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Review article

Diabetes mellitus during pregnancy as a risk factor for neonatal complications: systematic review and meta-analysis

Diabetes mellitus na gestação como fator de risco para complicações neonatais: revisão sistemática e metanálise

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Abstract

Objective: to carry out a systematic review and meta-analysis of neonatal complications resulting from GDM. **Materials and Methods**: this is a systematic review following the PRISMA statement methodology, which is based on the following guiding question "What are the impacts of gestational Diabetes mellitus on the health of the newborn child?". After this, the PICO methodology was used, with the population being pregnant women, the intervention would be gestational diabetes, control group healthy pregnant women and the outcomes analyzed complications in the neonatal period. The Virtual Health Library (VHL), LILACS, SciELO and PubMed were used as database. After the process, 12 studies were selected on the impacts of the approach diagnosis and therapy of GDM in newborn health. **Results:** most of the publications were published in 2019. The authors of the articles were from Australia, Pakistan, Switzerland, Portugal, Brazil, Iran and Egypt. Of the 12 articles selected, 6 were cohort studies and the other half were randomized clinical trials. A total population of 8553 diabetic pregnant women was obtained. The meta-analysis revealed that the use of metformin by pregnant women was associated with a lower risk of neonatal hypoglycemia and neonatal jaundice. The frequency of neonatal hypoglycemia in these pregnancies of mothers with gestational diabetes was 9%, neonatal macrosomia 14% and use of neonatal intensive care unit (ICU) 12%. **Conclusion:** appropriate management of GDM during pregnancy is crucial to reduce maternal-fetal risks and improve neonatal outcomes.
Keywords: Gestational Diabetes. Pregnancy. Diabetes Complications. Pregnancy Complications.

Resumo

Objetivo: realizar uma revisão sistemática e metanálise das complicações neonatais decorrentes do diabetes mellitus gestacional (DMG). **Materiais e Métodos:** trata-se de uma revisão sistemática seguindo a metodologia PRISMA *statement*, que possui como base a seguinte pergunta norteadora "Quais os impactos do Diabetes mellitus gestacional na saúde da criança recém-nascida?". Após, foi utilizada a metodologia PICO, sendo a população mulheres grávidas; a intervenção seria o diabetes gestacional; grupo controle grávidas saudáveis e os desfechos analisados as complicações no período neonatal. Foram utilizadas as bases Biblioteca Virtual em Saúde (BVS), LILACS, SciELO e PubMed. Após o processo de análise, foram selecionados 12 estudos sobre os impactos da abordagem diagnóstica e terapêutica do DMG na saúde do recém-nascido. **Resultados:** a maior parte das publicações foi de 2019. Os autores dos artigos eram da Austrália, Paquistão, Suíça, Portugal, Brasil, Irã e Egito. Dentre os 12 artigos selecionados, seis tratavam-se de estudo coorte e a outra metade eram ensaios clínicos randomizados. Obteve-se uma população total de 8.553 gestantes diabéticas. A metanálise revelou que o uso de metformina pelas gestantes esteve associado a um menor risco de hipoglicemia neonatal e icterícia neonatal. A frequência de hipoglicemia neonatal nessas gestações de mães portadoras de diabetes gestacional foi de 9%, macrossomia neonatal 14% e uso de CTI neonatal 12%. **Conclusão:** o manejo adequado do DMG durante a gravidez é crucial para reduzir os riscos materno-fetais e melhorar os resultados neonatais.
Palavras-chave: Diabetes gestacional. Gravidez. Complicações do diabetes. Complicações na gravidez.

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Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by persistent hyperglycemia, resulting from a deficiency in the production or action of insulin, or both mechanisms[1]. During pregnancy, two types of hyperglycemia can be identified: diabetes mellitus diagnosed during pregnancy (DMDP), also known as overt diabetes, and gestational diabetes mellitus (GDM), which are distinguished by the level of hyperglycemy[2]. GDM presents risks for both mother and fetus and newborn, usually being diagnosed in the second or third trimester of pregnancy. This type of diabetes may be transient or persist after delivery, representing an independent risk factor for the future development of type 2 diabetes[3].

Changes in maternal blood sugar levels are common during pregnancy. About 16% of live births are from women who presented some type of hyperglycemia during pregnancy, with 8% of these cases occurring in mothers with pregestational diabetes[1]. In Brazil, it is estimated that 18% of the pregnant women assisted by the Brazilian Unified Health System (UHS) meet the current diagnostic criteria for GDM. Risk factors include: obesity, maternal age over 25 years, family and/or personal history of diabetes, twin pregnancy, hypertension, dyslipidemia, smoking, sedentary lifestyle, previous macrosomia, and fetal death without apparent cause, among others[4].

To address the growing prevalence of GDM globally, it is essential to perform routine screening for GDM during prenatal care. However, only few countries adopt the universal practice of routinely testing pregnant women[5]. In Brazil, it is recommended to investigate pre-existing diabetes in the first trimester of pregnancy, ideally at the first prenatal consultation, through routine tests, since these patients have a higher risk of fetal malformations and other gestational and neonatal complications[2,6].

It is important to note that the reference value for fasting blood glucose during pregnancy is different from the one considered normal for non-pregnant women, being below 92 mg/dL at any stage of pregnancy. Values between 92 and 126 mg/dL are diagnostic of GDM at any time during pregnancy, and above 126 mg/dL indicate pre-gestational DM. All pregnant women without a previous diagnosis of diabetes or GDM should perform the Oral Glucose Tolerance Test (OGTT) with 75g of glucose, after fasting at least 8 hours, between 24 and 28 weeks of gestation, with glucose collection on fasting, 1 and 2 hours after ingestion, according to the recommendations of the IADPSG and WHO[2,6].

GDM screening is crucial, since pregnancy is a condition known to increase the risk of diabetes due to the production of hormones and enzymes by the placenta that degrade insulin, leading to a compensatory increase in insulin production and insulinresistence[7]. This process intensifies with the advance of pregnancy, being well defined in the 24th week. If the maternal pancreatic β cells are unable to respond adequately to the increasing demand for insulin, due to the increased fetal glucose

need, an imbalance in glycemic levels occurs, favoring the development of GDM. Hyperglycemia during pregnancy increases the risk of maternal and perinatal morbidity, with medium- and long-term consequences for mother and child[8].

The objective of this study was to analyze, through a systematic review and meta-analysis, gestational diabetes mellitus and complications in the neonatal period.

Materials and Methods

This is a systematic literature review, prepared following the guidelines of the methodology Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement), which is based on the following guiding question "What are the impacts of gestational diabetes mellitus on the health of the newborn child?". After this, the PICO methodology was used, being pregnant women the population, the intervention would be gestational diabetes, healthy pregnant women control group and outcomes analyzed the complications in the neonatal period.

The data collection in the Virtual Health Library (VHL), LILACS, SciELO and PubMed databases used the descriptors (Table 1) combined with the Boolean operators AND/OR and in English and Portuguese. The materials were selected by two authors independently, without disagreement between the parties.

