

Retrospective Cohort Study

Does parity worsen diabetes-related chronic complications in women with type 1 diabetes?

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Abstract

AIM: To determine the relationship between parity, glycemic control, cardiovascular risk factors and diabetes-related chronic complications in women with type 1 diabetes.

METHODS: This was a multicenter cross-sectional study conducted between December 2008 and December 2010 in 28 public clinics in 20 cities from the 4 Brazilian geographic regions. Data were obtained from 1532 female patients, 59.2% Caucasians, and aged 25.2 ± 10.6 years. Diabetes duration was of 11.5 ± 8.2 years. Patient's information was obtained through a questionnaire and a chart review. Parity was stratified in five groups: Group 0 (nulliparous), group 1 (1 pregnancy), group 2 (2 pregnancies), group 3 (3 pregnancies), group 4 (≥ 4 pregnancies). Test for trend and multivariate random intercept logistic and linear regression models were used to evaluate the effect of parity upon glycemic control, cardiovascular risk factors and diabetes-related complications.

RESULTS: Parity was not related with glycemic control and nephropathy. Moreover, the effect of parity upon hypertension, retinopathy and macrovascular disease did not persist after adjustments for demographic and

clinical variables in multivariate analysis. For retinopathy, the duration of diabetes and hypertension were the most important independent variables and for macrovascular disease, these variables were age and hypertension. Overweight or obesity was noted in a total of 538 patients (35.1%). A linear association was found between the frequency of overweight or obesity and parity ($P = 0.004$). Using a random intercept multivariate linear regression model with body mass index (BMI) as dependent variable a borderline effect for parity ($P = 0.06$) was noted after adjustment for clinical and demographic data. The observed variability of BMI was not attributable to differences between centers.

CONCLUSION: Our results suggest that parity has a borderline effect on body mass index but does not have an important effect upon hypertension and micro or macrovascular chronic complications. Future prospective evaluations must be conducted to clarify the relationship between parity, appearance or worsening of diabetes-related chronic complications.

Key words: Type 1 diabetes; Parity; Glycemic control; Cardiovascular risk factors; Diabetes-related chronic complications

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Core tip: To the best of our knowledge, this was the largest study ever conducted with pregnant women with type 1 diabetes in Brazil and maybe in Latin America. Our results suggest that parity did not have an important effect upon hypertension and micro or macrovascular diabetes-related chronic complications. Further prospective studies with a larger number of patients must be addressed to clarify the relationship between parity, appearance or worsening of diabetes-related chronic complications.

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INTRODUCTION

There is a controversy about the impact of pregnancy and parity on the appearance of diabetes-related chronic complications or the progression of its course if they are already present in women with preexisting type 1 diabetes (T1D)^[1,2].

Some studies found a worsening of retinopathy during pregnancy^[3-5], which was not confirmed by others^[2-4,6]. The worsening of retinopathy could be explained by several risk factors such as pregnancy *per se*, hypertension, hyperglycemia, duration of diabetes and a rapid drop in blood glucose levels aiming to reach normoglycemia^[5].

Also the presence of increased circulating levels of insulin-like growth factor (IGF-1) that occurs normally during pregnancy could accelerate the progression of an already existing retinopathy^[7]. The association between pregnancy and nephropathy is related to an increased albuminuria or alterations on glomerular filtration rate^[8]. So far, the mechanisms linking pregnancy to both chronic complications are still unclear and controversial. Some studies showed an association between improvement of glycemic control under intensive insulin therapy and worsening of retinopathy but not nephropathy^[5,9].

Other conditions involved in the pathophysiology of diabetes-related chronic complications must be addressed such as pre-pregnancy body mass index (BMI) and blood pressure levels, which have been increasing in the last three decades in some populations^[10]. In a Swedish study, it was found that the combination of T1D and overweight/obesity confers a high risk for adverse outcomes, like pre-eclampsia, that increases proportionally to BMI^[11]. Otherwise, when women with T1D presenting the features of metabolic syndrome become pregnant, they generally have the coexistence of vascular complications^[12]. It has also been shown that women with T1D and pre-eclampsia or pregnancy-induced hypertension present high risk of severe retinopathy later in life^[13].

In the Eurodiab study a better glycemic control was found among parous women than nulliparous, and parity did not influence the levels of microalbuminuria and preexisting retinopathy^[14]. In a Finnish study it was found a slower progression of retinopathy in parous women than in nulliparous^[15].

