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Prediction of insulin therapy in women with gestational diabetes: a systematic review and meta-analysis of observational studies

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Abstract

Objectives: To identify antenatal risk factors that may predict the need for insulin treatment upon diagnosis of gestational diabetes (GDM), that is, to identify the specific characteristics of women diagnosed with GDM who did not achieve good glycemic control through lifestyle modifications.

Methods: We performed a comprehensive literature search in PubMed, Science Direct, Ebsco, and Scielo for studies evaluating the associations between antenatal factors and the need for insulin treatment published until January 28th, 2021. Random-effects models were used to estimate risk ratios and their 95% confidence interval. The quality of studies was assessed using the Newcastle-Ottawa Scale. Random-effects models were used to estimate outcomes, and effects reported as risk ratio and their 95% confidence interval. The systematic review and meta-analysis were registered in the International Prospective Register of Systematic Reviews.

Results: Eighteen observational studies were selected, reporting 14,951 women with GDM of whom 5,371 received insulin treatment. There were statistically significant associations between the need for insulin treatment and BMI ≥ 30 (RR:2.2; 95%CI: 1.44–3.41), family history of type 2 diabetes mellitus (RR:1.74; 95%CI: 1.56–1.93), prior personal history of GDM (RR:2.10; 95%CI: 1.56–2.82), glycated hemoglobin value at GDM diagnosis (RR:2.12; 95%CI: 1.77–2.54), and basal glycemia obtained in the diagnostic curve (RR: 1.2; 95%CI: 1.12–1.28). Nulliparity and maternal age were not determinants factor. There was moderate-to-high heterogeneity among the included studies.

Conclusions: the strong causal association between BMI ≥ 30, family history of type 2 diabetes mellitus, prior history of GDM and glycosylated hemoglobin with the need for insulin treatment was revealed.

Keywords: diabetes; drug therapy; gestational; insulin; meta-analysis; risk factors.

Introduction

Gestational diabetes (GDM) has traditionally been defined as any degree of intolerance to glucose diagnosed for the first time during pregnancy [1]. The American Diabetes Association [2] recently defined it as diabetes diagnosed in the second or third trimester of pregnancy; it is therefore differentiated from pregestational diabetes.

GDM is a common complication, with variable incidence depending on ethnic origin and diagnostic strategy used. Its frequency grows with increasing frequency, secondary to late motherhood, obesity and sedentary lifestyles [3].GDM entails increased matern al and fetal morbimortality [2, 4, 5].

Treatment is essentially based on control of maternal hyperglycemia. First line therapy is diet and physical exercise together with monitoring capillary glycemia [2]. Many women can attain euglycemia with nutritional therapy alone. However, up to 30% will require pharmacologic treatment [6], either with insulin or oral hypoglycemic agents.

Hartling et al. [7] in their meta-analysis report that proper control of glycemia – either with nutritional or insulin treatment – can reduce the risk of pre-eclampsia, macrosomia and shoulder dystocia.

Against this backdrop, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [8] reveals a continuous relationship between maternal glycemia levels

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and adverse outcomes of pregnancy, mainly neonatal macrosomia.

Crowther et al. [9] studied whether treatment of GDM leads to less perinatal complications. More than 1,000 pregnant women were randomly assigned to an intervention group (diet, exercise and insulin if necessary) or to a control group in which no treatment was administered. For the intervention group, severe perinatal complications such as death, shoulder dystocia, fractures, and nerve lesions, were less common. A total of 34 women needed to be treated to avoid an adverse perinatal outcome.

For its part, The American Diabetes Association in 2020 [10] mentioned, "maternal/neonatal risks increase with gradual hyperglycemia".

Therefore, accurate monitoring of maternal glycemia during GDM appears to be important. Current guidelines [2, 10, 11] recommend that glycemia levels must be as close as possible to euglycemia but hypoglycemia must be avoided. They also indicate that when euglycemia is not attained with nutritional treatment, medical treatment needs to be introduced to prevent perinatal complications.

It is crucial for obstetricians to be able to identify specific characteristics of women diagnosed with DGM who failed to achieve good glycemic control by lifestyle modifications only. However, to date there is confusing evidence in the medical literature.

The identification of these predictors could classify women with DGM and high risk of insulin therapy from the diagnosis of the entity, so that a stricter control of this group could be made, optimizing the planning and management of health resources.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines [13].

The protocol was registered with the international Prospective Register of Systematic Reviews (PROSPERO: CRD42020175060). A Review Board approval was not required since this investigation consisted of pooling results of published studies.

Literature search strategy and inclusion criteria

We searched PubMed, Science direct, Ebsco, and Scielo for observational studies published between 1975 and January 2021.

A search strategy was developed with the assistance of a clinical librarian. The strategy included keywords and MeSH terms both medical subject headings and free text words covering "gestational diabetes"; "pregnancy diabetes"; "pregnancy hyperglycemia"; "insulin need"; "insulin during pregnancy"; "prediction of insulin theraphy". These terms were applied to the title, summary and keywords of publications depending on the filters available in the different databases. The full search strategy is provided in the Supplementary Material. All duplicate records were removed.

The inclusion criteria were: (i) prospective and retrospective cohort and case-control studies published in either English or Spanish; (ii) reporting risk or predictive factors to require insulin treatment in women with GDM; (iii) that they included 75 or 100 g oral glucose tolerance test (OGTT) as a diagnostic strategy.

