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Maternal and perinatal outcomes associated with multiple pregnancy in patients with gestational diabetes.

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Abstract

OBJECTIVE: To evaluate and compare the association between gestational diabetes and adverse maternal-perinatal outcomes in patients with multiple pregnancy.

MATERIALS AND METHODS: Retrospective cohort study, undertaken in patients with twin pregnancy, without diagnosed comorbidities, admitted to a reference center in Medellín, Colombia, between January 2013 and January 2017. Maternal and perinatal outcomes were compared until discharge of the newborns of mothers with and without gestational diabetes. For the statistical analysis, crude and adjusted associations were estimated.

RESULTS: A total of 87 patients with twin pregnancies were registered: 35 vs 52, with and without gestational diabetes, respectively, among 228 twin pregnancies seen in the study period. Overweight/obesity predominated in both groups (n = 30 of 35) vs (n = 35 of 52); p = 0.112. The variables: primigravida, history of gestational diabetes, and macrosomia were significantly more frequent in the gestational diabetes group (p < 0.05). The median gestational age at diagnosis was 27 weeks (interquartile range between 24.3-30). No statistically significant differences were found in the maternal outcomes of both groups. The gestational age at birth was 35 weeks in both groups (RR: 0.01; -0.90-0.92; p = 0.980). Neonatal deaths were only recorded in the group of pregnant women without gestational diabetes (n = 52 of 87), in 3 (2.9%) of the 104 live births. Birth weight was similar in both groups; However, pregnant women with gestational diabetes had a higher risk of transient tachypnea than the control group (RR: 2.06; 95%CI: 1.08-3-92), even after adjusting for birth weight (RR: 2.59; 95%CI: 1.35-4.57). Gestational diabetes was an independent risk factor for hydroelectrolytic disorders, especially potassium disorders (RR: 8.09; 95%CI: 1.60 -41.01).

CONCLUSIONS: Gestational diabetes in women with twin pregnancies is not a factor that, in general, worsens adverse maternal and perinatal outcomes.

KEYWORDS: Gestational diabetes; Multiple pregnancy; Perinatal outcome; Maternal outcome; Transient tachypnea; Hydroelectrolytic disorder.

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INTRODUCTION

Gestational diabetes is an alteration of the metabolism of carbohydrates identified for the first time during pregnancy; it is the most frequent diagnosis of pregnant women who suffer some kind of diabetes.[1-2]

Gestational diabetes is associated with complications in 5 to 6% of the cases; it is associated with a high risk of adverse maternal outcomes:[3-4] primigravidas who undergo a C-section, preterm birth, pregnancy hypertensive disorders, late intrauterine death, perineal trauma, higher risk of cardiovascular disease, and long-term diabetes.[5-6] There is also a high risk of complications for the newborn: macrosomia, shoulder dystocia, increased abdominal circumference, birth trauma, decrease in pulmonary surfactant, neonatal hypoglycemia;[4,7] even risk at the neonatal stage: hypoglycemia, respiratory disorders, polyglobulia, hypocalcemia, hyperbilirubinemia, and renal vein thrombosis.[4,8]

In normal conditions, patients with multiple pregnancy have a higher risk of maternal-fetal complications, than singleton pregnancy mothers,[7,9] besides a higher risk of gestational diabetes.[10] The question whether gestational diabetes increases the risk of adverse outcomes in patients with multiple pregnancy remains debated.[5]

Based on the aforementioned, the goal of the present study was to evaluate and compare the association between gestational diabetes and adverse maternal-perinatal outcomes in patients with multiple pregnancy.

MATERIALS AND METHODS

Retrospective cohort study, carried out with patients with twin pregnancy, without associated comorbidities, admitted in the *Clínica Universitaria Bolivariana de Medellín*, Colombia, between January 2013 and January 2017. Perinatal and maternal outcomes were compared until discharge of the newborns of mothers with and without gestational diabetes. For the statistical analysis, crude and adjusted associations were estimated.

