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Review

Clinicopathological correlation of large-for-gestational age placenta in pregnancies with pregestational diabetes

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ABSTRACT

Studies have demonstrated an association between pregestational diabetes (preGDM) and a higher prevalence of large-for-gestational age placentas (LGA). However, frequency of placental pathologies and perinatal outcomes in LGA placentas is lacking. We aimed to determine differences in perinatal outcome or placental pathology between LGA placentas and appropriate-for-gestational age (AGA) placentas from pregnancies complicated by preGDM. We found LGA placentas are associated with significantly higher neonatal weight but lower fetal-to-placental weight ratio (f/p) for both T1DM and T2DM. T2DM LGA placentas possessed a significantly higher prevalence of placental insufficiency (f/p < 10^{th} percentile). Compared to LGA groups, more chronic villitis were seen in the AGA T2DM group, and more acute chorioamnionitis in the T1DM AGA group. No significant differences were seen in maternal BMI or glycemic control. In pregnancies complicated with preGDM, LGA placentas had generally lower placental efficiency than AGA placentas.

1. Introduction

Diabetic pregnancy is known to have adverse effects on offspring, including congenital anomalies, large-for-gestational age infant and macrosomia [1,2]. Infants born from diabetic mother with high birth weight often have additional complications such as respiratory distress syndrome, hypoglycemia and increased predisposition to type 2 DM (T2DM) later in life. Offspring of diabetic mothers overcome the excess glucose concentrations by producing higher levels of insulin, causing transient hyperinsulinemia.

Placenta is the key organ for pregnancy. Pathologic examination of placenta can shed light on the intrauterine experience. Placental examination usually includes the macroscopic part including weight, dimensions and searching for visible lesions. Microscopically placental pathology can be classified in a simplified way to infectious/inflammatory, maternal circulation malperfusion, fetal circulation malperfusion and others [3,4]. Diabetic pregnancy is often associated with relatively specific macroscopic and microscopic placental pathology, including large placenta, delayed villous maturation (villous dysmaturity) and increased villous vascularity [5–8]. Since placenta weight increases with gestational age, the description of large placenta needs to take gestational age into consideration. Placentas can be divided into 3 categories based on the gestational age related weight percentile: small for gestational age (SGA), large for gestational age (AGA) and appropriate for gestational age (AGA). SGA's are placentas whose weights fall below the 10th percentile, AGAs falling between 10th and 90th percentile [9], and LGAs above the 90th percentile. Our previous study revealed that large-for-gestational age (LGA) placenta could be seen in 25–30% of pregnancies complicated with pregestational diabetes [10].

Few studies have looked into the placental pathology of LGA infants [11]. Evers IM et al reported higher histological placental abnormalities in pregnancies associated with LGA infants in type 1 pregestational diabetes (T1DM) [11]. While the placenta can be regarded as a record of intrauterine experience, there has not yet been studies that have explored the clinical and pathological correlations with large (LGA) placenta. In recent decades, there has been a sharp increase of type 2 diabetes (T2DM). This study aims to investigate the clinicopathological

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Table 1
Demographics and Glycemic Control.

Variable	T1 DM			T2 DM		
	LGA Placenta (n = 32)	AGA Placenta (n = 63)	p-Value	LGA Placenta (n = 46)	AGA Placenta (n = 90)	p-Value
Age Mean (SD) IQR (Q3-Q1)	26.5 (6.1) (30.5-23.0)	28.5 (5.6) (32.0-25.0)	0.14[3]	32.3 (6.0) (37.0-29.0)	32.9 (5.8) (37.0-29.0)	0.62[3]
BMI Mean (SD) IQR (Q3-Q1)	29.7 (5.8) (33.3-25.2)	27.6 (6.3) (30.2-23.9)	0.12[3]	38.1 (9.2) (41.7-32.4)	37.2 (7.7) (42.8-31.8)	0.58[3]
Hgb A1c Levels Mean (SD) IQR (Q3-Q1)	8.6 (1.9) (10.0-7.4)	8.3 (1.9) (9.0-6.8)	0.51[3]	7.3 (1.7) (8.3-6.0)	7.5 (1.7) (8.7-6.3)	0.42[3]
Fasting blood glucose Mean (std) IQR (Q3-Q1)	123.9 (30.1) (141.6-104.2)	114.5 (21.7) (124.7-98.1)	0.14[3]	101.2 (16.0) (106.0-92.0)	96.4 (17.3) (100.7-86.0)	0.10[3]
Post-prandial glucose Mean (std) IQR (Q3-Q1)	138.2 (21.9) (148.3-119.6)	128.0 (19.6) (139.6-111.8)	0.04[3]	121.4 (20.0) (132.5-107.3)	116.5 (19.5) (121.3-106.3)	0.17[3]

Abbreviations: AGA appropriate for gestational age; BMIbody mass index; IQRinterquartile range, LGA, large for gestational age, std, standard deviation.

correlation of LGA placentas in both T1DM and T2DM by comparing pregnancies with LGA placentas to those with AGA placentas, both complicated by pregestational diabetes (preGDM). While this is a single-institution experience, we hope our current study can help fill a knowledge gap.

