Physical exercise and metformin in gestational obesity and prevention on gestational *diabetes mellitus*: a systematic review

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Abstract

Objectives: identify the action of metformin and physical activities to reduce weight gain and prevent mellitus diabetes in obese pregnant women.

Methods: the electronic search was performed in PubMed / MEDLINE, LILACS, Web of Science, Scopus and Cochrane library databases between 2008 and 2018. The selection took place between April and July 2018, through the descriptors "pregnancy, obesity, metformin, treatment, exercise". A protocol was programmed and consecutively a selective research on the inclusion / exclusion phase. The "PICO" strategy was used. Population: obese pregnant women. Intervention: physical exercises and metformin. Control: The main indicator established was therapeutic outcomes with physical activity and metformin. Outcome of interest: body weight control.

Results: by selecting the database, 3,983 articles were identified on the topic of interest. After selecting and eligibility, only 16 scientific studies were selected, of which 81.25% were clinical trials related to diet programs, physical activity, metformin use and possible outcomes, 18.75% were prospective cohort on causes of obesity in gestation and its association with gestational mellitus diabetes and preventive therapies. The study pointed out the possibility of adapting physical therapy programs with the correct metformin dosage for a greater control in gestational weight gain. However, there is a need for greater awareness and changes in habits for obese woman during the gestational period.

Conclusions: the drug presents similarity to physical activity by activating AMPK and may be added to treatments that propose changes in pregnant women's lifestyle to reduce weight gain and prevent gestational diabetes mellitus with a better understanding of the optimal dosage. Thus, the study suggests the use of metformin is not only for the prevention and the intercurrence of gestational diabetes mellitus, but a strictly careful investigation allowing its use to non-diabetic obese pregnant women.

Key words *Pregnancy, Obesity, Metformin, Treatment, Exercise*

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Introduction

The association between obesity and different pathologies have been arising concerns in the world scenrio.[1] In Brazil, the negative impact on the incidence of obesity and diseases are already known in publications, having among others, metabolic and endocrine disorders, hypertension, diabetes and certain types of cancer.[2,3]

Under specific pregnancy conditions, there are multifactorial causes that lead to obesity, and it is associated with the development of gestational diabetes mellitus (GDM)[2,3] Among the metabolic problems in pregnancy, GDM is characterized as the most common, with an incidence of 25% of the pregnancies, taking into account the criteria on applied diagnosis, the studied population and ethnic group.[4] GDM increases as gestational obesity does as well.[5]

However, the lack of overweight and obesity control before and during pregnancy requires more efficient means to manage weight gain during the gestational trimesters, prevention on neonatal outcomes and childhood obesity.[6] Among the main therapeutic methods for obesity and GDM control are physical activity programs and restricted eating habits.[7]

Due to the low adherence of patients to dietary programs, there is no showing of significant reduction in obese pregnant women's weight and in the incidence of GDM,[8] as well as physical activity programs, since specialists have identified the difficulties and the need of greater awareness on pregnant women to reduce gestational obesity and GDM outcomes.[5,9,10]

Oral antidiabetic of metformin hydrochloride has provided significant results in gestational obesity which is one of the primary causes of GDM. However, the use of metformin during pregnancy is controversial, although it is safe to use the drug, but the lack of long-term data requires more studies and cautious prescriptions.[11] The combination of the drug with physical activity programs and changes in the pregnant woman's behavior, shows efficacy for obesity and GDM.[5] The drug has been demonstrating positive outcomes by improving glycemic abnormalities and blood pressure levels. It also has been used in obese pregnant women with GDM and effective in decreasing body mass index (BMI).[12] Prevention is one of the key aspects in the fight against outcomes resulting in increased body weight on pregnant woman, incidence of GDM and intercurrence. Therefore, therapies with metformin, its different dosages and results, suggest possibilities of associating it with physical therapies in a greater perspective to improve pregnant women's quality of life, and so the procedures and resources for gestational obesity prophylaxis and GDM are still obstacles to overcome in the obstetric scenario.[5,9,11,13] However, this study aims to identify the action of metformin and physical activity to reduce weight gain and prevent GDM in obese pregnant women

