CLINICAL SCIENCE

Macroscopic placental changes associated with fetal and maternal events in diabetes mellitus

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OBJECTIVES: The current study sought to identify macroscopic placental changes associated with clinical conditions in women with or without diabetes and their newborns.

METHODS: The study population consisted of 62 pregnant women clinically diagnosed with diabetes and 62 healthy women (control group).

RESULTS: Among the subjects with diabetes, 43 women (69.3%) were diagnosed with gestational diabetes mellitus, 15 had diabetes mellitus I (24.2%), and four had diabetes mellitus II (6.5%). The mean age of the women studied was 28.5 ± 5.71 years, and the mean gestational age of the diabetic women was 38.51 weeks. Of the 62 placentas from diabetic pregnancies, 49 (79%) maternal surfaces and 59 (95.2%) fetal surfaces showed abnormalities, including calcium and fibrin deposits, placental infarction, hematoma, and fibrosis. A statistical association was found between newborn gender and fetal and maternal placental changes ($p = 0.002$). The mean weight of the newborns studied was $3{,}287 \pm 563$ g for women with diabetes mellitus, $3{,}205 \pm 544$ g for those with gestational diabetes mellitus, $3{,}563 \pm 696$ g for those with diabetes mellitus II, and $3{,}095 \pm 451$ g for those with diabetes mellitus I.

CONCLUSIONS: Infarction, hematoma, calcification, and fibrin were found on the maternal and fetal placental surfaces in women with diabetes. Women with gestational diabetes and post-term infants had more calcium deposits on the maternal placental surface as compared to those with type I and type II diabetes.

KEYWORDS: Diabetes Mellitus; Newborn; Placenta; Pregnancy.

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INTRODUCTION

The human placenta regulates maternal and fetal physiological changes during pregnancy. It also plays a major role in pregnancy-related complications, such as diabetes mellitus (DM) (1).

DM is a common clinical condition that affects approximately 1 to 15% of pregnant women. Maternal metabolic control has been directly associated with complications and deaths in pregnant women with DM (2). Diabetes during pregnancy can lead to or aggravate placental abnormalities, which will impact the systemic balance between the pregnant woman and her fetus. DM can increase the frequency of placental dysfunction and alter its structure and function, and it is also associated with increased rates of maternal and perinatal morbidity and miscarriage. The nature, extent, and specificity of these abnormalities depend on the gestational period and the severity and type of diabetes.

Although the mechanisms of pathogenesis are not fully understood, it is believed that hormonal adjustments during pregnancy, including increased levels of estrogen, progesterone, cortisol, prolactin, and human placental lactogen, play an important role. These changes lead to metabolic imbalance and may result in increased insulin resistance and DM onset in susceptible women and uncontrolled blood glucose levels in pre-diabetic women, especially during the last two trimesters of pregnancy (3).

DM complications during pregnancy include polyhydramnios (clinically diagnosed in pregnant women with poorly controlled DM); premature rupture of membranes and preterm births (4); hypertensive disorders of pregnancy, particularly preeclampsia (5); and higher rates of spontaneous abortion, macrosomia (6), birth defects, stillbirth, respiratory distress syndrome, and neonatal hypoglycemia (4).

No potential conflict of interest was reported.

Placental changes are believed to be partly responsible for the high incidence of fetal complications observed in pregnant women with DM (1). However, the relationship between DM and the macroscopic placental changes that occur during pregnancy is not well established. Thus, the current study aimed to identify macroscopic placental changes associated with clinical outcomes in women with and without DM and their newborns.

MATERIALS AND METHODS

This prospective study was conducted at a public maternity hospital and diabetes reference center in the city of Goiânia in Central-West Brazil between August 2009 and July 2010. The study population included 62 pregnant women clinically diagnosed with DM. These women were matched to a control group that comprised 62 healthy women considered to be at a low obstetric risk who had undergone vaginal delivery or cesarean section. These women had no maternal complications during pregnancy, their obstetric and laboratory tests were normal, and they had clinically normal babies born at term.