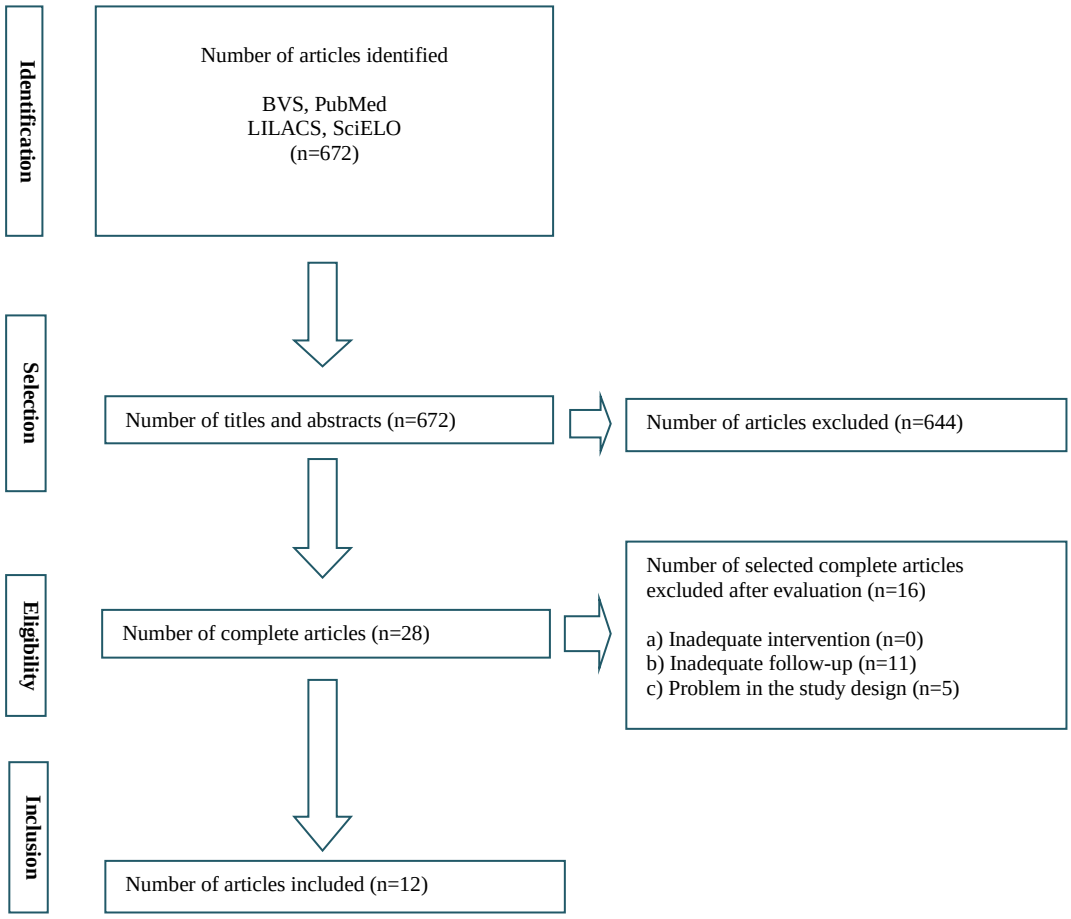
Table 1. Descriptors indexed in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) used in the search strategy.

Descriptors in Portuguese	Descriptors in English
Diabetes Gestacional AND Recém-nascido	*Gestational Diabetes AND Newborn*
Diabetes Gestacional AND Saúde da criança	*Gestational Diabetes AND Child health*
Diabetes Gestacional AND Diagnóstico	*Gestational Diabetes AND Diagnosis*
Diabetes Gestacional AND Tratamento	*Gestational Diabetes AND Treatment*

Original studies, available in full in English and Portuguese, published between 2013 and 2023, which reported the neonatal impacts of GDM were included. Abstracts, letters to the editor, theses and dissertations, expert opinions, editorial articles and case reports were excluded, as well as studies in duplicity.

The search was carried out on January 3, 2023. At first, 672 search results were found from the above descriptors and, after applying the inclusion and exclusion criteria, this number was reduced to 126 studies. Of these, 28 were chosen for analysis and separated by reading the title, abstract and keywords. Finally, 12 studies were selected to be read in full (Figure 1).

Figure 1. Flowchart of the article screening process for the review.



The New Castle Ottawa questionnaire was used to evaluate the quality of the identified articles and a data collection form for critical analysis of the studies, composed by the following information: title; authors; year; place of execution of the study; sample; objective; study design, methodological summary and main results. Chart 1 The Revman software was used for the evaluation of the risk of bias. Chart 2

For the preparation of the meta-analysis, models of random effects, heterogeneity tests and bias funnel graph were used. Regarding the heterogeneity analysis, the Q test of Cochran and the I^2 were used, considering acceptable values of I^2 below 25%. In case of I^2 above the values of 25%, it was chosen to withdraw the outliner work for correction of this value.

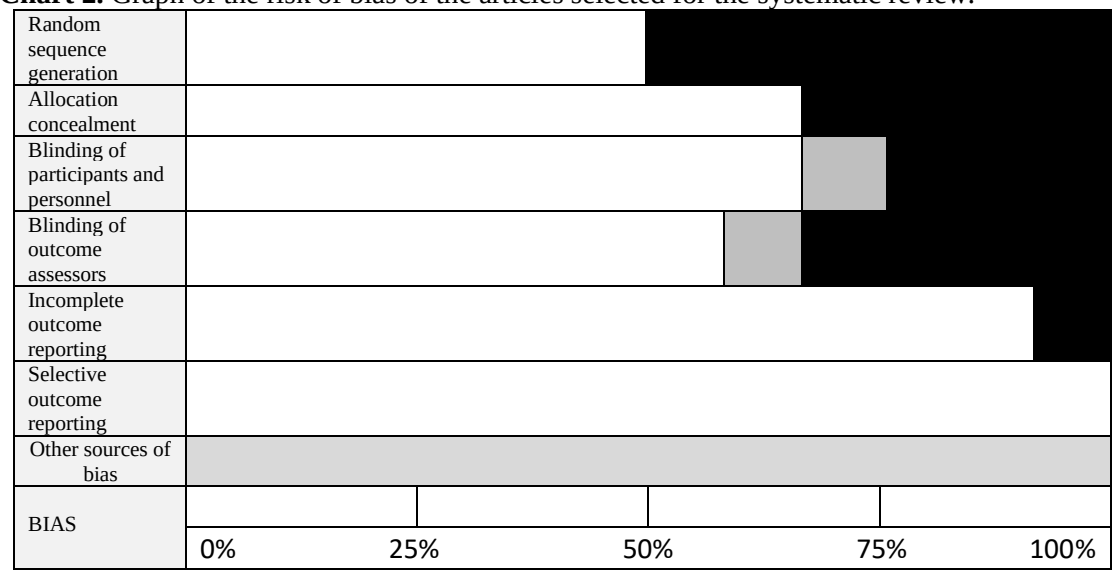
To calculate the weight or contribution of each study, models of random effects were used. In this case, the weights were assigned based on both variability within the studies and between the studies.

Chart 1. Summary of the risk of bias of the articles selected for the preparation of the systematic review.