Methods

A systematic literature review was carried out between 2008 and 2018, and the selection was between April and June 2018. A protocol was developed involving an assessment report with different scientific studies. In this organization, the 27 established items from PRISMA checklist were used.[14]

Eligibility criteria

In literary research, the "PICO" strategy was applied. Population: obese pregnant women. Intervention: physical exercises and metformin. Control: the main indicator established was therapeutic outcomes with physical activity and metformin. Outcome of interest: Body weight control. The preference was researches with results on metabolic action caused by physical activity programs and also results on pharmacokinetic action of metformin hydrochloride. Afterwards, a search on preventive action about physical activity, a drug for GDM and gestational obesity. A priority search was for studies on randomized clinical trials with the use of physical activities and metformin hydrochloride during pregnancy. However, non-randomized researches of greater importance to our purposes could be selected in the flowchart, as long as they were consistent with the topic addressed in this research. Such as among others: prospective, retrospective, case control and cross-sectional cohort studies. Clinical laboratory studies, systematic reviews and epidemiological studies were excluded from the qualitative selection and / or the selection in the flowchart.

The flowchart was organized during the search for scientific publications source through a flow diagram with languages in Portuguese, English or Spanish. The keywords were chosen according to the Health Science Descriptors of the Lilacs Virtual Health Library (DeCS) and the respective publication dates from 2008, in the PubMed/MEDLINE databases, Latin American and Caribbean Health Sciences Literature (LILACS), Web of Science, Scopus, with the descriptors "pregnancy, obesity, metformin, treatment, exercise"associated with

Boolean operators"*AND*" and "*OR*", with the purpose of achieving more adherent studies to the proposed theme. The population consisted of studies in the literature containing their methods samples with pregnant women who performed different exercise programs during pregnancy and researches that used metformin hydrochloride for preventive treatments for obesity and GDM.

Key word searches on different sites:

PubMed/MEDLINE, LILACS, Web of Science e Scopus
"pregnancy" AND "obesity" AND "metformin" AND "treatment" ; "pregnancy "AND "obesity" AND "metformin" AND "exercise"; "pregnancy "AND "obesity" AND"treatment"; "pregnancy "AND "obesity" AND "exercise" ; "obesity" AND "metformin" AND "treatment"; "obesity" AND "metformin" AND "exercise".
"pregnancy" OR "obesity" OR "metformin" OR "treatment"; "pregnancy "OR "obesity" OR "metformin" OR "exercise" "pregnancy" OR "obesity" OR "metformin"; "obesity" OR "metformin" OR "treatment"; "obesity" OR "metformin" "exercise".

Study Selection and data extraction

From the acquisition of the journals, three authors set aside relevant data. It is worth noting that if there was any unclear information or due to the lack of data on the characteristics in the trials, the main authors of the studies would be contacted for further clarification. The referential selection process for systematic reviews in electronic databases followed the following steps: identification, selection, eligibility and inclusion, according to PRISMA[14] (Figure 1).

Exclusion criteria: repeated work on different search sites; reading of titles and abstracts not consistent with therapies with the use of metformin or with physical activity programs during pregnancy; methodological analysis with unaccomplished criteria, few details in the method section and no scientific record and exclusion by objectives, in other words, there is no consensus among purpose, method, conclusion and, concomitantly, studies with few correlations related to the objective of the present research .

Inclusion criteria: the population of interest should be obese pregnant women aged 16 years or older. The outcome of interest was to identify the effectiveness of therapies on the pregnant woman's body weight. The researchers have compared studies with therapies related to physical activity and studies with the use of metformin hydrochloride. Randomized controlled studies or clinical trials only had primary order in the selection. However, it was possible to include other studies in the qualitative analysis as long as they were of total relevance to our objectives, allowing the inclusion of cohort studies, case control, and cross-section.