Considering the scarcity of data regarding the relationship between parity, glycemic control and diabetes-related chronic complications in women with T1D in Brazil, the Brazilian Type 1 Diabetes Study Group (BrazDiab1SG) conducted this survey aiming to analyze the impact of parity in the above mentioned clinical conditions.

MATERIALS AND METHODS

Patients and methods

This was a multicenter, cross-sectional, observational study conducted between December 2008 and December 2010 in 28 public secondary and tertiary care-level clinics from the National Brazilian Health Care System, located in 20 cities in all Brazilian geographic regions (North/Northeast, Mid-West, Southeast, and South). The details of the data collection methods have been published previously^[16]. Two thousand and ten patients, 56% female (2010, 56% female) patients that were diagnosed between 1960 and 2010 were included in the study. Among the 2010 enrolled women, only those who knew their age at menarche were included ($n = 1532$, 76.2%). Patients who did not have had menarche ($n = 467$, 23.2%) and women with incomplete information for parity ($n = 11$, 0.5%) were excluded.

Each local ethics committees approved the study (Appendix 1). All patients or their parents, when necessary, signed a written informed consent agreeing

with their participation in the study.

During a clinical visit, a questionnaire was applied in order to collect demographic, educational and economic data. The following variables were assessed then: Age, age at diagnosis, duration of diabetes, height (m), weight (kg), blood pressure, parity, comorbidities, smoking status and the use of metformin.

Data from the last clinical visit were obtained from medical records such as levels of glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Diabetes-related chronic complications were screened in all patients with diabetes duration longer than 5 years, such as retinopathy (by funduscopy; classified as absent, non-proliferative or proliferative), clinical nephropathy [according to American Diabetes Association (ADA)] recommendations^[17], macrovascular diseases (clinical coronary artery disease, stroke, and peripheral vascular disease), and foot alterations. The following goals for adequate metabolic control that are adopted by the ADA^[17] were also adopted by the BrazDiab1SG: HbA1c at goal was defined as HbA1c levels of < 58 mmol/mol (7.5%) for patients with T1D between 13 and 19 years old; < 64 mmol/mol (8%) for patients between 6 and 12 years old; between 58 mmol/mol (7.5%) and 69 mmol/mol (8.5%) for patients < 6 years old; and < 53 mmol/mol (7%) for adult patients^[17]. Poor glycemic control was considered as having HbA1c levels higher than 75 mmol/mol (9%).

Hypertension was defined as a systolic blood pressure (sBP) ≥ 140 mmHg and/or diastolic blood pressure (dBP) ≥ 90 mmHg, use of antihypertensive agents or self-reported for adults; in adolescents hypertension was defined as a sBP or dBP $\geq 95^{\text{th}}$ percentile for age, sex and height^[17].

Overweight was defined as a BMI ≥ 25 kg/m², and obesity as a BMI ≥ 30 kg/m² in adults^[18]. Overweight was considered as a BMI of $\geq 85^{\text{th}}$ percentile for age and gender, and obesity as a BMI of $\geq 95^{\text{th}}$ percentile for age and gender for adolescents^[18].

In 1347 patients (88.0%), HbA1c was measured using methods certified by the National Glycohemoglobin Standardization Program (NGSP): High-performance liquid chromatography in 733 patients (54.3%) and turbidimetry in 614 patients (45.7%). Measurement of HbA1c levels using methods that were not certified by the NGSP and patients with no data on HbA1c levels or use of methodology not certified by the NGSP were not included in the analyses of glycemic control ($n = 185$, 12.0%). Enzymatic techniques were used to measure FPG, triglycerides, HDL cholesterol, and total cholesterol. Friedewald's equation was used to calculate LDL cholesterol^[19]. Patients smoking more than one cigarette per day at the time of the interview were considered as current smokers.

Sample calculation and economic status

The study sample calculation was done according to a methodology described elsewhere^[16]. Our sample represented the distribution of T1D cases all over Brazil that was estimated using the overall population distribution reported in the 2000 Brazilian Institute of Geography and Statistics Population Census (IBGE)^[20]. These data were combined with national estimates of diabetes prevalence determined by a survey conducted in 1988 in order to determine the minimum number of patients that should be studied in each geographic region of the country^[21]. Economic status was defined according to the Brazilian Economic Classification Criteria^[22]. This classification also takes in account the education level: Illiterate/incomplete primary education, complete primary education/incomplete secondary education, complete secondary education/incomplete high school, complete high school/some college or college graduate. The following economic status categories were considered: High, middle, low, and very low^[22].