Inclusion criteria: patients with multiple pregnancy admitted in the institution. *Exclusion criteria*: patients with pregestational morbidity (arterial hypertension, immunosuppression, neoplastic disease, history of gestational diabetes, complications associated with monochorionic pregnancy that required surgical treatment). **Figure 1**

Two study groups were made, group 1 was conformed by patients with twin pregnancy and gestational diabetes, and group 2 (control) was conformed by patients with twin pregnancy without gestational diabetes.

We obtained sociodemographic information from the clinical history of the patients: age at the time of the first prenatal consultation at the institution, body mass index, and weight classification according to the World Health Organization. The obstetric history of parity, gestational diabetes, and macrosomia were also obtained.

We also gathered information about the current pregnancy regarding the gestational diabetes pregnancy diagnostic test, gestational age at diagnosis, and gestational diabetes treatment (only for study group), as well as the type of birth, gestational age at birth, and maternal outcomes: pre-term birth, polyhydramnios related to gestational diabetes, gestational cholestasis, pregnancy hypertensive disorder, and puerperal infection.

Among the perinatal variables, we obtained information about the weight at birth (in grams), fetal macrosomia perinatal outcomes, transient

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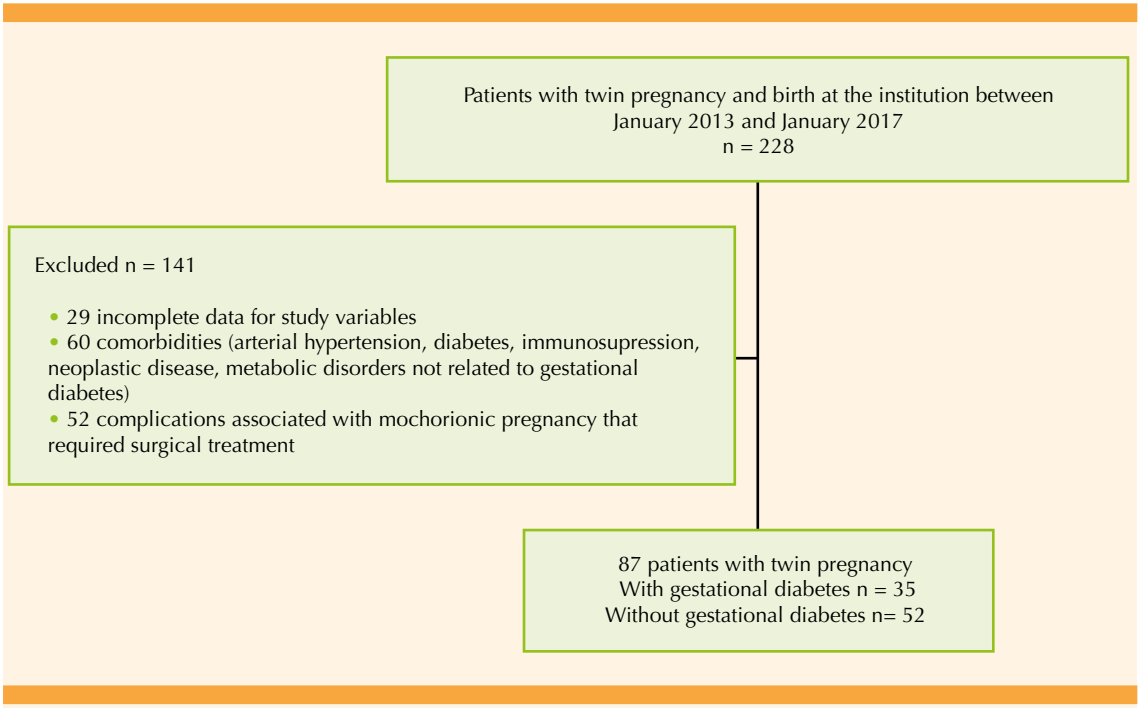


Figure 1. Twin pregnancy patient selection flow chart.

tachypnea of the newborn, hyaline membrane disease, jaundice requiring phototherapy, hypoglycemia requiring metabolic flux, intraventricular hemorrhage, hydroelectrolytic disorder, hypothermia, admission to the neonatal intensive care unit, vital status at birth, and hospital discharge.