The exclusion criteria were (i) studies that included multiple gestations; (ii) studies that did not evaluate risk factors; (iii) studies that did not provide relative risks or odds ratio and their confidence intervals, nor data for their possible calculation; and, (iv) studies that included patients diagnosed with GDM in the first trimester of pregnancy.

Data extraction and risk of bias assessment

All identified publications went through a three-step parallel review of title, abstract, and full text, performed by two researchers, based on predefined inclusion and exclusion criteria. We also screened the references of the retrieved articles for possible eligible papers. Any disagreement or controversies of the extracted data were discussed in order to reach a consensus.

Data extraction was performed independently by two investigators, and in case of discrepancies, the final decision was reached by consensus, involving a third investigator, when necessary. From each eligible study, we extracted information on the first author, year of publication, the examined risk factors, the total population, and number of cases for each study, the study-specific relative risk estimates (risk ratio, odds ratio, or standardized mean differences) along with the corresponding confidence intervals (CI).

Two authors using the Newcastle-Otawa Scale [14] independently assessed the methodological quality of the selected studies. This scale consists of three broad perspectives including the selection of the study group, the comparability of the groups, and the ascertain-ment of the primary outcome. The maximum score can be nine stars. Studies with seven star-items or more are categorized as high quality and those with six star-items or less are categorized as low quality.

Pre-specified outcomes

The following outcomes were evaluated: (i) Maternal age at the onset of gestation; (ii) obesity [body mass index (BMI) ≥ 30] according to the World Health Organization; (iii) nulliparity: women who have never completed a pregnancy beyond 20 weeks; (iv) a family history of type 2 diabetes mellitus (T2DM); (v) history of GDM in previous gestations; (vi) value of basal glycemia at OGTT; (vii) glycated hemoglobin (HbA_{1c}) value at diagnosis of GDM.

Data synthesis

The meta-analysis was performed using epidemiologic analysis software from the Pan American Health Organization Epidat v.4.2. and the statistical software R (available at http://www.r-project.org). Qualitative and quantitative studies were performed; 95%CI confidence intervals were calculated. Heterogeneity analysis was performed with

DerSimonian and Laird´s statistical test Q (Null hypothesis [Ho]: homogeneity = inter study variability is null). Heterogeneity (I^2) was subsequently estimated; in all cases this was completed with a Galbraith Plot.

After the data were combined, meta-analysis was performed with a random and fixed effects model for studies with ($I^2 \geq 50\%$) and without ($I^2 < 50\%$) heterogeneity, respectively. Effect size was shown as relative risk (RR). Cumulative meta-analysis was plotted with Forest Plot graphs.

For all possible predictive factors studied, risk of publication bias was estimated by means of Begg and Egger statistical tests. Moreover, their corresponding graphs were plotted.

Finally, in all cases the Sensitivity Analysis was estimated by means of which the influence of each study on the overall estimate of effect was examined.

Due to the fact that the incidence of GDM and need for insulin treatment was relatively low, odds ratios were treated as RR in most studies.

Results

Study selection and characteristics

The process of identification and selection of studies is summarized in PRISMA flowchart (Figure 1). A total of 18 studies that included 14,951 women with GDM of whom 5,371 received insulin treatment.

The main characteristics of the studies included are presented in Table 1. For practical reasons, the diagnostic criteria used in each study to diagnose GDM were included; in addition to articles analyzed for each possible predictive factor for insulin treatment.

Risk of bias of included studies

The quality of the studies was generally sufficient (median NOS = 8, range: 5–9). The data can be observed in the Supplementary Material, Supplementary Table 1.

Meta-analyses of outcomes

Maternal age at the onset of gestation index

Five studies analyzed maternal age as a risk factor to start insulin treatment [15–19]. There were a total number of pregnant women with GDM of 1,255, of whom 35.94% (n=451) received insulin treatment.