Evaluated bias	Mesdaghinia *et al.*, 2013[18]	Ibrahim *et al.*, 2014[17]	Ainuddin *et al.*, 2015[19]	Arshad *et al.*, 2017[16]	Feig *et al.*, 2017[10]	Silva *et al.*, 2017[15]	Absalom *et al.*, 2019[12]	Mendes *et al.*, 2019[13]	Mendes *et al.*, 2019[14]	Scholtens *et al.*, 2019[9]	Barnes *et al.*, 2022[20]	Corcillo *et al.*, 2022[11]
Random sequence generation	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	Low Risk of Bias	High Risk of Bias	High Risk of Bias
Allocation concealment	High Risk of Bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
Blinding of participants and professionals	Moderate Risk of Bias	High Risk of Bias	Low Risk of Bias	High Risk of Bias	High Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
Blinding of outcome assessors	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	Low Risk of Bias	Moderate Risk of Bias	High Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
Incomplete outcome	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	High Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
Selective outcome reporting	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias
Other sources of bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Unclear Risk of Bias	Low Risk of Bias	Low Risk of Bias	Low Risk of Bias

Source: https://training.cochrane.org/online-learning/core-software/revman

Chart 2. Graph of the risk of bias of the articles selected for the systematic review.



Low risk of bias.
Unclear risk of bias.
High risk of bias.

Source: https://training.cochrane.org/online-learning/core-software/revman

To calculate the sensitivity of the meta-analysis, individual studies were removed sequentially from the observation of the funnel plot in order to reduce bias and reduce heterogeneity. The confidence interval used was 95% and significant p-value <0.05.

The impact of insulin (control group) versus metformin use by pregnant women was evaluated on the following variables: need for ICU use by the newborn, neonatal respiratory stress, hypoglycemia and jaundice.

Among the studies presented in the systematic review, the prevalence of the following complications were evaluated: macrosomia, hypoglycemia, need for neonatal ICU.

Results

Among the studies evaluated for this review, most of the publications were published in 2019 (n=4) and 2017 (n=3). The authors of the articles were of multicenter origin (n=3), Australia (n=2), Pakistan (n=2), Switzerland (n=1), Portugal (n=1), Brazil (n=1), Iran (n=1) and Egypt (n=1). The starting point used was the study with pregnant diabetic women, focusing on perinatal outcomes associated with the therapy instituted. Among the 12 selected articles, half (n=6) were cohort studies and the other half (n=6) were randomized clinical trials, and a total of 8553 diabetic pregnant women were evaluated. Charts 1 and 2 present the risk assessment of the present bias. Chart 3 presents the general characteristics of each selected work and chart 4 evaluates the quality of each selected article.

Chart 3. Description of selected studies (n=12) according to author and year, design, sample and setting, objective and main results.

Author and year	Design	Sample and setting	Objective	Main results
Mesdaghinia *et al.*, 2013[18]	Randomized Clinical Trial	Study conducted with 200 women with GDM at 24–34 weeks comparing Metformin versus Insulin	To compare neonatal outcomes of metformin and insulin in the treatment of gestational diabetes	Metformin may be an excellent alternative to insulin in the treatment of GDM. It is associated with fewer complications for the fetus and maternal acceptance may be better.
Ibrahim *et al.*, 2014[17]	Randomized Clinical Trial	90 women with diabetes mellitus during pregnancy were approached and randomly allocated into two groups, one with the addition of Metformin to insulin therapy and the other with increased doses of Insulin.	To assess the impact of adding oral metformin to insulin therapy in pregnant women with insulin-resistant diabetes mellitus	Perinatal morbidity and mortality and neonatal hypoglycemia were lower in insulin-resistant GDM women who received additional metformin treatment.
Ainuddin *et al.*, 2015[19]	Randomized Clinical Trial	Study conducted with 150 patients with type 2 diabetes diagnosed before pregnancy and cases of newly diagnosed diabetes during pregnancy	To assess the effects of metformin therapy on type 2 diabetes mellitus in pregnancy and compare it with standard insulin treatment.	Metformin alone or with additional insulin is an effective and inexpensive treatment option for patients with type 2 diabetes mellitus in pregnancy with improved neonatal outcomes.
Arshad *et al.*, 2017[16]	Randomized Clinical Trial	Clinical trial conducted with 71 women with GDM, comparing the use of Metformin and insulin between 2010-2012	To assess and compare maternal-fetal outcomes and glycemic control in gestational diabetic women treated with metformin versus insulin.	Metformin produced better effects on maternal-fetal outcomes and glycemic control compared with insulin in GDM.
Feig *et al.*, 2017[10]	Randomized Clinical Trial	Multicenter, open, randomized and controlled study, with 325 pregnant women in 31 hospitals in seven countries	To examine the effectiveness of continuous glucose monitoring (CGM) on maternal glucose control and obstetric and neonatal health outcomes.	Continuous glucose monitoring (CGM) has demonstrated benefits for pregnant women with pre-existing diabetes, including improved HbA1c levels and neonatal outcomes in women with type 1 diabetes (T1D). However, intermittent use of CGM during pregnancy did not result in significant changes in neonatal outcomes in either T1D or gestational diabetes.
Silva *et al.*, 2017[15]	Cohort	Cohort of 705 pregnant women with GDM treated at a public maternity hospital from July 2010 to August 2014	To compare different neonatal outcomes according to the different types of treatments used in the management of gestational diabetes mellitus.	Women with GDM treated with Metformin had a lower chance of having babies with large-for-gestational-age status, and women treated with insulin had a lower risk of preterm birth.
Absalom *et al.*, 2019[12]	Cohort	The study involved 1,233 adult women with GDM who gave birth at a hospital in Melbourne, Australia, between July 2015 and May 2017.	To examine the associations between dietary intervention in women with GDM and maternal and neonatal health outcomes.	Dietary intervention plays a fundamental role in optimizing maternal and neonatal health outcomes for women with GDM, such as reducing the need for newborns to be admitted to intensive care units.

Mendes *et al.*, 2019[13]	Cohort	Between 2016 and 2017, 85 women with singleton pregnancies and GDM from an obstetric center were included in the study. Glycemic markers were compared between mothers of newborns with and without complications.	To investigate associations between glycated hemoglobin (HbA1c), glycated albumin (GA) and fructosamine with neonatal birth weight in GDM.	The association between glycated hemoglobin, glycated albumin, and fructosamine levels in mothers with GDM may serve as a predictor of neonatal birth weight and infants with large-for-gestational-age status.
Mendes *et al.*, 2019[14]	Cohort	Prospective cohort comprised 82 women with GDM and their newborns, enrolled between November 2016 and September 2017.	To investigate whether glycated albumin, fructosamine and HbA1c are associated with neonatal complications in newborns of pregnant women with GDM.	Elevated glycated albumin and fructosamine values were associated with particular perinatal complications in newborns of mothers with GDM, discriminating better between mothers of newborns with and without complications than HbA1c.
Scholtens *et al.*, 2019[9]	Cohort	International observational investigation that established associations of maternal glucose with adverse perinatal outcomes in 4832 eligible mother-child pairs from 2013-2016.	To analyze associations of maternal glycaemia during pregnancy with childhood glucose outcomes in the Hyperglycemia and Adverse Pregnancy Outcome cohort.	Glycemic dyscontrol with hyperglycemia and maternal overweight during pregnancy were significantly associated with increased hyperglycemia, insulin resistance and abdominal adiposity in offspring in adulthood
Barnes *et al.*, 2022[20]	Cohort	Retrospective audit of clinical data (2016–2019) for 1034 women with singleton pregnancies with gestational diabetes was performed in a multiethnic cohort.	To evaluate the impact of achieving a personalized weight goal in addition to conventional glycemic control after diagnosis of GDM on maternal and neonatal outcomes.	Weight control after a diagnosis of GDM confers additional benefits to the use of hypoglycemic agents, resulting in lower average insulin doses and lower rates of large-for-gestational-age infants, without increasing the risk of small-for-gestational-age infants.
Corcillo *et al.*, 2022[11]	Cohort	Prospective observational cohort of 780 women with GDM followed in a Diabetes and Pregnancy Unit of a Hospital in Switzerland, between 2012-2017.	To assess short- and long-term neonatal and obstetric risk factors and outcomes in a clinical context	Despite similar treatment, women with risk factors had more neonatal and obstetric complications, but had especially more frequent adverse metabolic outcomes in the short and long term.

