850 mg tablets, with prolonged release systems or not) available on the market (Oliveira et al., 2019).

After analysis and comparison of the data presented by the authors based on the indication of metformin hydrochloride, we agree and it can be evidenced the efficacy and proven safety, as well as an alternative of oral hypoglycemic drug for pregnant women in the treatment of gestational Diabetes Mellitus, mainly as monotherapy.

4. Conclusion

The present review found relevant studies in the databases with regard to drug therapy in pregnant women, since many drugs cross the placental barrier and may be teratogenic to fetuses. However, studies showed that Metformin Hydrochloride is a safe and effective medication in the treatment of Gestational Diabetes Mellitus, even surpassing insulin itself, where it most often becomes an inappropriate treatment, due to the difficult adherence on the part of patient.

Therefore, the indication for Metformin Hydrochloride has grown over the years, as it is a drug that is easy to adhere to therapy and can be administered almost exclusively once a day, in addition to having a great cost benefit for pregnant women. Above all, it is worth mentioning that this is a drug released free of charge by the Unified Health System and also in the Federal People's Pharmacy program, making it a pharmacotherapeutic indication easily accessible to the population, especially to pregnant women who have Diabetes Mellitus.

As perspectives for future research, additional studies on the use of Metformin Hydrochloride in the treatment of Gestational Diabetes Mellitus should be conducted, which would help to provide more data and greater dissemination of this medicina as a pharmacotherapeutic alternative.

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