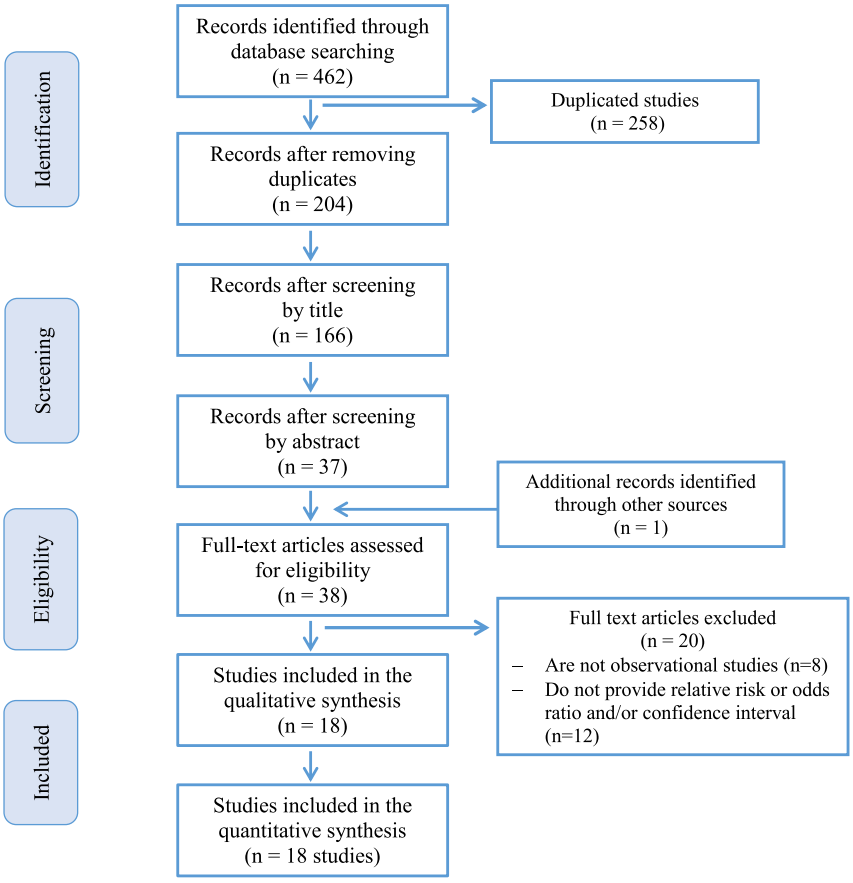

Figure 1: PRISMA flowchart: summary of evidence search and selection.

Table 1: Main characteristics of the included studies. Outcomes meta-analyzed.

References	Year	Country	Participants GDM-I, n	Participants GDM-NI, n	GDM total, n	Study design	Diabetes diagnosis	Age	Outcomes meta-analyzed					HbA1c, %
									Nulliparity	BMI ≥ 30	Family history for T2DM	Previous GDM	Fastin plasma glucose, mg/dl	
Alvarez-Ballano [23]	2006	Spain	45	56	101	CC	Carpenter/ Coustan			x	x		x	
Akinci B [15]	2008	Turkey	81	74	155	CC	ADA-2008	x	x		x		x	
Aktun LH [17]	2015	Turkey	89	167	256	PC	WHO	x		x	x	x	x	x
Ares J [29]	2014	Spain	36	155	191	RC	NDDG						x	
Bakiner O [28]	2013	Turkey	110	190	300	RC	ADA-2011				x	x	x	x
Barnes RA [20]	2016	Australia	1,302	2,713	4,015	PC	ADIPS		x	x	x	x		
Ducarme G [16]	2018	France	72	128	200	PC	ADA-2008	x	x	x		x	x	x
Koning SH [22]	2016	Netherlands	360	460	820	RC	WHO		x	x	x	x	x	
Kouhkan A [19]	2019	Iran	74	162	236	PC	ADA-2018	x					x	x
Matsumoto Y [25]	2019	Japan	51	63	114	RC	JAOG			x	x			
Meshel S [21]	2015	Israel	143	1,181	1,324	RC	Carpenter/ Coustan		x	x	x	x		
Ouzounian JG [26]	2011	USA	262	1,189	1,451	RC	ADA			x		x		
Pertot T [31]	2011	Australia	1,535	1,474	3,009	PC	ADIPS							x
Sapienza AD [27]	2010	Brazil	117	177	294	CC	ADA-2008			x	x			x
Sousa A [18]	2018	Brazil	135	273	408	RC	IADPSG	x		x	x	x	x	
Wong VW [24]	2011	Australia	323	289	612	RC	ADIPS			x			x	
Yanagisawa K [32]	2016	Japan	36	77	113	CC	IADPSG							x
Zhang Y [30]	2016	China	606	746	1,352	RC	IADPSG						x	x

CC, Case-control study; ADA, American Diabetes Association; ADIPS, Australasian Diabetes in Pregnancy; BMI, body mass index; GDM, gestational diabetes; GDM-I, gestational diabetes and antenatal insulin therapy; GDM-NI, gestational diabetes without insulin therapy; HbA1c, Glycosylated hemoglobin, JAOG, Japan Society of Obstetrics and Gynecology; IADPSG, The International Association of Diabetes and Pregnancy Study Groups; NDDG, National Diabetes Data Group; PC, Prospective cohort study; RC, retrospective cohort study; T2DM, Type 2 diabetes mellitus; WHO, World Health Organization.

No statistically significant differences were detected between maternal age and requirement for insulin treatment (RR: 1.04; 95%CI: 0.99–1.09); p=0.11 Table, and Forest Plot (Figure 2).

A high degree of heterogeneity was revealed by means of DerSimonian and Laird´s test; Cochran's Q statistic was (Q 14.28; p=0.006) and I^2=72%. Galbraith's Plot (Supplementary Figure 1) also highlights the lack of homogeneity between the studies included. Sensitivity analysis (Supplementary Figure 2).

Nulliparity in regard to multiparity

There were five studies that analyzed the effect of nulliparity on subsequent need for insulin treatment [15, 16, 20–22]. There was a total cohort of 6,514 pregnant women and a percentage of 30.05% (n=1,958) of pregnant women treated with insulin.

As can be observed in the Table and Forest Plot graph, analysis of nulliparity compared to multiparity as a risk factor to require insulin treatment was not statistically significant with an RR of 0.90 (95%CI: 0.53–1.52); p=0.68. Table and Forest Plot are included (Figure 3).

A high degree of heterogeneity was revealed by means of DerSimonian and Laird´s test; Cochran's Q statistic was (Q 14.28; p=0.001) and I^2=92%. As can be observed in the Galbraith Plot, the studies by Koning et al. [22] and Barnes et al. [20] most contributed to this effect, possibly because they presented a greater cohort of pregnant women with insulin.