The investigators independently assessed the risk of bias using the criteria described in the subsequent item. Three authors (Nascimento IB, Fleig R and Souza MLR) searched and / or selected the studies and if there was doubt among two or more studies, a fourth member of the group would have to do the analysis with the pre-established methodological parameters and strategies and, the choice, should be by consensus of the 4 authors. Subsequently, it was decided to develop a table with only clinical trial studies, which was the main objective of the search in qualitative analysis, as shown in Table 1.

Bias assessment and methodological quality in different studies

The clinical trials studies used the Cochrane handbook for systematic reviews of interventions guidelines (Version 5.1.0).[15] An adaptation of the tool was carry out considering the results as follows: the bias level corresponding to the domain (1) (selection) Generation of the random sequence, (2) (Selection) Concealment of allocation, (3) (performance) Blinding of participants and professionals, (4) (detection) Blinding of outcome evaluators, (5) (attrition) Incomplete outcomes, (6) (report) Selective outcome report, (7) (other bias), in other words, other sources of bias were considered: the tendentiousness of the collections, data analysis, the existence or not of impartiality in the researchers' choice of criteria.

Subsequently, the characteristics of the population were identified in different articles. Attempts were made to find the confounding effects on the outcomes obtained, such as gestational ages (GA) of entry in the research, treatment in the use of dosages of metformin, the design and comparison of patients' clinical characteristics included in each study and, subsequently, metformin administration period in the intervention groups. Consecutively, the search for recent statistical values with the highest impacts in comparation to with other previous results. At this moment, metformin was assessed in researches and physical activity programs, mainly in hospitals with multidisciplinary teams in order to verify the inte-

Figure 1

Diagram on bibliographic search adapted from PRISMA in the selection process (2008-2018).