CGM: Continuous glucose monitoring. GDM: Gestational diabetes mellitus. DM1: Type-1diabetes mellitus.

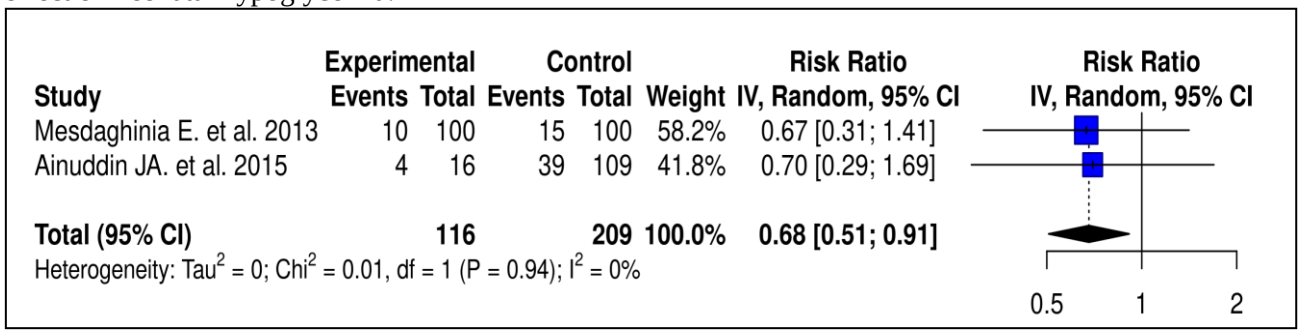
Chart 4. Application of the Newcastle-Ottawa Quality Assessment Scale tool to assess the quality of studies with Cohort and Case-control methodologies used in this Systematic Review.

Randomized studies			Silva *et al.*, 2017[15]	Absalom *et al.*, 2019[12]	Mendes *et al.*, 2019[13]	Mendes *et al.*, 2019[14]	Scholtens *et al.*, 2019[9]	Barnes *et al.*, 2022[20]	Corcillo *et al.*, 2022[11]
Selection	1) Representativeness of the exposed cohort	a) truly representative of the average _____ (describe) in the community	X	X	X	X	X	X	X
		b) somewhat representative of the average _____ in the community							
		c) selected group of users eg nurses, volunteers							
		d) no description of the derivation of the cohort							
	2) Selection of the non exposed cohort	a) drawn from the same community as the exposed cohort		X					
		b) drawn from a different source							
		c) no description of the derivation of the non exposed cohort	X		X	X	X	X	X
	3) Ascertainment of exposure	a) secure record (eg surgical records)	X	X	X	X		X	X
		b) structured interview					X		
		c) written self report							
		d) no description							
	4) Demonstration that outcome of interest was not present at start of study	a) yes	X	X	X	X	X	X	X
		b) no							
Comparability	1) Comparability of cohorts on the basis of the design or analysis	a) study controls for _____ (select the most important factor)	X	X	X	X	X	X	X
		b) study controls for any additional factor (This criteria could be modified to indicate specific.	X	X	X	X		X	X
Outcome	1) Assessment of outcome	a) independent blind assessment					X		
		b) Record linkage	X	X	X	X		X	X
		c) self report							
		d) no description							
	2) Was follow-up long enough for outcomes to occur	a) yes (select an adequate follow up period for outcome of interest)	X	X	X	X	X	X	X
		b) no							
	3) Adequacy of follow up of cohorts	a) complete follow up - all subjects accounted for	X	X	X	X	X	X	X
		b) subjects lost to follow up unlikely to introduce bias - small number lost - >____ % (select anadequate %) follow up, or description provided of those lost)							
		c) follow up rate <____% (select an adequate %) and no description of those lost							
		d) no statement							

Cohort studies			Mesdaghinia *et al.*, 2013[18]	Ibrahim *et al.*, 2014[17]	Ainuddin *et al.*, 2015[19]	Arshad *et al.*, 2017[16]	Feig *et al.*, 2017[10]
Selection	1) Is the case definition adequate?	a) yes, with independent validation	**X**				
		b) yes, eg record linkage or based on self reports		**X**	**X**	**X**	**X**
		c) no description					
	2) Representativeness of the cases	a) yes, with independent validation					
		a) consecutive or obviously representative series of cases	**X**	**X**	**X**	**X**	**X**
		b) potential for selection biases or not stated.					
	3) Selection of Controls	a) community controls					
		b) hospital controls	**X**	**X**	**X**	**X**	**X**
		c) no description					
	4) Definition of Controls	a) no history of disease (endpoint)	**X**	**X**	**X**	**X**	**X**
		b) no description of source.					
Comparability	1) Comparability of cases and controls on the basis of the design or analysis	a) study controls for _____ (Select the most important factor.)	**X**	**X**	**X**	**X**	**X**
		b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)		**X**	**X**		**X**
Exposure	1) Ascertainment of exposure	a) secure record (eg surgical records)	**X**	**X**	**X**	**X**	**X**
		b) structured interview where blind to case/control status					
		c) interview not blinded to case/control status					
		d) written self report or medical record only					
		e) no description					
	2) Same method of ascertainment for cases and controls	a) yes	**X**	**X**	**X**	**X**	**X**
		b) no					
	3) Non-Response rate	a) same rate for both groups	**X**	**X**	**X**		
		b) non respondents described					
		c) rate different and no designation					

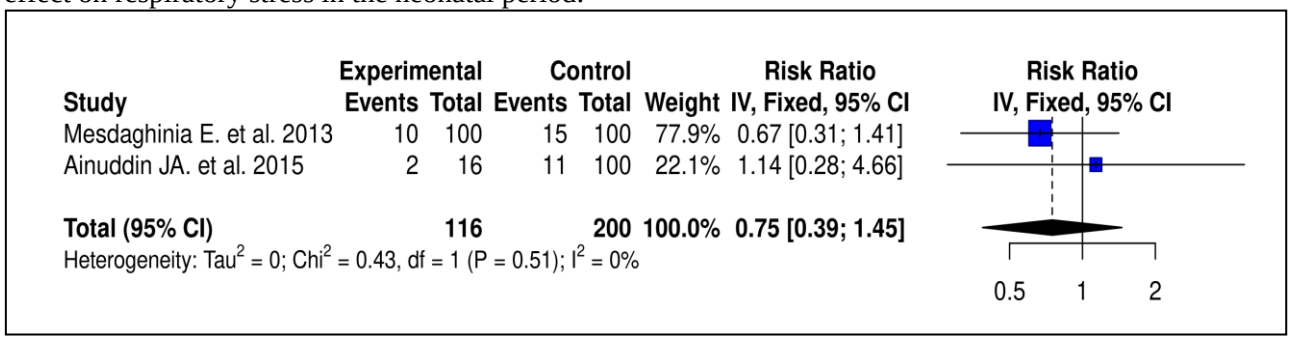
The meta-analysis revealed that metformin use by pregnant women was associated with a lower risk of neonatal hypoglycemia. There was low heterogeneity between studies (I^2=0) with statistical significance. The relative risk for hypoglycemia showed protective effect of metformin when compared to insulin use (RR 0.68) (Graph 1).