Body mass index ≥ 30

There were 11 studies analyzed during this meta-analysis to ascertain the impact of BMI ≥ 30 as a predictive factor for insulin treatment [16–18, 20–27] including 9,595 pregnant women of whom 30.21% (n=2,899) received insulin treatment. BMI ≥ 30 was associated with insulin treatment, RR: 2.21; (95%CI: 1.44–3.41), p=0.0003. Table and Forest Plot are included (Figure 4).

DerSimonian and Laird´s test revealed a high degree of heterogeneity with Q 223, p<0.05 and I^2=96%.

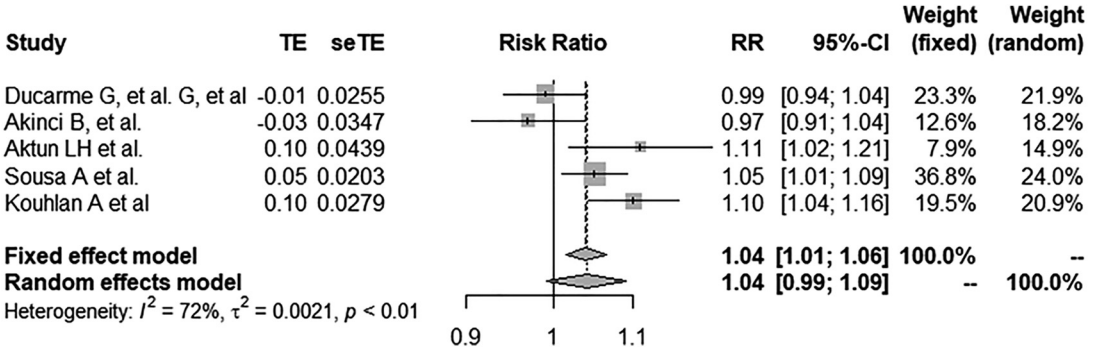

Figure 2: Estimation of the risk ratio of the association between maternal age and the need for insulin in gestational diabetes by using the random effect model. Forest Plot.

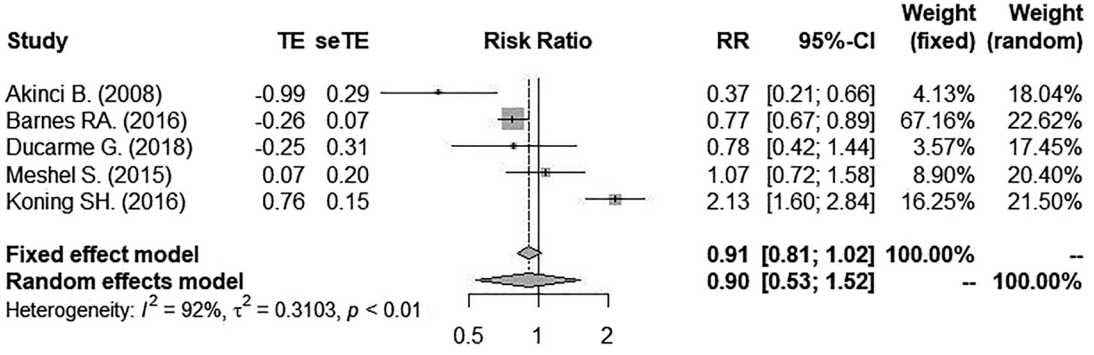

Figure 3: Estimation of the risk ratio of the association between nulliparity and the need for insulin in gestational diabetes by using the random effect model. Forest Plot.

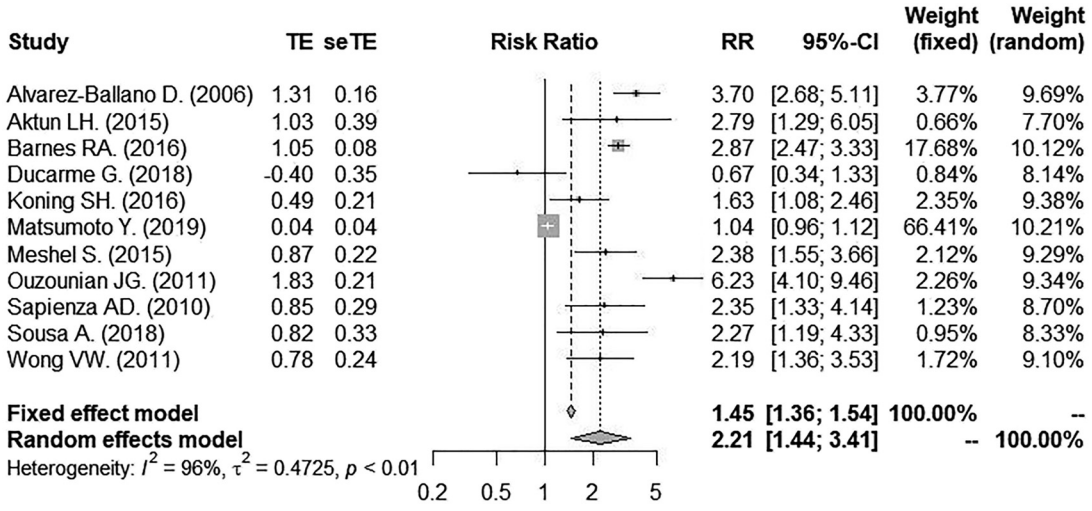

Figure 4: Estimation of the risk ratio of the association between maternal body mass index ≥ 30 and the need for insulin in gestational diabetes by using the random effect model. Forest Plot.