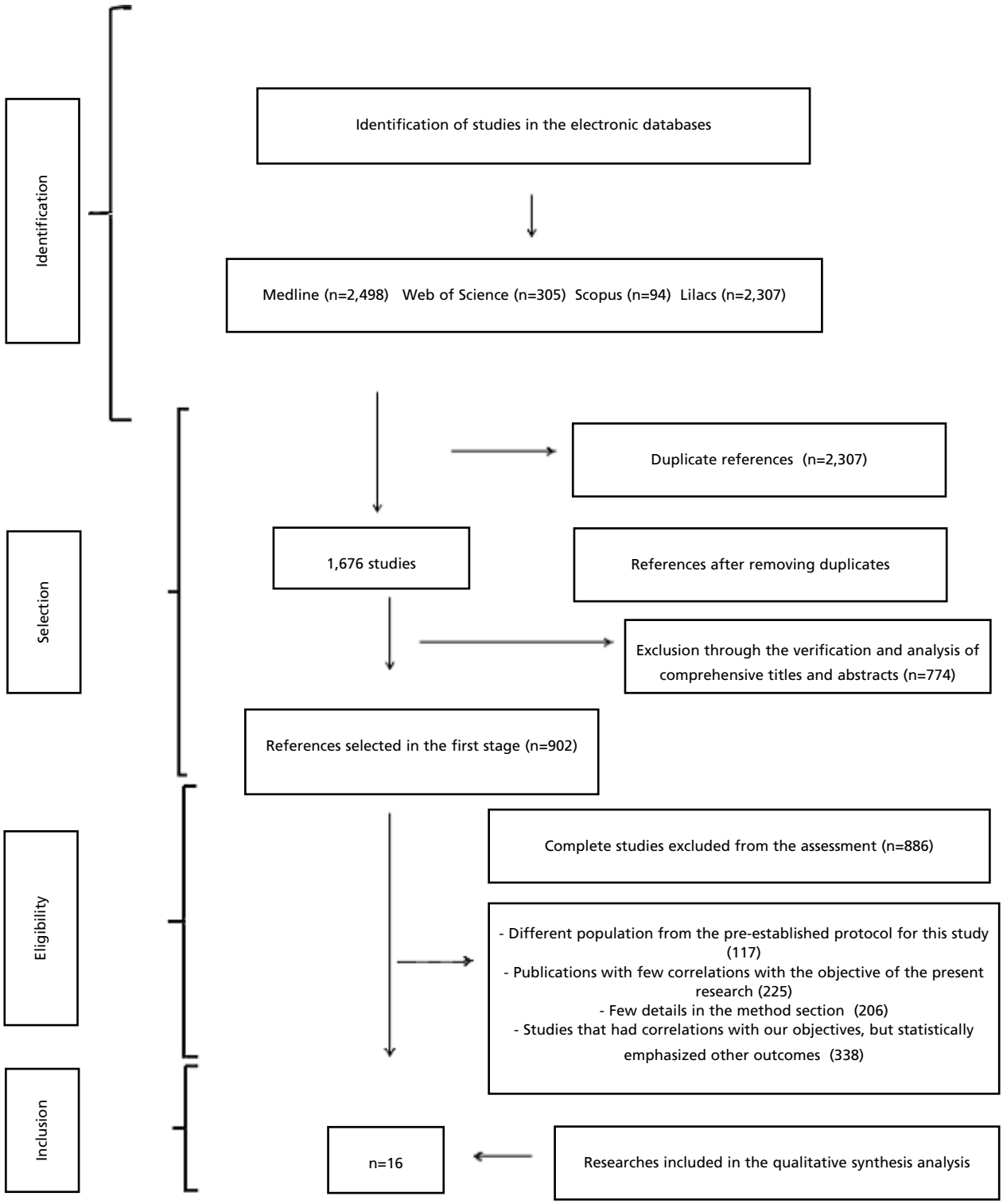

Table 1

Specific characteristics of clinical trial studies (2008-2018).

Author/year	Population	Type of study /Objective	Method	Outcomes
Koivusalo *et al*.[8] (2016)	293 pregnant women with a history of GDM and / or BMI pre-pregnancy ≥ 30 kg / m^2	Randomized controlled study Assess whether GDM can be prevented by moderate lifestyle intervention in pregnant women at high risk of the disease.	155 (intervention group): received instructions on physical activity and diet. 138 (control group): standard care	The incidence of GDM was 13.9% in the intervention group and 21.6% in the control group ([CI95% = 0.40-0.98%); *p*=0.044. The gestational weight gain was smaller in the intervention group (-0.58 kg (CI95%= -1.12 to -0.04 kg); *p*=0.037 adjusted.
Hayes *et al*.[9] (2015)	183 obese pregnant women	Randomized controlled study Explore patterns of physical activity and factors related to unfavorable intercurrence	Three different patterns of physical activity in three groups	Secondary outcome on gestational BMI did not reveal significant values in weight reduction.
Asbee *et al*.[10] (2009)	100 pregnant women	Randomized controlled study Physical exercise and change in lifestyle	57 (intervention group): received guidelines for physical activity and diet. 43 (Placebo group): standard service	The intervention group gained significantly less weight than the prenatal group (28.7+/- 12.5 pounds (lb) in comparsion to 35.6+/- 15.5 lb, *p*=0.01)
Brett *et al*.[20] (2015)	16 pregnant women	Randomized controlled study Assessment on physical activity and maternal quality diet in the expression of genes involving fatty acids, amino acids transport	Physical activity was measured directly with accelerometry, the diet composition was assessed in 24 h food recalls and the gene expression was measured with PCR arrangements.	Less expression on the transport of fatty acid 4 protein (FATP4) gene, with physical activity. There was a strong positive correlation between total sugar consumption (*p*<0.001).
Chiswick *et al*.[21] (2015)	400 pregnant women	Multicenter, double-blind, randomized study. Metformin effectiveness in obese pregnant women.	Placebo group Intervention group To test metformin effects on maternal-fetal outcomes. BMI and baby weight	Metformin has no teratogenic effects and is a low-cost drug.
Salles *et al*.[22] (2018)	164 obese pregnant women	Randomized controlled study To assess metformin effectiveness in the incidence of gestational diabetes mellitus (GDM) in obese pregnant women	82 control group (standard care). 82 intervention group (standard care in conjunction with metformin (1,000 mg / d)	There were no significant values observed in the BMI variation and in the GDM prevention.