The following exclusion criteria were applied: women with infectious diseases, placentas in formaldehyde, cases of stillbirths and intrauterine fetal deaths, pregnant women with autoimmune diseases or other diseases that could lead to immunological changes, and those who received corticosteroid therapy during labor. Stillborn fetuses were defined as any fetus at a gestational age of at least 22 weeks and/or fetal weight $\geq$500 g whose death occurred before complete separation from the maternal body and who did not show any of the following signs compatible with life at birth: heartbeat, umbilical cord pulsation, or voluntary muscle movements (7). The control group comprised pregnant women who did not experience complications during pregnancy and who had normal laboratory tests and clinically normal newborns.

We evaluated all macroscopic changes on the fetal and maternal placental and umbilical cord surfaces. All lesions were examined, recorded, and photographed.

The evaluation of macroscopic placental parameters was performed according to protocols published by Driscoll and Langston (1991) (8) and Benirsckhe and Kaufmann (1995) (9).

Data were collected from medical records and transcribed into study forms. We collected information about obstetric history; potential neonatal/fetal and maternal obstetric complications; neonatal anthropometric measurements, 1- and 5-minute Apgar scores; laboratory tests for the evaluation of DM; parity; and gestational age, which was determined according to the date of the last menstrual period, the first trimester ultrasound examination, and the Capurro method. When the results of the gestational age assessment were inconsistent, the results of the Capurro method (10) were used. Underlying maternal conditions were grouped according to the 10th Revision of International Classification of Diseases (ICD-10) criteria, and neonatal/fetal underlying conditions were grouped according to the Cartlidge and Stewart criteria (7).

Statistical analyses were performed with SigmaStat® version 2.0 (San Jose, California, USA), and an electronic spreadsheet was created. Categorical variables are presented as absolute (n) and relative values (percentages). Proportions were compared using the Yates' correction or chi-squared (χ^2) and Fisher's exact tests. Differences of $p<0.05$ were considered statistically significant.

The research project was approved by the Research Ethics Committee of the Federal University of Goiás (UFG) and was registered in the U.S. National Institutes of Health website (protocol number 101/2008).

RESULTS

Regarding the type of diabetes, 43 women (69.3%) were diagnosed with gestational diabetes mellitus (GDM), 15 were diagnosed with DM I (24.2%) and 4 were diagnosed with DM II (6.5%). The mean age of the women studied was 28.5 ± 5.71 years, and there was no statistical correlation between maternal age and maternal placental changes. There was a higher proportion of multigravida than secundigravida and primigravida women (23 cases [37.1%], 11 cases [17.7%], and 9 cases [14.5%], respectively) among women with GDM.

Of the 62 placentas that were macroscopically examined, 49 (79%) maternal surfaces and 59 (95.2%) fetal surfaces showed changes, including calcium and fibrin deposits, placental infarction, hematoma, and fibrosis (Table 1).

Calcification was predominantly observed on the maternal surface of 35 placentas (56.4%), although hematoma and fibrosis were not detected on the maternal surface. A greater number of placental changes were observed in pregnant women with GDM: 31 (50%) were detected on the maternal surface (Table 1) and 40 (64.5%) were detected on the fetal surface (Table 2).

The most common pathological change found on the fetal surface was the presence of fibrin, which was observed in 51 placentas (82.3%). Placental infarction and fibrosis were not found on the fetal surface (Table 2). The assessment of an association between GDM and placental changes showed that all 43 women with GDM (100%) demonstrated some sort of change in either the fetal or maternal placental surface. The most common placental changes included calcification (19; 44.1%), fibrin (11; 25.6%), and placental infarction (1; 2.3%) on the maternal surface; and fibrin (35; 81.4%), calcification (4; 9.3%), and hematoma (1; 2.3%) on the fetal surface. There were no placental changes on the maternal surface in 12 cases (28%) and on the fetal surface in three cases (7%).

Table 1 - Distribution of placental macroscopic changes on the maternal surface in 62 pregnant women with diabetes mellitus from Goiânia, Central-West Brazil, between August 2009 and July 2010.