Using the Begg test (z=0.93; p=0.35) and the Egger test (t=1.9; p=0.08) the risk of publication bias was also analyzed. Both were conclusive over the absence of bias (Supplementary Figure 3). Sensitivity analysis (Supplementary Figure 4).

Family history of T2DM

To meta-analyze this variable, 10 works [15, 17, 18, 20–23, 25, 27] were incorporated into the analysis; whereby a total of 7,787 pregnant women diagnosed with GDM with a percentage of cases that required insulin treatment of 31.24% (n=2,433), were included.

Our results are in accordance with the fact that "family history of T2DM" is a risk factor to need insulin treatment RR: 1.74 (95%CI: 1.56–1.93), p<0.0001. Table and Forest Plot are included (Figure 5).

The heterogeneity analysis revealed the absence of variability between studies by means of a Q test with statistical evidence of homogeneity (p=0.98) and an I^2 of 0%. A Galbraith Plot confirmed that heterogeneity was absent. Funnel and Egger´s Plot (Supplementary Figure 5). Sensitivity analysis (Supplementary Figure 6).

History of GDM in previous gestations

There were eight scientific articles included in this analysis [16–22, 26, 28], whereby a total of 8,774 pregnant women with gestational diabetes were included in the

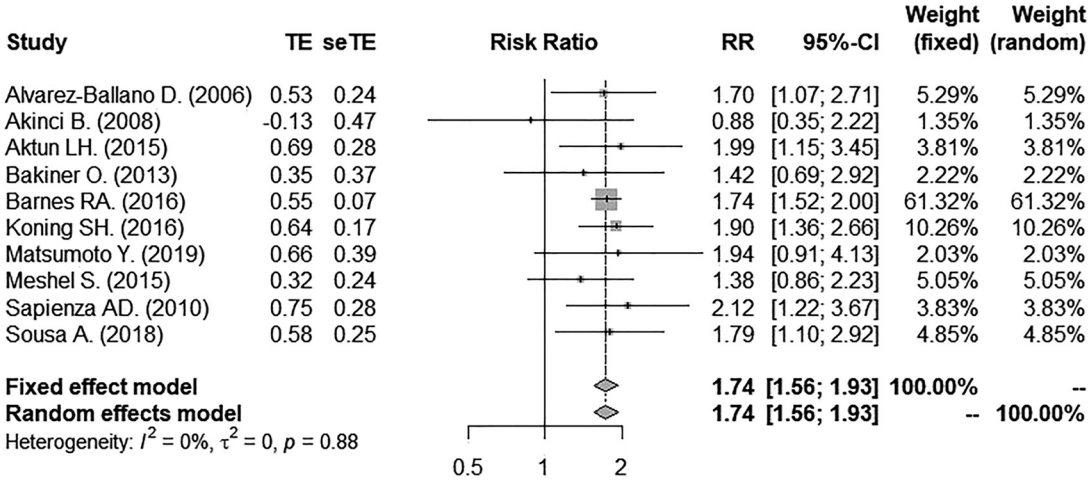

Figure 5: Estimation of the risk ratio of the association between family history of T2DM and the need for insulin in gestational diabetes by using the random effect model. Forest Plot.

meta-analysis, of whom 27.17% (n=2,384) required insulin treatment.

Our results indicate that the history of GDM is a risk factor to require insulin (RR: 2.10; 95%CI: 1.56–2.82), p<0.0001. Table and Forest Plot are included (Figure 6).

DerSimonian and Laird´s test revealed heterogeneity (p<0.05), with I^2=66%. In the Galbraith Plot (Supplementary Figure 7), we observe how the article that has most contributed to heterogeneity was the one by Meshel et al. [21]. Objective statistical tests to assess publication bias: Begg (z=1.11; p=0.26) and Egger tests (t=−0.98; p=0.36) were performed. Therefore, it can be assumed that there is no bias in this meta-analysis (Supplementary Figure 8). Sensitivity analysis (Supplementary Figure 9).

Value of basal glycemia at OGTT

A total of 11 articles [15–19, 22–24, 28–30] were reviewed to perform this meta-analysis. In total they provide a number of pregnant women with GDM of 4,641, of whom 40.01% (n=1,857) required insulin treatment because of poor metabolic control.

In the combined measure, it was concluded that basal glycemia when performing OGTT to diagnose GDM was a risk factor with a very weak measure of association. This was because the RR for need insulin therapy was 1.20 (95% CI: 1.12–1.28), p<0.0001. Table and Forest Plot are included (Figure 7).

In the individual studies a high heterogeneity was estimated by the Dersimonian and Laird's test (p<0.05) and I^2=92%. Against this backdrop the studies that most contributed to heterogeneity are Zhang Y et al. [30] and Wong VW et al. [24] possibly because they are the works with the largest sample size and patients with insulin therapy. Sensitivity analysis (Supplementary Figure 10).

Glycosylated hemoglobin at GDM diagnosis

A total of eight publications [16, 17, 19, 27, 28, 30–32] with a joint cohort of 5,724 pregnant women with GDM, and a percentage of insulin treatment of 46.1% (n=2,639), were analyzed.

We determined that the glycosylated hemoglobin value at GDM diagnosis can be considered a risk factor to require insulin treatment. RR: 2.12 (95%CI: 1.77–2.54), p<0.0001. Table and Forest Plot are included (Figure 8).

A statistical study of heterogeneity revealed this was absent; with a Q test with statistical evidence of homogeneity (p=0.87) and I^2 of 0%. Moreover, heterogeneity is represented in the Galbraith Plot (Supplementary Figure 3).