Statistical analysis

Quantitative variables were described with central tendency and dispersion measures, according to the normal distribution of variables, with the Shapiro-Wilks test; qualitative variables were described with absolute and relative frequencies.

The comparison of the clinical quantitative and qualitative variables, whether there was coexistence of gestational diabetes or not, was made with the chi-squared test, and the Student's *t* test, respectively.

According to the normal distribution of quantitative variables, we obtained the difference of means with a confidence interval of 95%, and of medians with the Hodges-Lehman estimator for independent samples.

The crude association of gestational diabetes and maternal-perinatal outcomes in patients with twin pregnancy was calculated with Poisson's multivariate model, taking gestational diabetes as the dependent variable, and maternal-fetal outcomes as the independent variable. The association between gestational diabetes and perinatal outcomes was adjusted for weight at birth.

The data was integrated in a database with the Excel software, and afterwards it was analyzed with the IBM SPSS statistics 24 software.

The research was approved by the Research Ethics Committee of *the Universidad Pontificia Bolivariana*, and the *Clínica Universitaria Bolivariana*.

RESULTS

Eighty-seven patients with twin pregnancies were registered: 35 with gestational diabetes, and 52 without gestational diabetes, from 228 events seen during the study period. **Figure 1**

The age average of the patients was 29.2 years (SD ± 7.1), without differences between the groups. Overweight and obesity were predominant in both study groups (n = 30 of 35 in comparison with n = 35 of 52; p = 0.112). The variables primigravida, history of gestational diabetes, and fetal macrosomia were significantly more frequent in the gestational diabetes group than in the control group ($p < 0.05$). **Table 1**

The gestational diabetes diagnosis was established in 29 of 35 patients with the 75 g oral glucose tolerance test, and the median gestational age at diagnosis was 27 weeks (interquartile range 24.3-30). Nutritional habit behavior modifications for the treatment of diabetes mellitus were recommended in 31 of 35 patients with twin pregnancy and gestational diabetes; simultaneously, oral treatment was initiated, or insulin treatment, when 35% or more of the metabolic control of mothers, was altered, as reported by glucometry assessment. Seven of 35 women received oral hypoglycemic agents, and 12 of 35 received insulin. **Table 1**

There were no statistically significant differences in maternal outcomes of both groups; however, pregnancy term by C-section in the gestational diabetes group was 0.83 times higher than in the group of pregnant women without gestational diabetes (RR: 0.83; CI95%: 0.69 – 0.99). **Table 2**

The weight at birth was similar in both groups, and there was an increased risk of transient tachypnea in pregnant women with gestational diabetes versus without the disease (RR: 2.06; IC95%: 1.08 - 3.92). Even after adjusting for weight at birth, we obtained a RR: 2.49; CI95%: 1.35 – 4.57. Gestational diabetes represented a risk factor independent of hydroelectrolytic disorder, mainly associated with potassium disorders (RR: 8.09; CI95%: 1.60 - 41.01). Neonatal deaths were only reported in the group of patients without gestational diabetes (3 of 104), and they all had a diagnosis of intrauterine growth restriction in common.

DISCUSSION

Age and weight are risk factors for gestational diabetes, and the mean age in our group of patients at the time of conception was higher in the gestational diabetes group (33 years), although there was no statistically significant difference, and it was similar to Alkaabi et al.'s cohort, who reported a mean of 30.1 years.[8] The gestation week at diagnosis was 27.1, slightly late in comparison with other populations, which report this variable at 25 weeks; however, the result in the present evaluation is in line with the American College of Obstetrics and Gynecology recommendation,[1] between weeks 24 and 28 of gestation.[11]

Maternal weight is related to high risk of gestational diabetes, although a study reported this risk to be less pronounced in patients with twin pregnancy compared with the same BMI in women with a singleton pregnancy.[12] Overweight was predominant in our cohort, especially in the gestational diabetes group (16 of 35), without a statistically significant difference. A retrospec-