Maternal surface alterations	DM		
	GDM	DM I	DM II
	n (%)	n (%)	n (%)
Calciphylaxis	19 (44.2)	13 (86.6)	3 (75)
Fibrin	11 (25.6)	1 (6.7)	1 (25)
Infarction	1 (2.3)	0 (0)	0 (0)
No alterations	12 (27.9)	1 (6.7)	0 (0)

DM = diabetes mellitus, GDM = gestational diabetes mellitus, DM I = type I diabetes mellitus, DM II = type II diabetes mellitus, n = number of cases.

Table 2 - Distribution of placental macroscopic changes on the fetal placental surface in 62 pregnant women with diabetes mellitus from Goiânia, Central-West Brazil, between August 2009 and July 2010.

Fetal surface alterations	DM		
	GDM	DM I	DM II
	n (%)	n (%)	n (%)
Calciphylaxis	4 (9.3)	3 (20)	0 (0)
Fibrin	35 (81.4)	12 (80)	4 (100)
Infarction	1 (2.3)	0 (0)	0 (0)
No alterations	3 (7.0)	0 (0)	0 (0)

DM = diabetes mellitus, GDM = gestational diabetes mellitus, DM I = type I diabetes mellitus, DM II = type II diabetes mellitus, n = number of cases.

Women with GDM had a greater amount of hydroxyapatite (calciphylaxis) deposited on the maternal placental surface as compared to those without DM ($p = 0.008$) (Table 3).

Among women with DM, there was a higher proportion of full-term births (45 cases, 72.6%), followed by pre-term (15 cases, 24.2%) and post-term births (two cases, 3.2 %) (Table 4).

No statistically significant relationship was found between fetal and maternal placental changes and gestational age. The mean gestational age among women with DM was 38.51 weeks. Table 5 shows the associations between gestational age and types of DM. Full-term births were more common among women with all types of DM: 29 full-term births (64.4%) occurred in women with GDM; 12 (26.7%) occurred in those with DM I; and four (8.9 %) occurred in those with DM II. There was no statistically significant relationship between gestational age and type of DM (Table 5).

A statistical association was found between newborn gender and fetal and maternal placental changes. Women who gave birth to females had more calcification on the maternal placental surface as compared to other groups ($p = 0.002$). In addition, larger fibrin deposits on the maternal placental surface were associated with mothers of male newborns ($p<0.001$), and placental macroscopic changes were less common in mothers with female newborns ($p = 0.021$). There was also a predominance of male (33, 53.2%) as compared to female (29, 46.8%) newborns born to the women in our study.

The mean newborn weight was $3,287 \pm 563$ g in women with DM; $3,205 \pm 544$ g in those with GDM, $3,563 \pm 696$ g in those with DM II, and $3,095 \pm 451$ g in those with DM I. There was no statistically significant association between newborn weight and type of maternal DM (Table 6).

The mean 1- and 5-minute Apgar scores in newborns born to mothers with DM were 7.6 ± 1.6 and 9.5 ± 0.6, respectively. The mean 1- and 5-minute Apgar scores of newborns of women with GDM, DM I and DM II were 7.8 ± 1.3 and 9.2 ± 0.6, 7.4 ± 2.4 and 9.5 ± 0.7, and 7.7 ± 1.2 and 9.7 ± 0.5, respectively.

DISCUSSION

Several changes occur in the human placenta during pregnancies that are complicated by DM. These abnormalities are directly associated with intrauterine blood glucose levels that lead to reduced maternal-placental blood circulation and maternal-fetal exchange (11). Both macroscopic and microscopic pathological changes are associated with complications during pregnancy. For example, clinical and obstetric complications accelerate placental calcification due to stress mechanisms (12).

The results of the current study demonstrated a significant association between fibrin deposits on the fetal surface of the placenta and full-term newborns. However, a previous study with a similar sample size presented findings that contrast with those presented here (13), and another publication reported that fertility in women with DM may be affected through different mechanisms. Preimplantation human conceptuses are sensitive to insulin and may be directly affected by maternal insulin resistance, and rat models have shown that excess

Table 3 - Association between macroscopic changes on the fetal and maternal placental surfaces and gestational diabetes mellitus in 43 women from Goiânia, Central-West Brazil, between August 2009 and July 2010.