Table 2 shows a summary of all results obtained.

Sensitivity analysis

Sensitivity analysis were performed and influence graphs were prepared for the variables BMI ≥ 30, family history of T2DM, history of GDM in previous gestations, glycosylated hemoglobin at GDM diagnosis, and value of basal glycemia at OGTT. The sensitivity tests highlight the robustness of our data given that the different included studies in the meta-analyzes present similar results, in the same line and scale, and they are statistically significant. Similar data were obtained upon observing the influence graphs (Table 3).

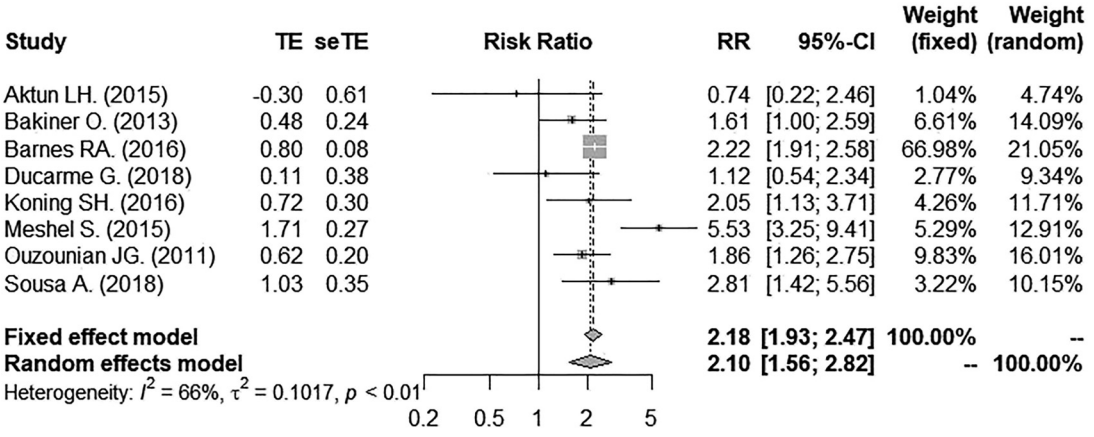

Figure 6: Estimation of the risk ratio of the association between history of gestational diabetes in previous gestations and the need for insulin in gestational diabetes by using the random effect model. Forest Plot.

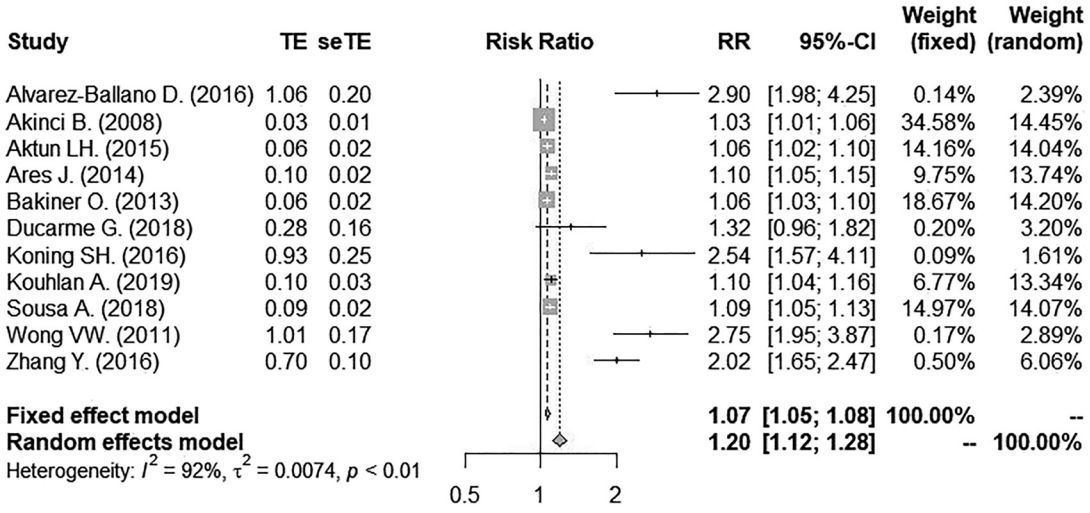

Figure 7: Estimation of the risk ratio of the association between fasting plasma glucose and the need for insulin in gestational diabetes by using the random effect model. Forest Plot.

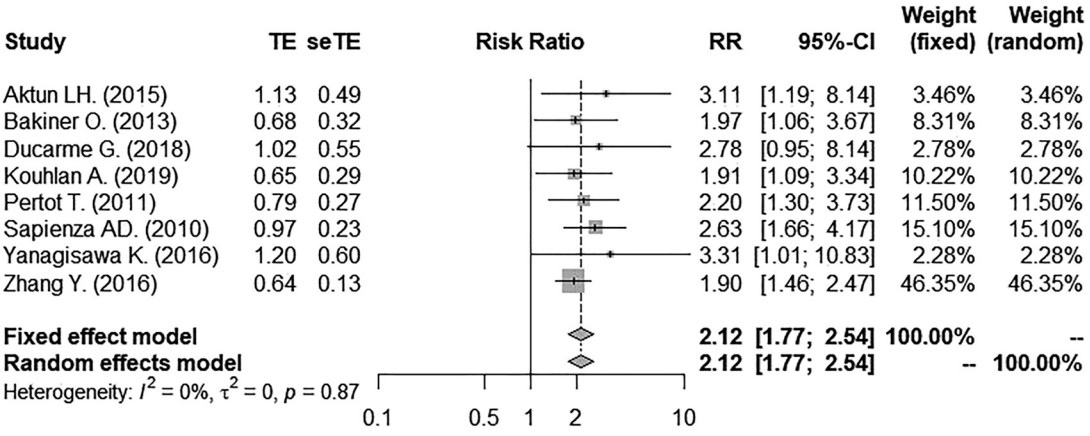

Figure 8: Estimation of the risk ratio of the association between glycosylated hemoglobin (%) and the need for insulin in gestational diabetes by using the random effect model. Forest Plot.