Statistical analysis

The data were summarized as means (\pm SD) and median (minimum-maximum) for continuous variables and as counts (relative frequencies) for discrete variables. Patients were stratified in five groups according to parity: Group 0 (nulliparous), group 1 (1 pregnancy), group 2 (2 pregnancies), group 3 (3 pregnancies) and group 4 (≥ 4 pregnancies).

ANOVA test with Sidak correction was used. Test for trend (linear association) was used to analyze the association between parity and frequency of retinopathy, albuminuria and hypertension. A multivariate random intercept logistic regression model was performed with retinopathy (yes/no) as the dependent (outcome) variable and parity as the independent (exposure) variable. Other independent variables, such as socioeconomic status, ethnicity (Caucasian or non-Caucasian based on self-reporting), age, duration of diabetes, HbA1c levels and hypertension (yes/no) were also controlled in the analysis. The same multivariate model was performed with the following dependent variables: Hypertension (yes/no), adding to the set of independent variables, creatinine levels, BMI and smoking status and excluding hypertension; macrovascular disease with the same demographic variables above-mentioned as independent variables adding to the model: Hypertension (yes/no), HbA1c and LDL-Cholesterol levels and smoking status (yes/no). A random intercept multivariate linear regression model was further applied to BMI as dependent variable (three nested models were considered). All analyses were performed using the SPSS version 17.0, SPSS, Inc., Chicago, Illinois, United States, except the random intercept models that were fitted using MLwiN^[23]. Odds ratios (ORs) with 95% CIs, variance and standard error

Table 1 Clinical and demographic data of the studied population

Variable	
<i>n</i>	1532
Age, yr	25.2 ± 10.6
Age at diabetes diagnosis, yr	11.4 ± 8.1
Age at menarche, yr	12.7 ± 1.7
Duration of diabetes, yr	11.5 ± 8.2
Ethnicity, <i>n</i> (%) ¹	
Caucasian	907 (59.2)
Non-caucasian ¹	625 (40.7)
Geographic region, <i>n</i> (%)	
Southeast	611 (39.9)
North/Northeast	454 (29.6)
South	367 (24.0)
Mid-west	100 (6.5)
Economic status	
High	104 (6.7)
Medium	383 (25.0)
Low	533 (34.8)
Very low	512 (33.4)
Level of care, <i>n</i> (%)	
Secondary	412 (26.9)
Tertiary	1117 (73.1)
Time of follow-up, yr	7.1 (< 1 to 49)

Data are presented as number (percentage), mean ± SD or median (minimum/maximum). ¹African-Brazilians, Mulattos, Asians, and Native Indians.

were calculated when indicated. A two-sided *P* value less than 0.05 was considered significant.

The statistical review of the study was performed by a biomedical statistician that is also a co-author (APL).

RESULTS

Overview of the studied population

Data were obtained from 1532 patients (excluded *n* = 478, 23.7%). The economic status of 1045 (68.2%) of the patients was either very low or low. Table 1 lists the demographic data of the studied population.

Overview of the studied population stratified according to parity, demographics and socioeconomic status data

The comparison between the patients stratified according to parity showed that patients from groups 0, 1 and 2 were younger than patients from group 4 (*P* < 0.001). Patients from groups 0 and 1 had been diagnosed with diabetes with lower age and had less duration of diabetes than patients from the other groups (*P* < 0.001). A difference between the five groups and geographic regions of the country was observed, being the difference accounted by Mid-West region, that had no patients in group four. These data are described in Table 2.

Overview of the studied population stratified according to parity, glycemic and cardiovascular risk factors control

Overweight or obesity was noted in 538 patients (35.1%). Patients from group 0 had lower BMI than patients from the other groups. A linear association was found between

the frequency of overweight or obesity and parity (*P* = 0.004). Using a random intercept multivariate linear regression model with BMI as dependent variable a borderline effect for parity (*P* = 0.06) was noted after adjustment for clinical and demographic data (model 2 and model 3). The significant effect of low insulin dose and age persisted. The observed variability of BMI was not attributable to centers. These data are described in Table 3.