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Table 1. Clinical characteristics of patients with twin pregnancy by gestational diabetes presence

Characteristics	Gestational diabetes		p
	Yes n = 35	No n = 52	
Age (years); mean (SD)	33.1	26.6	0.555[a]
Body mass index (mean and SD)	28.3	26.7	0.0713[a]
Normal	5	17	
Overweight	16	22	0.112[b]
Obesity	14	13	
Parity			
Primiparous	29	27	
Second pregnancy	4	15	0.012 [b]
Multiparous	2	10	
Gestational diabetes history	9	1	0.001 [b]
Macrosomia history	5	0	0.005 [b]
Gestational diabetes diagnostic test			
100 g oral glucose tolerance test	6	-	
75 g oral glucose tolerance test	29	-	
Gestational age at gestational diabetes diagnosis (weeks), median (IQR)	27.1 (24.3 – 30)	-	-
Gestational diabetes treatment			
Diet	31	-	-
Oral	7	-	-
Insulin	12	-	-

[a] Student's T; [b] χ^2.

tive cohort with 487,870 cases, with 7,860 twin pregnancy cases among them, evaluated the compound outcome of preeclampsia, gestational diabetes, and C-section birth as maternal BMI increased; however these associations were lower in patients with twin pregnancies versus singleton pregnancies (association of BMI ≥ 40 kg/m^2 with primary outcome: absolute relative risk [ARR] of 3.10; CI95%: 2.96 – 3.24 in singleton pregnancies versus ARR: 1.74; CI95%: 1.37 – 2.20 in twin pregnancies), and they conclude that the association between maternal obesity and adverse pregnancy outcomes is weaker than in singleton pregnancies.[12]

Glycemic control is one of the most important factors to modify to have an impact on perinatal and maternal outcomes. Most of the patients receive the indication of nutritional therapy, as it happened in 31 of 35 patients from the study, while 12 of 35 required additional insulin treatment, and 7 of 35 oral treatment. Other populations have required a higher administration of insulin (68%); however, there are also reports that state that there is a higher likelihood that nulliparous patients have adequate control with diet and exercise, which are characteristics we observed in our population.[11] C-section is the most frequent type of birth for twin pregnancies,

Table 2. Maternal outcomes by gestational diabetes in patients with twin pregnancy

Maternal outcomes	Gestational diabetes		Crude relative risk (CI95%), p value
	Yes n = 35	No n = 52	
Pregnancy finalization by C-section	28	50	0.83 (0.69 – 0.99). 0.039
Gestational age at birth (mean and SD)	35.2	35.1	0.01 (-0.90 – 0.92). 0.980*
Hypertensive disorder associated to pregnancy	14	14	1.48 (0.81 – 2.71). 0.199
Pre-term birth	18	18	1.48 (0.90 – 2.43). 0.116
Polyhydramnios	4	1	5.94 (0.69 – 50.97) 0.104
Puerperal infection	2	3	0.99 (0.17 – 5.62). 0.991
Gestational cholestasis	2	2	1.48 (0.21 – 10.05). 0.685

*Mean differences (CI95%).

and based on this, we didn't find an association of risk in patients with gestational diabetes.[7,11,13]

Most of our patients were primigravidas (29 of 35) in the study group, while in the control group they were roughly half (27 of 52), which is similar to Dave et al.'s cohort.[11] Nonetheless, other population groups show a higher number of patients with twin pregnancy, generally multiparous, almost always in their second pregnancy. This difference can be attributed to the fact that access to assisted reproductive therapy is not very easy for our population, which is thought of as one of the most frequent factors in twin pregnancies in other populations; as high as 43% in Alkkabi et al.'s[8] cohort, in contrast with other reports of 24 and 31% in this group of patients.[5,11] However, we didn't explore this factor in the sample of the present study and its prevalence is unknown to us. A history of gestational diabetes was registered in 9 of 35 of the twin pregnancy cases with gestational diabetes, versus 1 of 52 in the control group, with a statistically significant difference, and in line with the findings of previous cohorts, which registered 16 of 109 patients with gestational diabetes, with a history of gestational diabetes, and 6 of 295 patients without gestational diabetes,[8] which shows that a history of gestational diabetes in the previous pregnancy poses an additional risk for following pregnancies, and it doesn't show a different behavior for twin pregnancies.