Graph 1: Meta-analysis of the effect of maternal use of metformin versus insulin during pregnancy and its effect on neonatal hypoglycemia.



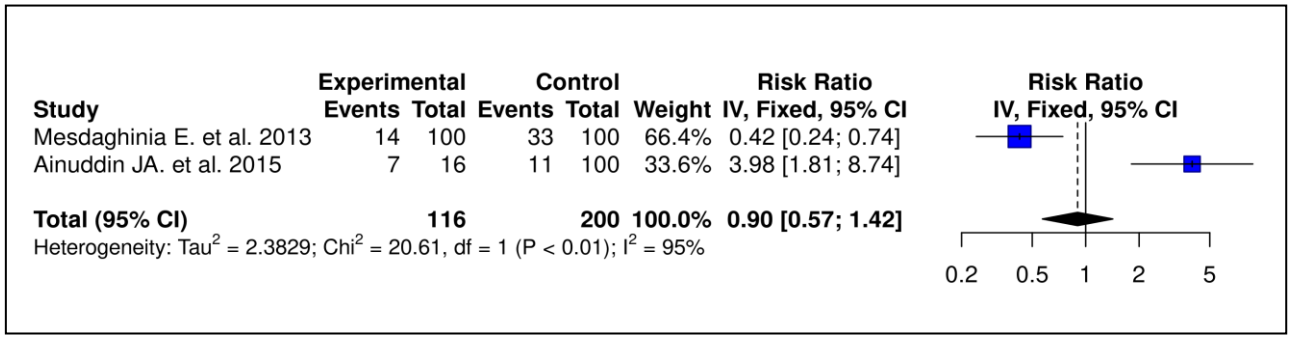
It was also shown that the use of metformin by pregnant women was not associated with a lower risk of neonatal respiratory stress. Low heterogeneity was observed between the studies (I^2=0%), however, without statistical significance (Graph 2).

Graph 2. Meta-analysis of the effect of maternal use of metformin versus insulin during pregnancy and its effect on respiratory stress in the neonatal period.



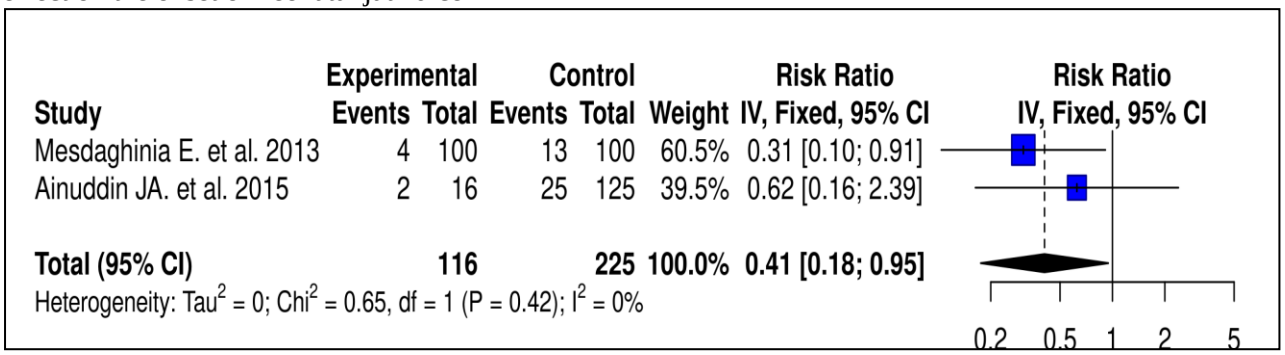
The meta-analysis data revealed that metformin use by pregnant women was not associated with a lower risk of admission to neonatal ICU. There was high heterogeneity between the studies (I^2=95%) and no statistical significance (Graph 3).

Graph 3. Meta-analysis of the effect of maternal use of metformin versus insulin during pregnancy and its effect on the need for neonatal ICU.



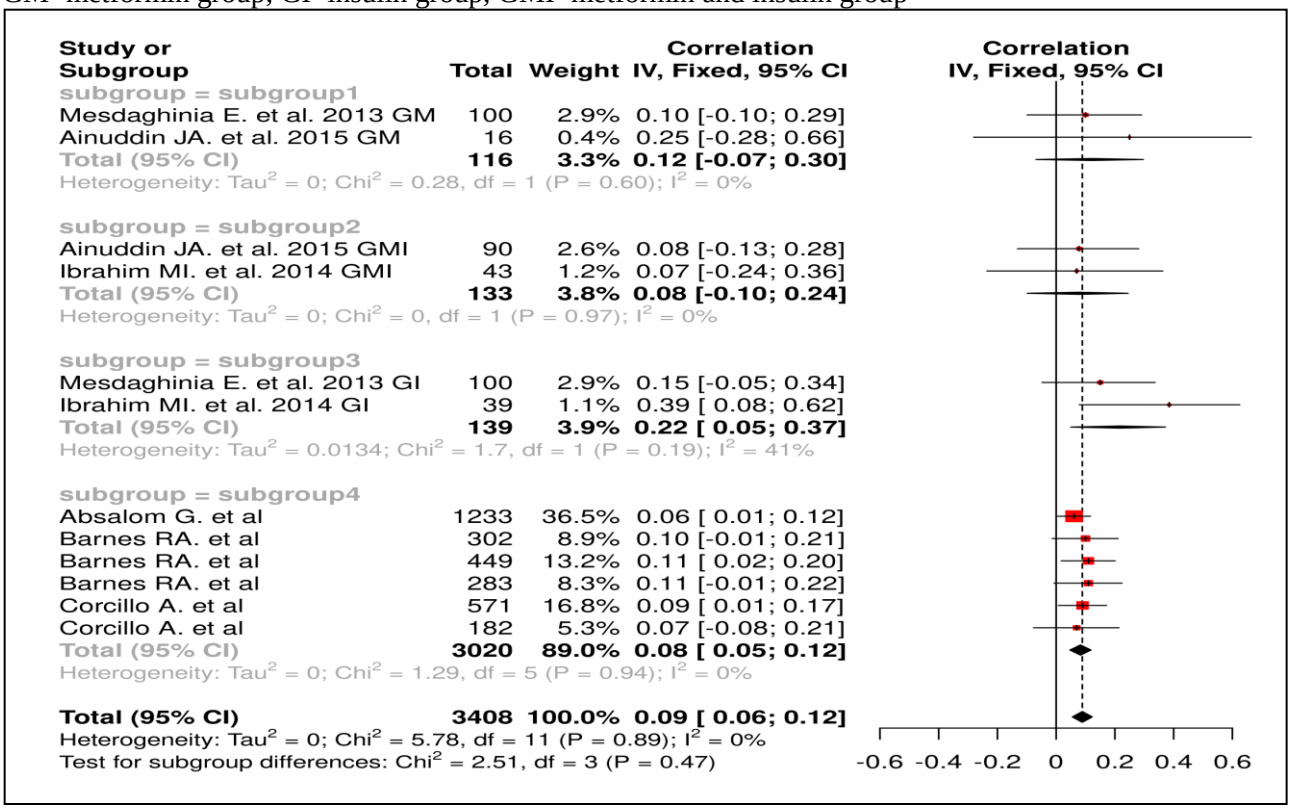
The data in the meta-analysis revealed that metformin use by pregnant women was associated with a lower risk of neonatal jaundice, (RR 0.41). There was low heterogeneity between studies (I^2=0%) and statistical significance (Graph 4).