continue

GDM =gestational *diabetes mellitus*; DM2 = *diabetes mellitus* type 2; CI95% = confidence interval 95%; FATP4 = transport of fatty acids; EG=epidimal fat; PCR = polymerase chain reaction; BW = body weight; 2HPG = 2 hour post-prandial blood; SHP = small heterodimer nuclear organ receptor; AMPK = protein kinase activated by adenosine monophosphate; PEPCK = phosphocnolpyruvate carboxylase.

Table 1 **concluded**

Specific characteristics of clinical trial studies (2008-2018).

Author/year	Population	Type of study /Objective	Method	Outcomes
Syngelaki *et al*.[24] (2016)	450 obese pregnant women Metformin (n=202) Placebo (n=198)	Randomized controlled study Identify the outcomes with the use of metformin in obese non-diabetic pregnant women .	Starting dose of metformin whether 1,000 mg/d in the first week and increased by 500 mg per week until reaching a maximum dosage of 3,000 mg/d in the fifth week	Median weight gain: 4.6 (1.3 to 7.2) metformin *vs* 6.3 (2.9 to 9.2) placebo
Beyuo *et al*.[26] (2015)	104 pregnant women with type 2 *diabetes mellitus* (DM2) or gestational *diabetes mellitus* (GDM).	Randomized controlled study Determine whether metformin alone or in combination with insulin is equally effective in controlling GDM.	The initial dose of metformin was 500 mg/d once daily and gradually increased over two (2) weeks to reach glycemic targets.	The two-hour postprandial blood glucose levels (2HPG) were significantly lower in the metformin group than in the insulin group (p=0.004).
Arshad et al.[27] (2016)	62 pregnant women with GDM	Clinical trial study Diet and physical activity control group Metformin 500 mg/d intervention group	To assess the effects of dietary control and metformin on placental morphology in gestational *diabetes mellitus* (GDM).	Metformin produced beneficial effects on placental morphology, being comparable to normal control in contrast to the diet group.
Rowan *et al*.[28] (2016)	751 pregnant women with GDM	Randomized controlled study Observe metformin acceptance compared to insulin and results	Of 363 women assigned to metformin, 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin. The primary composite outcome rate was 32.0% in the group designated for metformin and 32.2% in the insulin group.	More women in the metformin group than in the insulin group stated that they would choose to receive the assigned treatment again (76.6% *vs*. 27.2%, p<0.001).

GDM =*gestational diabetes mellitus*; DM2 = *diabetes mellitus* type 2; CI95% = confidence interval 95%; FATP4 = transport of fatty acids; EG=epidimal fat; PCR = polymerase chain reaction; BW = body weight; 2HPG = 2 hour post-prandial blood; SHP = small heterodimer nuclear organ receptor; AMPK = protein kinase activated by adenosine monophosphate; PEPCK = phosphocnolpyruvate carboxylase.

ractivity among professionals.

In other types of studies, the bias was assessed by an adaptation of the Downs and Black scale.[16] The authors observed a clear description of the factors in the checklist contained in the scale. It is worth noting that the Downs and Black scale assesses studies not related to randomized clinical trials; contains 27 questions / items applicable to assess the quality and bias of articles. It was organized as follows: each study group obtained a specific score; cohort articles with a maximum score of 22; cross-sectional studies with a maximum of 12 points and for case-control studies a maximum score of 27 points. To guarantee the proportion of the

results among categories, the score obtained in each article was divided by the maximum possible score for each of the established groups. The study to reach the inclusion criterion should achieve a score above 70% in the established score.

Interventions and assessed outcomes:

- Physical activity programs, gene regulation and outcomes;
- Metformin, gene regulation and outcomes.