A lower level of HbA1c was found in patients from group 2 in comparison to patients from group 0. No differences between the five groups were observed for the number of patients reaching the target of HbA1c. A higher frequency of hypertension and higher levels of sBP and dBP were observed in group 4 in comparison to the other groups (*P* < 0.01 for all comparisons).

A higher HDL-cholesterol was observed in group 4 in comparison to the other groups. No other difference in lipid parameters was noted. Metformin was used by 162 (10.6 %) patients, and its use was related to parity (*P* = 0.02). The use of metformin was more frequently found in patients from group 4 in comparison with patients from groups 0, 1 and 3, respectively 9 (17.3%) vs 103 (10.2%) vs 20 (8.4) vs 7 (7.4), *P* = 0.04. A higher insulin dose/kg was used by patients from group 0 in comparison to patients from the other groups. The demographic, clinical, and laboratory data of patients stratified by parity are described in Table 2.

Overview of the studied population stratified according to parity and diabetes-related chronic complications

Overall, 1219 (79.7%) of the patients had criteria to be screened for diabetes-related chronic complications. Parity was related to the presence of diabetes-related chronic complications both micro and macrovascular. Considering women with information regarding retinopathy, (*n* = 1033, 84.7%) a lower frequency of non-proliferative and proliferative retinopathy was noted in patients from group 0 in comparison to the other groups (*P* < 0.01). A tendency for an association between parity and nephropathy was observed (*P* = 0.08) in those patients with information obtained in the previous year (*n* = 1041, 85.4%). These data are shown in Table 2.

Using a multivariate random intercept logistic regression model with retinopathy as the dependent variable no effect of parity was noted but the OR for duration of diabetes and presence of hypertension were 1.11 (95%CI: 1.08-1.14, *P* < 0.001) and 3.51 (95%CI: 2.42-5.08, *P* < 0.001), respectively. The other independent variables did not reach statistical significance. The same model with macrovascular disease as dependent variable also showed no effect of parity but the OR for age was 1.067 (95%CI: 1.03-1.106, *P* < 0.0001), while for HbA1c levels it was 1.166 (95%CI: 1.023-1.330, *P* < 0.02) and for hypertension it was 2.29 (95%CI: 1.219-4.306, *P* < 0.02). The other independent variables did not reach statistical significance.