Graph 4. Meta-analysis of the effect of maternal use of metformin versus insulin during pregnancy and its effect on the onset of neonatal jaundice



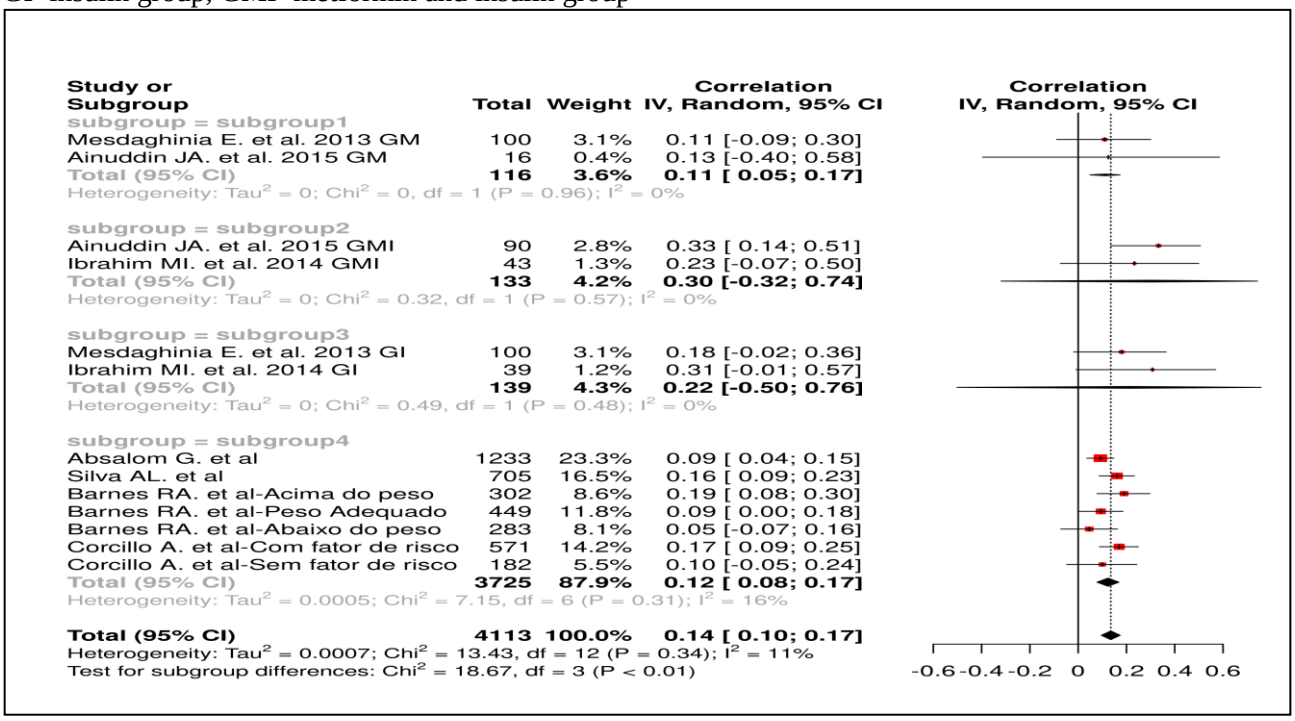
The meta-analysis comparing the different studies on the risk of neonatal hypoglycemia showed low heterogeneity between the studies (I^2=0%) and with statistical significance. The frequency of neonatal hypoglycemia in these pregnancies of gestational diabetes mothers was 9% (Graph 5).

Graph 5. Meta-analysis on the risk of gestational diabetes leading to neonatal hypoglycemia. GM=metformin group, GI=insulin group, GMI=metformin and insulin group



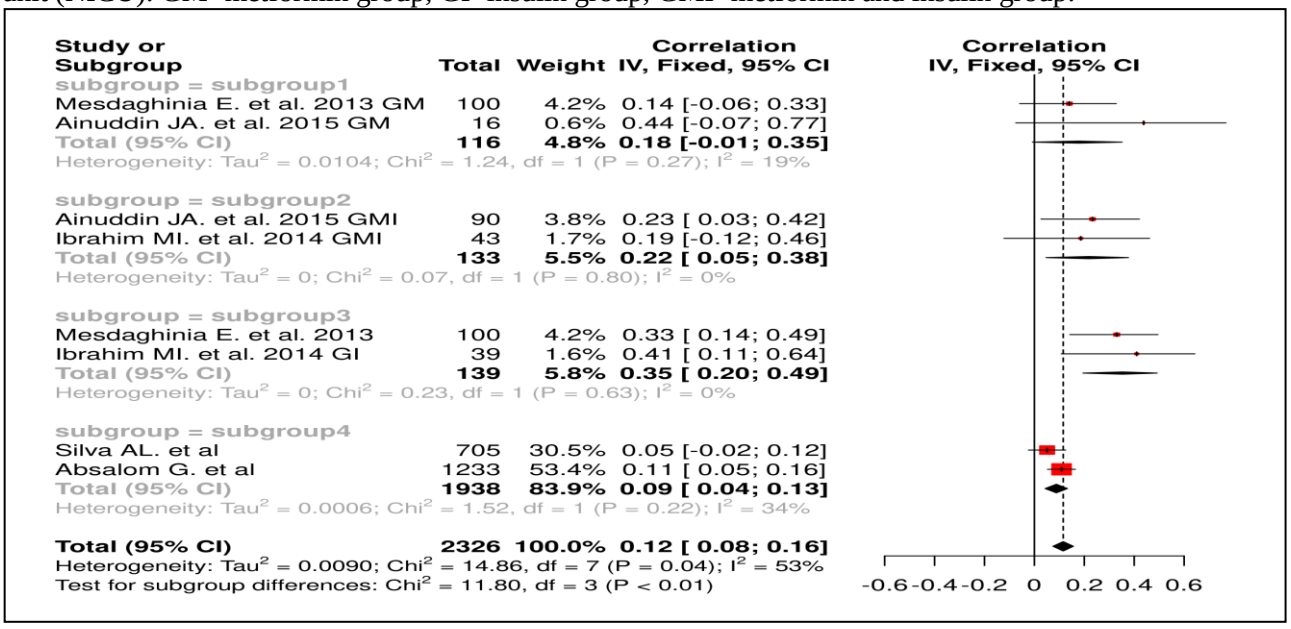
The meta-analysis that compared the different studies on neonatal macrosomia risk showed low heterogeneity between the studies (I^2=11%) and statistical significance. The frequency of neonatal macrosomia in gestational diabetes pregnancies was 14% (Graph 6).