MACROSCOPIC ALTERATIONS	GDM					
	MATERNAL SURFACE		*p*-value	FETAL SURFACE		*p*-value
Calcification	Yes	No		Yes	No	
Yes	19	24	0.008	4	39	0.665
No	16	3		3	16	
Fibrin						
Yes	11	32	0.310	35	8	1.000
No	2	17		16	3	
Placental infarction						
Yes	1	42	1.000	0	43	1.000
No	0	19		0	19	
Hematoma						
Yes	0	43	1.000	1	42	1.000
No	0	19		0	19	
Fibrosis						
Yes	0	43	1.000	0	43	1.000
No	0	19		0	19	
No alterations						
Yes	12	31	0.050	3	40	0.546
No	1	18		0	19	

Fisher's exact test.

Table 4 - Distribution of gestational age for 62 women with or without (control of) diabetes mellitus, according to diabetes type, from Goiânia, Central-West Brazil, between August 2009 and July 2010.

GESTATIONAL AGE	GDM	DM I	DM II	CONTROL
	n (%)	n (%)	n (%)	n (%)
Pre-term	12 (28)	3 (20)	0 (0)	25 (40.3)
Full-term	29 (67.4)	12 (80)	4 (100)	23 (37.1)
Post-term	2 (4.6)	0 (0)	0 (0)	14 (22.6)

DM = diabetes mellitus, GDM = gestational diabetes mellitus, DM I = type I diabetes mellitus, DM II = type II diabetes mellitus, n = number of cases
CONTROL: women without DM. ANOVA: $F = 7.282$ ($p = 0.02$), followed by Dunnett's method ($p < 0.05$) (control *vs.* DM II, control *vs.* DM I).

insulin leads to reduced preimplantation. Although findings in rat models cannot be directly applied to humans, they provide information on how insulin resistance may affect fertility (14).

Studies of vascular systems have shown that high glucose and insulin levels profoundly affect vascular endothelial growth factor, nitric oxide and protein kinase C levels, as well as alterations in junctional adhesion molecules, such as occludin and vascular endothelial-cadherin, which cause vascular albumin leakage. Increased superoxide and nitric oxide production may also induce placental oxidative stress via the effects of prooxidant peroxynitrite, which itself leads to vascular dysfunction (15). Nitrotyrosine residues are found in placental vessels of preeclamptic and diabetic pregnancies, which further highlight the effects of oxidative stress in these conditions (16). Moreover, the abnormal molecular mechanisms underlying vascular changes in the diabetic human placenta may be consequences of high glucose and hyperinsulinemia (15).

With regard to gestational age, Sgrott (17) reported a mean gestational time of 38.51 weeks at birth in women with DM, which is similar to what we observed in the current study. However, some studies have claimed that DM may cause pre-term births (less than 38 weeks of gestation) (18).

Pregnant women diagnosed with DM are at an increased risk of clinical and obstetric complications, such as pre-term delivery, gestational hypertension, urinary tract and other infections, periodontal disease, cesarean delivery, and obstetric trauma. Pre-term delivery before 35 weeks of gestation is directly related to the severity of diabetes and proteinuria in early gestation (19). Furthermore, one-third of all premature births in women with DM are a consequence of hypertensive complications. The factors involved in increased spontaneous pre-term births in women with DM are not yet clearly understood, although they have been associated with poor blood glucose control, polyhydramnios, and infection (20). It is believed that hospital management of women with DM may have contributed to a decrease in the number of premature births, although no reports on the relationship between DM and post-term births could be found in the literature.

In the current study, the control group demonstrated a high number of premature births, which we believe may have been because the study hospital serves a population of high-risk pregnant women. Although these women did not have clinical DM, they may have had other abnormalities that could have predisposed them to pre-term delivery and premature rupture of membranes, including urinary tract infections, polyhydramnios, and high blood pressure.

Regarding gestational age, one study found that newborns of mothers with DM I were born at lower gestational ages than those of mothers with GDM (21). In a similar study, the 1- and 5-minute Apgar scores of infants from women with DM I, DM II and GDM were 5 ± 2 and 9 ± 0.5, 8 ± 1.5 and 10 ± 0.5, and 9 ± 1.5 and 10 ± 0.5, respectively (22). In our study, there was no statistically significant relationship between Apgar scores and the type of maternal DM.