In multivariate random intercept logistic regression

Table 2 Clinical, demographic and laboratory data stratified by parity

Variable	Parity					¹ P-value
	Group 0 (nulliparous)	Group 1 (1 pregnancy)	Group 2 (2 pregnancies)	Group 3 (3 pregnancies)	Group 4 (≥ 4 pregnancies)	
<i>n</i> (%)	1014 (66.2)	238 (15.5)	147 (9.6)	81 (5.3)	52 (3.4)	
Demographic and economic status data						
Age, yr	20.7 ± 7.9	30.2 ± 8.5	34.6 ± 8.6	38.4 ± 9.6	42.3 ± 10.7	< 0.001
< 15	191 (18.7)	1 (0.4)	0	0	0	
15-30	706 (69.6)	117 (49.2)	42 (28.6)	12 (14.8)	6 (11.5)	
≥ 30	117 (11.5)	120 (50.4)	105 (71.4)	69 (85.2)	46 (88.5)	
Duration of DM, yr	9.4 ± 6.9	13.9 ± 8.2	15.3 ± 8.9	17.9 ± 8.9	19.0 ± 10.7	< 0.001
Age at diagnosis, yr	11.2 ± 6.4	16.2 ± 8.4	19.2 ± 8.1	20.5 ± 9.3	23.3 ± 8.8	< 0.001
Ethnicity, yr (%) ≥ ²						0.7
Caucasian	606 (59.8)	144 (60.5)	83 (56.5)	47 (58.0)	27 (51.9)	
Non-caucasian	408 (40.2)	94 (39.5)	64 (43.5)	34 (42.0)	25 (48.1)	
Geographic region, <i>n</i>						0.001
Southeast	410 (40.4)	94 (39.5)	54 (36.7)	31 (38.3)	22 (42.3)	
South	248 (24.5)	53 (22.3)	36 (24.5)	18 (22.2)	12 (23.1)	
North/Northeast	309 (30.5)	69 (29.0)	39 (26.5)	19 (23.5)	18 (34.6)	
Mid-West	47 (4.6)	22 (9.2)	18 (12.2)	13 (16.0)	0	
Economic status (%)						0.5
High	72 (7.1)	16 (6.7)	8 (5.4)	5 (6.2)	3 (5.8)	
Medium	273 (26.9)	56 (23.5)	29 (19.7)	18 (22.2)	7 (13.5)	
Low	340 (33.5)	85 (35.7)	55 (37.4)	33 (40.7)	20 (38.5)	
Very low	329 (32.4)	81 (34.0)	55 (37.4)	25 (30.9)	22 (42.3)	
Glycemic control and insulin dose						
HbA1c (%)	9.6 ± 2.6	9.4 ± 2.4	8.8 ± 2.0	9.4 ± 2.4	9.5 ± 2.0	0.02
HbA1c (mmol/mol)	81.9 ± 28.4	79.9 ± 26.3	73.4 ± 22.2	79.5 ± 26.8	80.4 ± 21.7	
HbA1c (good) <i>n</i> (%)	107 (11.9)	21 (10.3)	19 (14.6)	8 (11.3)	3 (6.5)	0.1
H1Ac (poor) <i>n</i> (%)	480 (53.5)	99 (48.8)	51 (39.2)	37 (52.1)	27 (58.7)	
Insulin dose (U/kg per day)	0.98 ± 0.4	0.8 ± 0.3	0.8 ± 0.3	0.7 ± 0.4	0.8 ± 0.4	0.001
Metformin use, yr (%)	103 (10.2)	20 (8.4)	24 (16.3)	6 (7.4)	9 (17.3)	0.04
Cardiovascular risk factors						
sBP (mmHg)	110.8 ± 14.6	117.5 ± 15.7	119.6 ± 18.7	119.8 ± 18.9	124.0 ± 21.4	< 0.001
dBp (mmHg)	72.3 ± 10.1	75.2 ± 11.3	74.9 ± 11.5	75.9 ± 11.5	75.9 ± 10.2	< 0.001
Hypertension, yr (%)	158 (16.6)	76 (32.2)	53 (36.3)	29 (35.8)	25 (48.1)	< 0.001
Cholesterol (mg/dL)	176.9 ± 43.7	186.4 ± 43.4	181.3 ± 41.6	182.3 ± 42.0	183.5 ± 44.5	0.055
Triglycerides (mg/dL)	98.74 ± 75.0	102.0 ± 61.1	103.2 ± 64.4	116.2 ± 110.6	105.8 ± 94.9	0.3
HDL cholesterol (mg/dL)	54.1 ± 14.4	58.3 ± 18.4	55.2 ± 15.8	55.3 ± 15.3	61.5 ± 17.4	0.01
Non-LDL cholesterol (mg/dL)	122.5 ± 42.6	128.2 ± 39.9	126.0 ± 41.0	124.9 ± 41.2	122.8 ± 43.4	0.5
LDL cholesterol	103.8 ± 34.7	107.6 ± 35.5	105.5 ± 36.5	103.1 ± 31.2	103.3 ± 37.6	0.7
BMI (kg/m ²)	22.8 ± 3.4	23.9 ± 3.8	24.3 ± 3.5	24.4 ± 5.1	25.5 ± 4.6	< 0.001
Overweight or obesity, <i>n</i> (%) ¹	338 (33.5)	153 (35.2)	56 (38.1)	36 (44.4)	25 (49.0)	0.004
³ Retinopathy, yr (%)						< 0.001
Absent	649 (66.9)	154 (73.3)	104 (77)	60 (76.5)	32 (65.3)	
Non-proliferative	50 (6.7)	36 (17.1)	15 (11.1)	11 (14.1)	10 (20.4)	
Proliferative	48 (6.4)	20 (9.5)	16 (11.9)	7 (9.0)	7 (14.3)	
⁴ Nephropathy, yr (%)						0.08
Absent	527 (70.7)	128 (60.7)	91 (67.4)	49 (62.8)	30 (61.2)	
Microalbuminuria	90 (12.1)	43 (20.4)	17 (12.6)	12 (18.8)	8 (28.0)	
Clinical nephropathy	23 (3.1)	9 (4.3)	8 (5.9)	3 (4.7)	2 (5.0)	
⁵ Macrovascular complications, yes (%) ⁶	23 (3.1)	16 (7.6)	13 (9.6)	5 (6.4)	7 (14.3)	< 0.001