Graph 6. Meta-analysis on the risk of gestational diabetes leading to macrosomia. GM=metformin group, GI=insulin group, GMI=metformin and insulin group



The meta-analysis comparing different studies on the risk of admission to neonatal ICU showed moderate heterogeneity among the studies (I^2=53%) and presented statistical significance. The frequency of use of neonatal ICU in gestational diabetes pregnancies was 12% (Graph 7).

Graph 7. Meta-analysis on the risk of gestational diabetes leading to the need for neonatal intensive care unit (NICU). GM=metformin group, GI=insulin group, GMI=metformin and insulin group.



Discussion

This survey allowed the analysis of the neonatal impacts of GDM treatment, showing that perinatal mortality and neonatal hypoglycemia were related to inadequate maternal treatment[9] and early onset of GDM manifestations, in the first trimesters of pregnancy[10]. This patient group, consequently, exhibited a higher risk of unfavorable perinatal complications.

Early diagnosis, the number of consultations with specialized professionals[12] and frequent evaluation of glycemic levels are important for adequate control of diabetes and to avoid major maternal-fetal complications. Studies show that continuous glucose monitoring (CGM) showed good results in both patients with GDM and those with previous DM, having improved HbA1c levels and improved neonatal outcomes, including lower rates of large babies for gestational age (LGA), in addition to lower demand for the admission of these patients into a Neonatal Intensive Care Unit (NICU) for a period exceeding 24 hours, less incidence of neonatal hypoglycemia and about one day less in the time of hospitalization[10].

Regarding the late effect of GDM in childhood, such as obesity, it is observed that despite similar treatment among patients with GDM, women with risk factors such as obesity or overweight had more neonatal and obstetric complications, in addition to especially more frequent adverse metabolic outcomes in the short and long term. Children born to mothers with GDM had higher rates of childhood obesity and fat measurements in increasing categories according to the maternal glycemic and fat levels[9,11]. It illustrates the effect described in the previous paragraph, the study Hyperglycemia and Adverse Pregnancy Outcome (HAPO) conducted in 10 countries, which found that maternal hyperglycemia during pregnancy was significantly associated with increased hyperglycemia and insulin resistance in offspring at the age of adult[9].

Concerning laboratory markers for predicting outcomes in neonates, it is observed that, in the monitoring of diabetic pregnant women, the association between glycated hemoglobin levels, glycated albumin and fructosamine in mothers with GDM may serve as a predictor of neonatal birth weight and infants with status large for gestational age[13]. Elevated levels of glycated albumin and fructosamine were associated with at least one neonatal complication and respiratory disorders at birth. HbA1c was not associated with these outcomes. All biomarkers were associated with the status of large for gestational age (LGA)[14].

In relation to the impact of metformin, insulin or combination of both drugs, most studies compared the perinatal results of GDM treatment with these possible combinations[15,16,17,18,19]. In some studies, metformin produced better effects on maternal-fetal outcomes and glycemic control compared to insulin in GDM, including lower maternal weight gain, absence of maternal hypoglycemia, and lower cost[17], lower hospitalization rate and greater ease of adherence, for its oral administration and not requiring vigorous monitoring, being an excellent alternative to insulin in the

treatment of GDM, and may even reduce the need for high doses in insulinotherapy[17,18,19]. After the meta-analysis, it was possible to identify that the use of metformin by pregnant women reduced the risk of neonatal jaundice and neonatal hypoglycemia, however, it did not present statistical significance for reduction of respiratory stress in the neonatal period and need for use of NICU.

Regarding the influence of maternal weight, in a clinical trial with 150 pregnant women with GDM or previous diabetes, it was observed that there was less maternal weight gain and lower rates of pregnancy-induced hypertension, which significantly affected neonatal outcomes. Neonatal hypoglycemia was significantly lower, as well as the stay in the NICU unit for a period longer than 24 hours in the metformin group. Nevertheless, it is worth noting that almost 85% of these patients require additional insulin therapy between the 2nd and 3rd trimesters[17].

Concerning neonatal jaundice and respiratory discomfort, a clinical trial with 200 women carriers of GDM found no difference in glycemic control, gestational hypertension rates and delivery route. In addition to little influence of treatment on birth weight, Parot's dystocia, Apgar score, hypoglycemia and stillbirth. Nonetheless, in the control group that used only insulin, there was a higher maternal weight gain, premature labor and higher levels of glycated hemoglobin (HbA1c), as well as a higher incidence of neonatal jaundice, respiratory discomfort and hospitalization in the NICU in the insulin group. The metformin group showed better neonatal results, but about 22% also needed supplemental insulin[18]. After the meta-analysis, it was possible to identify that the use of metformin by pregnant women reduced the risk of neonatal jaundice (Graph 4). On the other hand, the meta-analysis did not show statistical significance between the use of metformin or insulin as a risk factor for respiratory discomfort among newborns.

On neonatal and maternal hypoglycemia, Ibrahim *et al*. (2014)[19] also demonstrated that the addition of metformin to insulin therapy in women with insulin-resistant DM in pregnancy appears to be effective in adequate control glycemic control in a considerable proportion of women, with shorter hospitalization time, lower frequency of childbirth, hypoglycemia, as well as reduced frequency of hypoglycemia, hospitalization in NICU and Acute Respiratory Distress Syndrome. A clinical trial with 150 pregnant women with GDM or previous diabetes showed that the lower maternal weight gain and lower rates of pregnancy-induced hypertension occurred, which significantly affected neonatal outcomes. Neonatal hypoglycemia was significantly lower in the metformin group[17]. The meta-analysis confirmed that metformin use by pregnant women was associated with a lower risk of neonatal hypoglycemia and revealed a neonatal hypoglycemia rate of 9% in pregnancies of GDM carriers.

In relation to the weight of the newborn, women with GDM treated with metformin had lower chances of babies with LGA status[15], and a small portion presented with babies small for gestational age (SGA)[17]. Women treated with insulin evolved with the lowest risk of preterm delivery[15], but with

a higher number of caesareans due to fetal-maternal disproportion. The association of insulin and metformin use presented a higher chance of LGA newborns and lower risk of premature delivery[15]. It was observed that weight control and dietary intervention, especially in obese or overweight pregnant women, proved effective as adjuvant therapy to the use of hypoglycemics[11,12,20]. The meta-analysis confirmed that the risk of neonatal macrosomia was 11% among women with GDM.

About the need of the newborn for NICU, the non-drug therapy instituted to assist the glycemic control of these pregnant women, such as weight control and dietary intervention, especially in obese or overweight pregnant women, proved to be effective as an adjuvant therapy to the use of hypoglycemic agents that resulted in lower need for hospitalization of neonates in NICU[11,12,20]. It was also observed that maternal-fetal complications were more likely to be experienced by women who needed pharmacotherapy than those who did not need pharmacotermic treatment[12]. In this meta-analysis, the frequency of use of neonatal ICU in these pregnancies of mothers with GDM was 12%.

The studies demonstrate limitations of behaviors in the prevention of health problems of newborn from diabetic mothers during pregnancy. Moreover, it was also possible to observe a lack of adaptation of the literature to the Brazilian context. There is a need for more research and reflection on the work of experts involved in the care of pregnant diabetic women to ensure successful treatment to reduce maternal-fetal morbidity.