The literature provides conflicting results on Apgar scores. For example, one study found no significant difference in 1- and 5-minute Apgar scores of newborns from mothers with DM as compared to a control group (23), whereas another publication showed that placental changes consistent with reduced blood flow were associated with lower 1- and 5-minute Apgar scores (24).

The mean weight of newborns from women with DM II was higher than that of newborns from women with GDM and DM I. Neither our study nor that of Szylit et al. (21) found any significant differences in the mean weights of newborns born to women with different types of DM.

Fetal macrosomia, which is commonly defined as a birth weight of more than 4.000 g, is the most common fetal

Table 5 - Gestational ages for 62 pregnant women with different types of diabetes mellitus from Goiânia, Central-West Brazil, between August 2009 and July 2010.

GESTATIONALAGE	DM								
	GDM		*p*-value	DM I		*p*-value	DM II		*p*-value
<38 weeks of gestation	Yes	No		Yes	No		Yes	No	
Yes	12	3	0.356	3	12	0.214	0	15	0.564
No	31	16		12	35		4	43	
38-40 weeks of gestation									
Yes	29	16	0.291	12	33	0.528	4	41	0.568
No	14	3		3	14		0	17	
>40 weeks of gestation									
Yes	2	0	1.000	0	2	1.000	0	2	1.000
No	41	19		15	45		4	56	

Fisher's exact test. DM = diabetes mellitus, GDM = gestational diabetes mellitus, DM I = type I diabetes mellitus, DM II = type II diabetes mellitus, n = number of cases.

Table 6 - Characteristics of infants born to 62 women with or without (control of) diabetes mellitus, according to type, from Goiânia, Central-West Brazil, between August 2009 and July 2010.

ANTHROPOMETRIC PARAMET ERS	GDM	DM I	DM II	CONTROL GROUP
	n	n	n	n
Weight (g)	3.205	3.095	3.563	3.072
Head circumference (cm)	34.6	34.6	35.5	33.7
Chest circumference (cm)	33.0	34	33.2	32
Abdominal circumference (cm)	31.2	32.2	32.6	31.5
1-min Apgar score	7.8	7.4	7.7	7.4
5-min Apgar score	9.2	9.5	9.7	9.2

DM = diabetes mellitus; GDM = gestational diabetes mellitus; DM I = type I diabetes mellitus; DM II = type II diabetes mellitus; CONTROL: women without DM; min: minute; n = number of cases. ANOVA: F = 5.351 ($p = 0.864$) followed by Dunnett's method: control *vs.* DM II, control *vs.* DM I, control *vs.* GDM.

complication of maternal DM. This condition increases the risk of perineal lacerations and delivery complications (fetal dystocia) that often necessitate cesarean section. There is also a high risk of immediate complications for infants born to mothers with DM, including intracranial hemorrhage, shoulder dystocia, neonatal hypoglycemia, jaundice, and respiratory distress (25). These infants are also at an increased risk of long-term complications. Early nutritional adjustments during gestation can permanently alter carbohydrate metabolism and cause adult-onset disorders. In addition, high birth weight is a predisposing factor for insulin resistance, obesity and DM II during childhood, as it reflects inadequate glucose control that is often due to delayed prenatal care (18). Childhood obesity has become a major public health concern, and the population of overweight children in Brazil increases by 0.5% annually (26).

In conclusion, we observed infarction, hematoma, calcification, and fibrin on the maternal and fetal placental surfaces of women with DM. In addition, women with GDM and post-term infants had more calcium deposits on the maternal placental surface of the placenta, and mothers of female newborns had a larger number of calcium and fibrin deposits on the maternal placental surface.

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AUTHOR CONTRIBUTIONS

Rocha KM, Xavier RM, Ramalho WS, Rocha EL, Guimarães JN, Rossi and Silva RC, Siqueira KM and Abdalla DR conceived the study, participated in its design, coordination and participants recruitment, drafted the manuscript, performed the statistical analysis and interpretation of data, and read and approved the final manuscript. Salge AK, Michelin MA and Murta EF conceived the study, participated in the study design, coordination, and participants recruitment, drafted the manuscript, performed the statistical analysis and interpretation of data, and read and approved the final manuscript.

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