The data are presented as *n* (%) mean ± SD or median (minimum/maximum). ¹The *P* value is related to the comparison among all groups (ANOVA); ²African-Brazilians, Mulattos, Asians, Native Indians; ^{3,4,5}Retinopathy, nephropathy and macrovascular complications were considered in patients with criterion to be screened (duration of diabetes ≥ 5 years, *n* = 1219); ⁶Overweight or obesity were considered together. HbA1c: Glycated hemoglobin; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; BMI: Body mass index.

model with hypertension as the dependent variable the OR for age was 1.041 (95%CI: 1.021-1.061, *P* < 0.001) for duration of diabetes was 1.031 (95%CI: 1.012-1.056, *P* < 0.005), for BMI was 1.069 (95%CI: 1.029-1.110, *P* = 0.005), and for plasma creatinine level was 2.280 (95%CI: 1.722-3.017, *P* < 0.001). The other independent variables did not reach statistical significance.

A small variability attributable to centers was noted only

for macrovascular disease with a variance and standard error of 0.376 (0.276).

DISCUSSION

Our study showed an association between parity with retinopathy, macrovascular disease and hypertension that disappeared after adjustment for variables that

Table 3 Effect of parity on body mass index evaluated by random intercept multivariate linear regression and adjusted for clinical and demographic data

Variable	Model 1	Model 2	Model 3	P value
Parity				
Nulliparous (reference)				
1	0.400 (0.278)	0.291 (0.276)	0.291 (0.277)	NS
2	0.366 (0.350)	0.320 (0.347)	0.326 (0.350)	NS
3	0.171 (0.456)	0.119 (0.453)	0.111 (0.454)	NS
≥ 4	1.013 (0.563)	1.029 (0.558)	1.051 (0.560)	0.06
Age	0.081 (0.014)	0.069 (0.014)	0.069 (0.014)	NS
Duration of diabetes (yr)	0.007 (0.015)	0.011 (0.015)	0.013 (0.015)	NS
Insulin dose (U/kg per day)		-1.237 (0.253)	-1.239 (0.254)	(< 0.001)
Metformin use (yr)		-0.960 (0.678)	-0.994(0.679)	NS
Economic status (classes)				NS
High (reference)				
Medium			0.677 (0.392)	
Low			0.551 (0.386)	
Very low			0.353 (0.397)	
Ethnicity (non-caucasian)				NS
Intercept	23.233 (0.166)	23.281 (0.171)	23.814 (0.377)	
Variability attributable to centers				
Variance	0.296 (0.148)	0.340 (0.161)	0.321 (0.155)	
Variability attributable to patients				
Variance	12.475 (0.456)	12.251 (0.448)	12.226 (0.447)	
-2 × loglik	8.192.640	8167.357	8.163.366	

Data are presented as B coefficient or variance (standard error); continuous independent variables are centered on the mean. Model 1: Adjusted for age and duration of diabetes; Model 2: Adjusted for age, duration of diabetes, insulin dose and metformin use; Model 3: Adjusted for age, duration of diabetes, insulin dose, metformin use, economic status and ethnicity. NS: Not significant.

could influence these outcomes, such as age, duration of diabetes, plasma creatinine levels, HbA1c, daily insulin dose and use of metformin. However a borderline effect of parity upon BMI was observed.

The impact of pregnancy and parity on the appearance of diabetes-related chronic complications or the progression of its course is still a matter of controversy^[2]. Some studies have found no difference in the prevalence of diabetes-related chronic complications between nulliparous and parous women^[24], less progression of retinopathy in multiparous than in nulliparous women^[15] and even a limitations of the progression of nephropathy and retinopathy probably due to a better glycemic control found in parous women compared to nulliparous women^[14].

An unexpected finding was that a lower daily insulin dose was associated with a higher BMI. The use of metformin had no effect on BMI probably because the majority of women with increased BMI were under the use of metformin; the use of metformin in patients with T1D has not its clear benefits well established but a decrease in insulin daily dose has generally been described^[25].

Nevertheless, it is important to emphasize that the absence of data on body weight before each pregnancy and consequently the weight gain during each pregnancy does not allow us to take any conclusions about this relationship. However, recently a study^[26] has shown that around 20% of T1D patients have been diagnosed with overweight/obesity. Although weight before the diagnosis of diabetes was not recorded in our sample,

more than one-third of the nulliparous women had overweight or obesity. Overweight and obesity are related to insulin resistance which is strongly associated with cardiovascular disease^[27]. We have found no effect of parity on cardiovascular disease in our study.