A history of macrosomic fetus in the previous pregnancy was found in 5 of 35 patients with gestational diabetes versus none in the control group, with a statistically significant difference, and posing a higher likelihood of gestational diabetes in the following pregnancy. Polyhydramnios, even though there was no significant difference, was more frequent in women with twin pregnancy and gestational diabetes. Gestational diabetes is a predictor of macrosomia in singleton pregnancies, but it does not show the same behavior in twin pregnancies; as it is even less likely to be associated with accelerated fetal growth,[14] on the contrary, patients with gestational diabetes and an adequate metabolic control can show an opposite effect to the expectation of fetal weight gain, and it has been associated

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with small fetuses. It has even been shown that there is a higher incidence of small newborns for their gestational age.[7,15] In our cohort we observed women with gestational diabetes and fetuses under 2,500 g, without significant difference to allow for a statistical association. One of the plausible explanations for this effect is the growth restrictions due to placental size, which is a hyperglycemic state that can benefit the high demands of energy in a twin pregnancy, and the competition between the fetuses for nutrients, which can limit the consequences of excessive fetal growth associated with intrauterine growth restriction, hypertrophic myocardiopathy, death, dystocia, and neonatal trauma in patients with singleton pregnancy. However, the mechanism remains unknown.[7]

There were no differences regarding gestational age at the time of birth in patients with twin pregnancy, with and without gestational diabetes, which is in line with other population groups.[8,11] However, other researchers associate gestational diabetes in twin pregnancies with older gestational age in comparison with control groups, they even consider it a protecting factor in terms of pre-term birth,[7] but it is not correct to ascertain that a pathological process can have a beneficial effect, and further research is needed about it.

The pregnancy hypertensive disorder in all its spectrum appeared frequently associated with gestational diabetes in patients with twin pregnancies (40%), in comparison with the control group (26.9%), which is in line with other researchers' reports.[5,11]

Mei et al.'s study[16] evaluated the influence of gestational diabetes in perinatal outcomes of patients with twin pregnancies and its repercussion in their children's growth, from 6 weeks to 12 months of corrected age, and they didn't find that gestational diabetes was correlated with perinatal outcomes. However, in patients with monochorionic diamniotic twin pregnancies it was correlated with pregnancy hypertensive disorders, and small fetuses for their gestational age (OR: 2.68; CI95%: 1.16 – 6.04 and OR: 0.35; CI95%: 0.16 – 0.76, respectively); with high risk of childhood overweight at 6 months of corrected age in fetuses from patients of diamniotic monochorionic and dichorionic pregnancies (OR: 2.32; CI95%: 1.05-5.09 y OR: 2; CI95%: 1.13-3.53, respectively).

There was no significant difference regarding admittance to the neonatal intensive care unit, in fact it was more frequent in the children of mothers without gestational diabetes (35 of 104), compared with the study group (18 of 70; Table 3). The same was observed when it was adjusted for gestational age, which is in line with other reports.[5,11] On the contrary, in a retrospective cross-sectional study, carried out with 645 women with dichorionic twin pregnancies, they found a higher risk for admittance to the neonatal intensive care unit (OR: 1.70; CI95%: 1.06-2.72), albeit of little significance.[17] The lack of association with these outcomes can be due to the high base risk of complications for women with twin pregnancies, even without comorbidities, especially due to the high rate of pre-term births.[18]

Similarly to the findings of a meta-analysis about outcomes in twin pregnancies with gestational diabetes, we didn't find a difference regarding gestational age at birth in the present study, nor for weight at birth.[19] On the contrary, we found an association between patients with twin pregnancies with gestational diabetes and birth transient tachypnea (RR: 2,057; CI95%: 1.078-3.924: p = 0.029), which remained when adjusted for gestational age at birth (RR: 2.491; CI95%: 1.35-4.57; p = 0.003). There was an elevated risk of hydroelectrolytic disorder in newborns when adjusting for gestational age **(Table 3)**. Even though in the literature there are no reports of differences regarding respiratory difficulties at birth, some studies inform of this