Results

The scientific studies that participated in this systematic review were found between the years (2000-2017). Through the selection of the database, 3,983 articles were identified on the topic of interest. After removing 2,307 duplicate articles, 1,676 articles in English, Portuguese and Spanish were obtained for the analysis. Consecutively, a verification on the most comprehensive titles and abstracts: 774 articles were eliminated, resulting in 902 articles in the first stage of the study and eligibility for the second stage on the systematic review. Of the 902 studies analyzed in full, 886 were excluded, in Figure 1 shows more detailed reasons.

In this present systematic review, after applying the selection consistent with the criteria mentioned above, 16 scientific studies were obtained for inclusion,of which 81.25% (n=13) were clinical trials regarding diet programs, physical activity, use of metformin and possible outcomes (Table 1); 18.75% (n=3) were cohort on the causes of obesity during pregnancy and its association with GDM and preventive therapies.

Using the manual for interventions on systematic reviews, 13 studies on clinical practices were obtained, of which 8 (61.53%) studies had a low risk of bias and 5 (38.46%) had a moderate risk of bias.

Concerning other types of studies, absolute and relative values were observed in the Downs and Black scale.The score and the absolute and relative numbers were presented as follows: The results of this review found three cohort studies with the pre-established purpose and greater relation to the theme, 16/22 (72.72%),[3] 18/22 (81.81%)[5] and 16/22 (72.72%).[11] The absolute and relative numbers found were at least 72.72% and at most 81.81%, indicating an mean score of 75.75%.

In regard to treatment and prevention of GDM, the present study identified a difference of 1.21 less glucose two hours (2HPG) in the postprandial period in patients in the metformin group compared to the group that administered insulin and a greater acceptance for metformin hydrochloride in comparation to those who used insulin, and a 49.4% difference between the two groups. In non-diabetic obese pregnant women, scientific findings demonstrated that pregnant women who administered metformin, the average weight gain reduction was 1.7 kg less compared to the placebo group and reduced chances for the incidence of preeclampsia of (0.24; CI95%=0.10–0.61) (p<0.01).

The results showed that physical activity and food programs for obese pregnant women have not demonstrated values of greater significance. However, there is a need for greater awareness and changes in habits of obese women during the gestational period. Scientific publications have been showing the effects of the pharmacokinetic action of metformin hydrochloride with greater control on gestational weight gain, as well as the need for further research on the dosage and / or regarding the use of the drug. Contemporary studies are necessary, with the possibility of primary therapies aiming to change lifestyles combined with specific metformin dosages at pregnancy, since there is a similarity between both methods in activating the protein kinase enzyme activated by adenosine monophosphate (AMPK).

Discussion

Physical activity and gene regulation programs

Obesity is strongly related to the increased risk of pathologies, among them are dyslipidemia, type 2 *diabetes mellitus* (DM2) and insulin resistance.[17] There is a difficulty in carrying out refined treatment methods to adapt obese pregnant women to the ideal weight parameters during pregnancy.[18]

Among the most recommended therapeutic methods for obesity during pregnancy and possible unfavorable outcomes are physical activity and nutritional programs. Physical activity can activate AMPK and reduce conversions of "*aglicanos*" compounds.[19]

A recent study showed that pregnant women who followed the guidelines on physical activities and diet composition altered gene expression that relates to fatty acid transport. Active women had lower expression of fatty acid transport protein 4 (FATP4).[20] The study also revealed a strong positive correlation between total sugar consumption and glucose transport 1 (GLUT1) (p<0.001).