Conclusion

Pregnant women with GDM or previous diabetes have an increased risk of obstetric and neonatal complications, especially when the disease is not addressed correctly in relation to its treatment and follow-up. The practice of physical activity associated with diet and consequent weight control has a great impact on gestational results. Furthermore, the studies demonstrated greater benefits with the use of oral hypoglycemic metformin in the main treatment or adjuvant to insulin therapy.

The meta-analysis revealed that metformin use by pregnant women when compared to insulin was associated with a lower risk of neonatal hypoglycemia, lower risk of neonatal jaundice. The meta-analysis also showed that metformin use by pregnant women was not associated with a lower risk of neonatal respiratory stress or a reduced need for NICU. The meta-analysis revealed that the frequency of neonatal hypoglycemia in these pregnancies of gestational diabetes mothers was 9% and macrosomia 14%, and need for NICU12%.

However, it is clear that a greater number of studies are needed, especially in the Brazilian context, to evaluate the possibility of metabolic complications in the fetus and the long-term effects on children born to mothers who have undergone these therapeutic interventions.

Authors contributions

All authors approved the final version of the manuscript and declared themselves responsible for all aspects of the work, including ensuring its accuracy and integrity.

Competing interests

The authors declared that there are no competing interests.

References

1. InternationalDiabetes Federation. IDF Diabetes Atlas. 9. ed.Brussels, Belgium: International Diabetes Federation, 2019. Disponível em: https://diabetesatlas.org/. Acesso em: 03 jan. 2023.

2. WHO. Diagnostic criteria and classification of hyperglycemia first detected in pregnancy: A World Health Organization Guideline. WHO, editor. Diabetes Res ClinPract [Internet]. 2014 Mar;103(3):341–63. Available from: http://www.ncbi.nlm.nih.gov/books/nbk169024/

3. Sociedade Brasileira de Diabetes.SBD. Diretrizes da Sociedade Brasileira de Diabetes: 2019-2020. São Paulo: Clannad; 2019. Seabra ALR.Availablefrom: https://diretriz.diabetes.org.br/. Acesso em: 03 jan. 2023.

4. Brasil. Ministério da Saúde; Organização Pan-americana da Saúde. Federação Brasileira das Associações de Ginecologia e Obstetrícia. Sociedade Brasileira de Diabetes. Rastreamento e diagnóstico de diabetes mellitus gestacional no Brasil. Brasília, DF: OPAS, 2016. 32p. Available from: https://iris.paho.org/handle/10665.2/34278?show=full. Acesso em: 03 jan. 2023.

5. Caughey AB, Turrentine M. ACOG Practice Bulletin No. 190 Summary: Gestational Diabetes Mellitus. Obstet. Gynecol. 2018;131:406–8. Availablefrom: https://doi.org/10.1097/aog.0000000000002501

6. Li-Zhen L, Yun X, Xiao-Dong Z, Shu-Bin H, Zi-Lian W, Adrian SD et al. Evaluation of guidelines on the screening and diagnosis of gestational diabetes mellitus: systematic review. BMJ Open. 2019;9(5):e023014. Available from: https://doi.org/10.1136%2Fbmjopen-2018-023014

7. Negrato CA, Zajdenverg L, Montenegro Júnior RM. Diabetes melito e gestação. In: Vilar L, editor. Endocrinologia clínica. 6. ed. Rio de Janeiro: Guanabara Koogan; 2016. p. 716-29.

8. Plows JF, Stanley JL, Baker PN, Reynolds C., Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol ciência. 2018; 19:3342. Availablefrom: https://doi.org/10.3390/ijms19113342

9. Scholtens DM, Kuang A, Lowe LP, Hamilton JK, Lawrence JM, Lebenthal Y., Brickman WJ,

Clayton R., Ma RC, McCance D., et al. Estudo de Acompanhamento de Resultados Adversos da Hiperglicemia e da Gravidez (HAPO FUS): Glicemia Materna e Metabolismo da Glicose na Infância. Cuidados com o Diabetes. 2019; 42:381–392. Availablefrom: https://doi.org/10.2337/dc18-2021

10. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017;390(10110):2347-59. Available from: https://doi.org/10.1016/S0140-6736(17)32400-5

11. Corcillo A, Quansah DY, Kosinski C, Benhalima K, Puder JJ. Impact of Risk Factors on Short and Long-Term Maternal and Neonatal Outcomes in Women with Gestational Diabetes Mellitus: A Prospective Longitudinal Cohort Study. Front Endocrinol (Lausanne). 2022; 13:866446. Availablefrom: https://doi.org/10.3389/fendo.2022.866446

12. Absalom G, Zinga J, Margerison C, van der Pligt P. Associations of dietetic management with maternal and neonatal health outcomes in women diagnosed with gestational diabetes: a retrospective cohort study. J Hum Nutr Diet. 2019 Dec;32(6):728-736. Available from: https://doi.org/10.1111/jhn.12682

13. Mendes N, Alves M, Andrade R, Ribeiro RT, Papoila AL, Serrano F. Association between glycatedhaemoglobin, glycated albumin and fructosamine with neonatal birthweight and large-for-date status infants in gestational diabetes mellitus: a prospective cohort study. J ObstetGynaecol. 2019;39(6):768-773. Availablefrom: https://doi.org/10.1080/01443615.2019.1584886

14. Mendes N, Alves M, Andrade R, Ribeiro RT, Papoila AL, Serrano F. Association between glycated albumin, fructosamine, and HbA1c with neonatal outcomes in a prospective cohort of women with gestational diabetes mellitus. Int J Gynaecol Obstet. 2019;146(3):326-32. Available from: https://doi.org/10.1002/ijgo.12897

15. Silva AL, Amaral AR, Oliveira DS, Martins L, Silva MR, Silva JC. Desfechos neonatais de acordo com diferentes terapias para diabetes mellitus gestacional. J Pediatr (Rio J) 2017; 93 (1):87–93. Available from: https://doi.org/10.1016/j.jped.2016.04.004

16. Arshad R, Khanam S, Shaikh F, Karim N. Feto-maternal outcomes and Glycemic control in Metformin versus insulin treated Gestational Diabetics. Pak J Med Sci. 2017;33(5):1182–7. Available from: https://doi.org/10.12669/pjms.335.13286

17. Ainuddin JA, Karim N, Zaheer S, Ali SS, Hasan AA. Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. J Diabetes Res. 2015;2015:325851. Availablefrom: https://doi.org/10.1155/2015/325851

18. Mesdaghinia E, Samimi M, Homaei Z, Saberi F, Moosavi SG, Yaribakht M. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: a randomised blinded trial. Int J Prev Med. 2013;4(3):327-33. Available from: https://pubmed.ncbi.nlm.nih.gov/23626890

19. Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. ArchGynecol Obstet. 2014;289(5):959-65. Availablefrom: https://doi.org/10.1016/s2213-8587(20)30310-7

20. Barnes RA, Flack JR, Wong T, Ross GP, Griffiths MM, Stephens M, Kourloufas L, Smart CE, Collins CE, MacDonald-Wicks L. Does weight management after gestational diabetes mellitus diagnosis improve pregnancy outcomes? A multi-ethnic cohort study. Diabet Med. 2022;39(1):e14692. Available from: https://doi.org/10.1111/dme.14692