Table 3. Perinatal outcomes by gestational diabetes in patients with twin pregnancy

Outcomes	Gestational diabetes		Relative risk (CI95%) and p value (?²)	
	Yes n = 70	No n = 104	Crude	Adjusted*
Weight at birth (g)	2237 (2017 - 2465)	2285 (1875 - 2550)	0 (-140 - 120)	
Weight at birth under 2,500 g	54	73	1.09 (0.91 - 1.31) 0.311	
Transient tachypnea	18	13	2.06 (1.08 - 3.92) 0.029	2.49 (1.35 - 4.57) 0.003
Hyaline membrane	4	7	0.85 (0.26 - 2.792) 0.788	1.14 (0.33 - 3.84) 0.837
Intraventricular hemorrhage	1	2	0.74 (0.07 - 8.03) 0.807	1.30 (0.39 - 4.25) 0.668
Admittance to intensive care unit	18	35	0.78 (0.48 - 1.25) 0.299	0.896 (0.56 - 1.39) 0.601
Severe hypoglycemia	4	2	3.014 (0.57 - 16.01) 0.195	3.28 (0.59 - 18.11) 0.173
Jaundice and phototherapy	14	27	0.782 (0.44 - 1.38) 0.396	0.946 (0.54 - 1.62) 0.812
Hydroelectrolitic disorder	5	2	3.76 (0.75 - 18.87) 0.107	8.09 (1.60 - 41.01) 0.012
Hypothermia	-	1	0.01 (0.00 - 0.07) < 0.001	0.68 (0.61 - 0.77) < 0.001
Neonatal death	-	3	0.03 (0.00 - 0.09) < 0.001	

*Relative risk adjusted for weight at birth.

variable in children of mothers with gestational diabetes and twin pregnancies.[5,19]

As it was expected, hypoglycemia was more frequent in newborns of mothers with twin pregnancy and gestational diabetes (4 of 70) in comparison with the control group (2 of 104), without statistically significant difference. Similarly to the study by Guillén-Sacoto,[20] which included 120 patients with twin pregnancy and 240 with singleton pregnancy, we observed that the newborns of mothers with gestational diabetes and twin pregnancy had a higher risk of hypoglycemia (OR: 4.71; CI95%: 1.38-16.07; p = 0.013). Other cohorts have informed of similar results in patients with twin pregnancies with and without gestational diabetes;[5] nonetheless, different researchers point out that diabetes represents a determining risk factor for clinical hypoglycemia (OR: 4.87; CI95%: 3.74-6.29).[13]

Gestational diabetes has been associated with high risk of polyglobulia,[20] jaundice, and requirement of phototherapy in patients with singleton pregnancy, and up to this date there are no reports that this risk increases with patients with twin pregnancies. We didn't find in the present study significant differences, and in fact it was more frequent in newborns of patients with twin pregnancies without diabetes (26% compared with 20.3%). This finding can be attributed to the limited size of the sample, given that a study with 3,901 patients with twin pregnancies reported

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10.6% of neonatal jaundice versus 6.7% in the control group (RR: 1.56; IC95%: 1.1-2.2).[5]

There is currently little knowledge about the behavior of glycemia in patients with twin pregnancy and the severity of the alteration. A Japanese study, carried out with 471 patients with twin and singleton pregnancies with gestational diabetes, reported 20 women with gestational diabetes and twin pregnancy. When comparing gestational age at the time of diagnosis, results from the 75 g oral glucose tolerance, glycosylated hemoglobin, insulin secretion sensibility index, and insulin requirements before birth, there were no statistically significant differences between both groups in none of those outcomes, which suggests that the severity of the glycemic alteration in patients with twin pregnancy and gestational diabetes is similar to that of women with singleton pregnancy,[21] and it also coincides in that perinatal outcomes are affected by other factors than gestational diabetes itself.[22] Thus, there is no morbidity risk associated with this alteration, but one of the determining factors is gestational age at birth.[23]