Considering microvascular complications, retinopathy was the most prevalent diabetes-related chronic complication associated with parity but after adjustments for other clinical and demographic variables this association did not show to be significant. Indeed, the most significant variables related to retinopathy were duration of diabetes and the presence of hypertension. The majority of the studies relating pregnancy with retinopathy were prospective and the results were controversial^[1,3,4]. The DCCT^[1] and the Eurodiab^[14] compared women with incident pregnancies during the study period with women who did not conceive. The DCCT study showed a transient worsening of retinopathy, which disappeared 12 mo post-partum and the Eurodiab study did not find any relationship between retinopathy and pregnancy. Indeed, in the Eurodiab study^[14] the duration of diabetes and the level of HbA1c were the most important predictors of the occurrence of retinopathy. Two other recent studies showed that progression of sight-threatening retinopathy during pregnancy some years post-partum was related to duration of diabetes, to the presence of macular edema and higher blood pressure levels during pregnancy but not to HbA1c levels^[13,28]. Rosenn *et al.*^[29] performed a large retrospective study with 776 nulliparous women and 582 parous women with T1D and have found an inverse association with parity and the presence of retinopathy.

Considering nephropathy, our data is in accordance with the findings of Reece *et al*^[8] that conducted a study with 31 pregnancies complicated by nephropathy and have found a significant increase in maternal blood pressure, proteinuria and nephrotic syndrome in 71% of pregnancies but no adverse effects of pregnancy on the natural course of the underlying renal disease. Miodovnik *et al*^[30] have followed a group of 182 pregnant women with T1D, with and without nephropathy. They have found that pregnancy does not increase the risk of nephropathy and does not accelerate its progression.

These studies regarding the progression of retinopathy and nephropathy were prospective. So, our results must then be interpreted with caution due to its cross-sectional design, that does not allow us to deny a causal relationship between parity and occurrence/worsening of retinopathy and nephropathy in our population. Nevertheless, many women had already retinopathy and nephropathy and also important risk factors for the development or progression of both complications such as the presence of overweight or obesity, hypertension, as described in other studies^[8,10-13,29,30].

We should also take in account that for hypertension parity did not reach statistical significance in multivariate analysis. Indeed, age, duration of diabetes BMI, ethnicity (Caucasian) and plasma creatinine levels were the most important factors.

The main strength of our large sample size is that it represents the diverse, young Brazilian population with T1D, with a multi-ethnic and different socioeconomic backgrounds. Also a uniform, standardized recruitment protocol in all participating centers was used.

Finally, some limitations must be addressed in our study. The mean age of our patients is around 25 years, which could represent a short time frame to the appearance of diabetes-related chronic complications. Additionally, we do not have data about how long patients had the diagnosis of diabetes at the time of each pregnancy, occurrence of stillbirth, prematurity, neonatal mortality and no information concerning screening for retinopathy and nephropathy during pregnancies.

In conclusion, our data did not find an effect of parity upon diabetes-related chronic complications and hypertension, but a borderline effect on BMI. These findings should allow us not to discourage women without severe and progressive diabetes-related complications to become pregnant if they reach and maintain a good glycemic control. Further prospective studies must be addressed to clarify the mechanisms underlying the relationship between parity, and the appearance or worsening of diabetes comorbidities and the effect of parity on diabetes-related chronic complications.

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COMMENTS

Background

It is generally believed that pregnancy itself or an increasing number of pregnancies might worsen diabetes-related chronic complications.

Research frontiers

So far, the mechanisms linking pregnancy to both chronic complications are still unclear and controversial.

Innovations and breakthroughs

For a long time women with diabetes have been discouraged to become pregnant regarding the possibility that an already existing complication might worsen and new complications might appear during pregnancy. This study has shown no relationship between higher parity and the worsening or appearance of diabetes-related chronic complications.

Applications

This study showed an association between parity with retinopathy, macrovascular disease and hypertension that disappeared after adjustment for variables that could influence these outcomes, such as age, duration of diabetes, plasma creatinine levels, HbA1c, daily insulin dose and use of metformin.

Peer-review

The manuscript is well written, and the study results and evaluation means are well defined in detail. It provides additional information on a controversial area, while suitably mentioning the shortcomings of the study as well. It will be of good concern to clinicians/researchers working on this subject, while further research will still be needed for clarification of the mentioned links, as the authors also mention.

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