Variations in maternal physical activity and diet composition altered the expression of genes involved in the transport of fatty acids, amino acids, glucose and signaling of the target rapamicide factor

(mTOR), which regulates energy in the intracellular space.[19] Physical activity activates AMPK in several ways and in different routes. In order to reduce gluconeogenesis, physical exercise increases the consumption of glucose by the organism and, subsequently, there is a negative regulation of the genes encoded in the MO25 protein.[19] When the MO25 protein is suppressed, there is a positive regulation of the AMPK coding genes that activates the regulatory CREB protein 2 (TORC2) transducer, which has the function of controlling protein activities and inhibiting liver conversions of "*aglicanos*" compounds (pyruvate), reducing gluconeogenesis.[19]

Metformin, gene regulation and outcomes

Due to the close relation between obesity and GDM, prevention on both is of utmost importance in order to reduce immediate adverse pregnancy results, complications, risks in childbirth and costs directed to the treatment of GDM.[21]

Metformin has been used for gestational obesity and the prevention of GDM.[22] The strategy to prevent GDM can be added in a woman's lifestyle, nutritional interventions, physical activity programs and pharmacological measures.[23] As for the use of the drug in obese non-diabetic pregnant women, a study in 2017 showed a lower median weight gain when comparing metformin and placebo 4.6 (1.3 to 7.2) *vs* 6.3 (2.9 to 9.2) respectively and, in the outcomes of pre-eclampsia (PE), a reduced odds ratio for the metformin group (OR=0.24; CI95%=0.10–0.61) (p<0.01),[24] since PE has strong relation with gestational obesity and GDM.[25]

The use of the drug has been shown to be effective in reducing plasma glucose and glycated hemoglobin in patients with DM2.[13] Another study comparing metformin with insulin decreased glucose two hours (2HPG) in the postprandial period in patients with DM2, identifying the values of (7.84 ± 1.43) in the metformin group *versus* (9.05 ± 1.89) in the insulin group (p=0.004) (p<0.01).[26]

Metformin is seen as a safe drug used to control blood glucose, reduce BMI, cholesterol levels and fractions, and is not considered to be teratogenic.[13,27] Intolerance to a drug is an important factor in its acceptance.[26] A study showed better acceptance with the administration of metformin compared to insulin (76.6% *vs* 27.2%), respectively (p<0.01).[28]

The drug appears to induce gene expression of the small nuclear orphan heterodimer receptor (SHP; NR0B2), which contains an active constituent for AMP activation via PK protein kinase (AMPK).[29] Authors have made evident that the expression of the hepatocyte SHP gene can be induced by metformin inhibiting the activity of cholesterol metabolism mediated by the hepatocyte nuclear factor 4-alpha or by the encoded protein 2 (FoxA2) of phosphoenolpyruvate carboxokinase (PEPCK). Thus, the researchers observed that metformin, by inhibiting these nuclear factors by activating SHP and AMPK, reduces hepatic gluconeogenesis and the formation of lipids.[29]

However, specialists express the need for extremely careful studies that improve the dosage to be applied according to its pharmacodynamics and pharmacokinetic properties during pregnancy, since there may be uncertainty about the use of the drug.[30]

It can be highlighted as a limiting aspect in this research, the limited number of scientific researches with the use of metformin in obese non-diabetic pregnant women and the method on different studies, the absence of information about what was being used, both by the examiner and the examinee (double-blind). This way, they would reduce the expectations of pregnant women, as well as the consequences of the placebo effect. The strong point was the laboratory researches that focused on the balance of genetic signals that control gluconeogenesis, which comes to elucidate and add to a new perspective weight reduction in obese pregnant women and prevention of GDM. Studies are suggested with a larger number of pregnant women contemplating the double blind and with a domain more directed on gestational BMI and GDM from the administration of metformin.

Metformin has been gaining its autonomy with better acceptance by pregnant women. The drug is similar to physical activity when activating AMPK and, in an adjunctive way, it can be an important drug along with main treatments that propose changes in pregnant women's lifestyle to reduce weight gain and prevent GDM, with a need to a better understanding of the ideal dosage. Thus, the study suggests that the use of metformin is not only for the prevention and complications of GDM, but also with a strictly careful investigation to allow its use to obese non-diabetic pregnant women.

Authors' contribution

Nascimento IB contributed to the design, interpretation, results analysis and the writing of the method. Fleig R helped to write the results, collect and interpret data. Souza MLR performed the design and writing of the introduction, data collection and discussion. Silva JC contributed with critical review, coordination, analysis, interpretation. All authors approved the final version of the article.

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