A possible explanation is when placental histopathological characteristics and neonatal outcomes of singleton pregnancies are compared with dichorionic-diamniotic twin pregnancies with gestational diabetes. Patients with a singleton pregnancy showed higher rates of poor vascular perfusion (54.4 vs 30.7%; $p < 0.001$), villitis of unknown etiology (5.7 vs 0.9%, $p = 0.040$), villous immaturity (10.1 vs 0.9%; $p = 0.001$), and placental weight less than the 10th percentile (10.1 vs 0.9%; $p = 0.001$), while the compound neonatal outcome was more common in women with twin pregnancy (54.3 vs 14% $p = < 0.001$), and was only associated with lower gestational age. These findings suggest that placental alterations associated with gestational diabetes are different in patients with twin pregnancy, and they can differ in the effects on placental development and function, as well as on the fetus condition and perinatal outcomes. Also, lesions due to poor vascular perfusion, which result in hypoxia and ischemia, have been correlated with placental insufficiency, pre-term birth, intrauterine growth restriction and pregnancy hypertensive disorders, and frequent lesions in obese women with gestational diabetes. However, these histopathological studies did not correlate with maternal glycemic control.[23]

Even though patients with twin and singleton pregnancies with gestational diabetes are considered high-risk pregnancies, and require optimal treatment to diminish adverse outcomes, the evidence is not so strong as to guide a well-defined protocol, nor there is consensus as to the right moment to end the pregnancy. Based on the aforementioned, further studies are needed to define clear guidelines for these clinical scenarios. Even though neonatal outcomes differ between multiple and singleton pregnancies, it is important to continue using the established criteria for singleton pregnancies.[14] Likewise, fetal growth differences of patients with gestational diabetes with twin or singleton pregnancies pose the need to know these characteristics among the diagnostic criteria.[18,24] Even though it is clear that patients who have gestational diabetes during pregnancy have a high risk of evolving to diabetes type 2, it is currently unknown whether a history of twin pregnancy is related, or has a enhancing effect for this risk. One of the main limitations of the published literature for patients with twin pregnancy and gestational diabetes is a small sample size and that most studies are retrospective, which highlights the need to carry out more prospective studies that allow to guide diagnostic, monitoring, and treatment consensus for this population.

This study stands out for its specific focus on twin pregnancies, which is a population with unique obstetric characteristics and challenges. The inclusion of all the patients allowed to obtain conclusions with a broader applicability to this kind of patients. Also, there is an emphasis on

the evaluation on specific outcomes (maternal and perinatal) which provides a broad vision of the possible complications linked to gestational diabetes in twin pregnancies. However, the weaknesses that must be taken into account when interpreting the results, and the inherent limitation of a retrospective design, imply possible restrictions on the availability and quality of the compiled information, the lack of control of some information biases, as well as the capability to establish causal relations.

CONCLUSIONS

A twin pregnancy is a high-risk condition, with or without the coexistence of other morbidities, but diabetes (as an additional diagnosis) does not behave consistently as a factor that worsens neonatal adverse outcomes, and this can be explained with different pathophysiological mechanisms that remain unclear, included placental affectation. The lack of association with these outcomes can be due to the higher basal risk of this type of complications in twin pregnancies, even without comorbidities, especially because of the pre-term birth rate. However, birth transient tachypnea and the hydroelectrolytic disorder are frequently associated with gestational diabetes. Among the maternal outcomes, there still is a clear association between gestational diabetes and pregnancy hypertensive disorders. The current data shows different neonatal outcomes between patients with gestational diabetes and singleton or multiple pregnancies, which poses the need for different cutoff points for the diagnostic tests, treatment objectives in the assessment of fetal growth, and the ideal period to finalize the pregnancy, without extrapolating the available information about the behavior of diabetes in patients with singleton pregnancy.

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