Table 2: Pooled effects reported as standardized mean differences (SMDs) and 95% confidence interval (CI) using random effect models and heterogenity (I^2) in diabetic pregnant women with and without insulin treatment.

Outcome (Figures)	Included studies	Participants GDM-I/GDM-NI	SMD and 95% CI	I^2, %	p
Maternal age (Figure 2)	5	451/804	1.04 (0.99, 1.09)	72	0.11
Nulliparity (Figure 3)	5	1,958/4,556	0.90 (0.53, 1.52)	92	0.68
BMI ≥ 30 (Figure 4)	11	2,899/6,696	2.21 (1.44, 3.41)	96	0.0003
Family history of T2DM (Figure 5)	10	2,433/5,354	1.74 (1.56, 1.93)	0	<0.0001
History of DGM in previous gestations (Figure 6)	8	2,384/6,390	2.10 (1.56, 2.82)	66	<0.0001
Value of basal glycemia al OGTT (Figure 7)	11	1,857/2,784	1.20 (1.12, 1.28)	92	<0.0001
Glycosylated hemoglobin at GDM diagnosis (Figure 8)	8	2,639/3,085	2.12 (1.77, 2.54)	0	<0.0001

BMI, body mass index; CI, confidence interval; GDM, gestational diabetes; GDM-I, gestational diabetes and antenatal insulin therapy; GDM-NI, gestational diabetes without insulin therapy; OGTT, glucose tolerance curve; T2DM, type 2 diabetes mellitus.

Table 3: Sensitivity analyses (by excluding one trial at one time) reporting SMD and 95% confidence interval (CI) for BMI ≥ 30, Family history of DM2, value of basal glucemia at OGTT and glycosylated hemoglobin.

Deleted publication [reference]	BMI ≥ 30 SMD (95 %CI)	Family history of DM2 SMD (95 %CI)	History of GDM in previous gestations SMD (95 %CI)	Value of basal glycemia at OGTT SMD (95 %CI)	Glycosylated hemoglobin SMD (95 %CI)
Álvarez-Ballano [23]	2.09 (1.34, 3.28)	1.76 (1.57, 1.97)	–	1.14 (1.08, 1.21)	–
Akinci B [15]	–	1.76 (1.58, 1.97)	–	1.24 (1.14, 1.33)	–
Aktun LH [17]	2.16 (1.38, 3.39)	1.75 (1.56, 1.96)	2.25 (1.54, 3.28)	1.22 (1.13, 1.32)	2.11 (1.78, 2.49)
Ares J [29]	–	–	–	1.21 (1.23, 1.30)	–
Bakiner O [28]	–	1.77 (1.58, 1.97)	2.17 (1.42, 3.31)	1.23 (1.14, 1.33)	2.14 (1.81, 2.55)
Barnes RA 20]	2.14 (1.34, 3.41)	1.79 (1.49, 2.14)	2.02 (1.23, 3.32)	–	–
Ducarme G [16]	2.45 (1.56, 3.85)	–	2.26 (1.53, 3.34)	1.18 (1.11, 1.26)	2.12 (1.79, 2.50)
Koning SH [22]	2.47 (1.42, 3.63)	1.74 (1.55, 1.96)	2.09 (1.37, 3.18)	1.18 (1.11, 1.25)	–
Kouhkan A [19]	–	–	–	1.20 (1.12, 1.29)	2.15 (1.81, 2.26)
Matsumoto Y [25]	2.44 (1.81, 3.30)	1.75 (1.57, 1.97)	–	–	–
Meshel S [21]	2.19 (1.38, 3.46)	1.77 (1.59, 1.98)	1.9 (1.54, 2.34)	–	–
Ouzounian JG [26]	1.98 (1.30, 3.0)	–	2.11 (1.6, 3.29)	–	–
Pertot T [31]	–	–	–	–	2.11 (1.74, 2.55)
Sapienza AD [27]	2.19 (1.39, 3.45)	1.75 (1.56, 1.95)		–	2.07 (1.73, 2.47)
Souza A [18]	2.20 (1.39, 3.46)	1.76 (1.57, 1.97)	2.01 (1.32, 3.04)	1.22 (1.13, 1.31)	–
Wong VW [24]	2.20 (1.39, 3.49)	–	–	1.14 (1.08, 1.21)	–
Yanagisawa K [32]	–	–	–	–	2.11 (1.79; 2.50)
Zhang Y [30]	–	–	–	1.12 (1.06, 1.18)	2.30 (1.85, 2.84)
All available studies	**2.20 (1.43, 3.39)**	**1.76 (1.58, 1.96)**	**2.10 (1.56, 2.82)**	**1.18 (1.11, 1.26)**	**2.13 (1.80; 2.51)**

BMI, body mass index; CI, confidence interval; GDM, gestational diabetes; OGTT, glucose tolerance curve; SMD, standardized mean difference; DM2, type 2 diabetes mellitus. Bold values: hazard ratio estimation of the association between different factors and insulin requirement in gestational diabetes.

Publication bias

Possible publication bias was analyzed for the variables BMI ≥ 30, family history of T2DM, history of GDM in previous gestations, glycosylated hemoglobin at GDM diagnosis, and value of basal glycemia at OGTT. The funnel graphs showed point symmetry for the different variables studied with the exception of value of basal glycemia at OGTT. The study was also completed by performing objective statistical tests, the Begg and Egger tests, thus corroborating the absence of this bias for all variables except for the value of basal glycemia at OGTT. (Supplementary Material)

Discussion

The aim of this meta-analysis was to identify possible predictors of "poor response" to first line treatment of GDM and the need for medical treatment, so that by knowing these factors from the time of diagnosis of the disease, we can differentiate which groups of pregnant women are more likely to have poor metabolic control with diet and physical exercise. For this purpose, 18 studies were reviewed that included 14,951 women diagnosed with GDM, of whom 5,371 received insulin treatment, which enables a greater extrapolation of results obtained, more accuracy in the parameter assessed and higher statistical power, which is an important datum provided by this analysis.

The most important clinical and biochemical factors previously reported in the medical literature that could act as risk predictors were analyzed.

Furthermore, after reviewing the most important sources of scientific evidence, we were unable to detect any prior meta-analysis that analyzes this clinical problem. Nor was any systematic review found that assessed predictive factors of “non-response to first line treatment”. The fact that there is no prior literature lends further value to our work but also prevents us from comparing and validating our results.

Our findings reveal that the best predictors of insulin treatment (or of poor response to first line treatment) were glycosylated hemoglobin, history of GDM in a prior gestation and BMI ≥ 30 at the onset of gestation. All of these presented a relative risk higher than two for prediction of insulin treatment with a high degree of robustness and statistical significance. The predictive factor “family history of DM2” was also presented as a good marker. However, its relative risk was lower than previous factors. The

basal glycemia obtained at OGTT also predicted need for insulin treatment. However, statistical analysis reveals high heterogeneity and bias. To assess the robustness of the association results, we performed a sensitivity analysis which indicated that our results were not driven by any one study and that similar results could be obtained after excluding any of the studies included, confirming the robustness of our data.

Maternal age or nulliparity did not behave as predictive factors to start insulin treatment.

From the statistical study performed the high degree of heterogeneity detected among publications for the factors: age, nulliparity, BMI ≥ 30, previous GDM and basal glycemia value at OGTT, are especially noteworthy. This absence of homogeneity could be accounted for by the different populations included in the articles studied (multiethnic, Asian, European, etc.) and their lifestyles that will determine an unequal prevalence of GDM. Furthermore, the authors used different criteria for diagnosis, whereby the incidence of GDM is going to be modified. We cannot rule out either that there are pregnant women in the control group who – were more restrictive diagnostic criteria applied – would be classified as diabetics. Although it is true that finding different diagnostic criteria is not very likely to modify our results to a large extent given that starting insulin treatment depends on metabolic control (glycemia profiles); and all authors report that medical treatment began with similar criteria. In the most recent articles the criteria proposed by The American Diabetes Association [2] and American College of Obstetricians and Gynecologists [33] were explicitly applied.

Clinical implications

The requirement for insulin treatment could be a starting point to characterize pregnant women with more severe GDM. Risk stratification for GDM may improve the efficiency of health services provision, optimizing resources for those pregnant women with a higher probability of a poor response to initial treatment (diet and exercise). A risk prediction tool could theoretically be useful.

However, to analyse this tool, randomized clinical trials would need to be performed. The aim would be to demonstrate whether clinical benefits might be observed after identifying this group of patients at more risk of insulin treatment and after implanting measures that entail greater clinical monitoring.

Strength and limitations

As mentioned above, the important strength of this study is that this is the first work to compile available evidence and analyze data published on possible predictive factors for insulin treatment in patients diagnosed with GDM. That is to say, it compiles possible predictors of "poor response" to diet and exercise treatment in the GDM.

Therefore, and to the best of our knowledge, this is the first meta-analysis published on the topic at issue. 18 studies with a large sample size of more than 14,000 pregnant women, among whom 35.92% required insulin to manage their GDM, was also analyzed.

Given that this pathology and the requirement for insulin treatment present a relatively low incidence, this work offers results with a greater statistical power than those published to date.

Thus, a review of longitudinal observational studies was carried out, not finding any paper with a higher level of evidence. In this regard, randomized clinical trials would provide more scientific rigor than observational studies. However, clinical trials that complied with inclusion criteria were not detected in the bibliographic search of the different databases. Furthermore, there is a high degree of heterogeneity among publications for the various factors mentioned above. This should be borne in mind and results must therefore be interpreted with some caution. In addition, the absence of homogeneity in the test performed to diagnose GDM used by the different authors (oral overload of 75 mg or 100 mg of glucose), only enabled us to compare the value of basal glycemia but not the different glycemia values obtained after OGTT, with the aim of avoiding bias in our results.

Conclusions

Maternal age and parity do not behave as predictive factors of a poor response to first line treatment of GDM. The glycosylated hemoglobin value at diagnosis, BMI ≥ 30 and history of GDM during a prior gestation are the best predictors of a need for medical treatment, doubling the basal risk.

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