2. Materials & methods

2.1. Study design

This was an observational retrospective study of women who received prenatal care at the Women and Infants Hospital of Rhode Island (WIHRI, a tertiary care center) from 2003 to 2011. Women were identified through registration in the "Diabetes in Pregnancy Program" at our institution. The study protocol was approved by the Institutional Review Board (IRB 10-0058).

2.2. Data collection

Data collected from obstetric records included maternal demographics and general, obstetric, and diabetic information. Maternal age, BMI and ethnic group association were considered "general" information. Obstetric information included gravidity and parity, while diabetic information included type of pregestational diabetes mellitus, earliest gestational age when the HbA1c was measured, and HbA1c levels (For the purpose of the study we recorded earliest HbA1c from six weeks preconception and up to 20 weeks gestation). Glycemic control later in pregnancy was measured using fasting and post-prandial glucose levels. The fasting and two hour post prandial levels were recorded from each patient's glucometer electronically into the database by our nurse, a certified diabetic educator. We used mean fasting and 2 h postprandial blood glucose values (all values measured).

Adverse outcomes were defined as birth before 37 weeks (preterm birth), preeclampsia, intrauterine growth restriction (IUGR, defined as estimated fetal weight below 10th percentile), intrauterine fetal demise (IUFD), or neonatal death.

2.3. Placental pathology

During the study period, all placental examinations were performed in the Division of Perinatal Pathology, WIHRI, following the standard protocol [12] and as previously described [13]. Briefly, placentas received were examined grossly (macroscopically) for membrane abnormalities, maternal and fetal surfaces, and umbilical cord. Trimmed weight (without membrane and cord) was recorded. Placental disc was then sliced and examined for lesions. Sections submitted included representative portion of the membrane, cord, 3 parenchymal sections from the central two-third of the disc (including one section from cord insertion site), and additional sections from lesions identified. Histopathological features were diagnosed following society consensus [14–16], depending on whether the condition was related to features often seen in diabetic placenta, maternal vascular malperfusion, fetal vascular malperfusion, infection/inflammation, or some other causes. In our department, there are five pediatric pathology-board-certified perinatal pathologists. About ten percent of all slides were reviewed by a second pathologist, and if a disagreement arose, the slides are reviewed at the weekly conference until a consensus was reached.

2.4. Statistics

Statistical analysis was performed with SAS program version 9.2 (Cary, NC) with computation of 95% confidence intervals. Continuous variables were first examined for normality. Student *t*-test or Mann-Whitney U was used to assess continuous variables as appropriate. Chi square analysis and Fisher's exact test were used for the analysis of categorical variables. Logistic regression analysis was used to calculate odds ratio (OR) and 95% confidence intervals (CI). For all tests, a P-value less than 0.05 was considered statistically significant.

3. Results

A total of 293 gravida women with pregestational diabetes and placental pathology reports were identified, with maternal ages ranging from 26.5 to 32.9 years. Among this study population, 117 type 1 diabetes mellitus (T1DM) and 176 type 2 diabetes mellitus (T2DM) patients were identified. These patients were further stratified based on type of diabetes and placental weight range. The T1DM group consisted of 32 LGA placentas (32/117, 27.4%) and 63 AGA placentas (63/117, 53.8%). The T2DM included 46 LGA placentas (46/176, 26.1%) and 90 AGA placentas (90/176, 51.1%). The remaining placentas were characterized as small for gestational age (SGA) placentas. This study primarily focuses on comparing the outcomes of LGA placentas versus AGA placentas.

Information pertaining to patient demographics of the LGA and AGA placenta groups including glycemic control is summarized in Table 1. The only statistically significant value was the post-prandial blood sugar levels and it was noted to be significantly higher in the T1DM LGA group (138.2 SD ± 21.9) than in the AGA group (128SD

Table 2
Summary of placental pathology between LGA and AGA groups.

	T1 DM			T2 DM		
Variable	LGA Placenta (n = 32)	AGA Placenta (n = 63)	p-Value	LGA Placenta (n = 46)	AGA Placenta (n = 90)	p-Value
Histopathology related to villous development and vascularity						
Delayed Villious maturity	4 (12.5)	2 (3.2)	0.17[2]	6 (12.8)	11 (12.2)	0.93[2]
Yes	28 (87.5)	61 (96.8)		41 (87.2)	79 (87.8)	
No						
Increased villous capillaries	1 (3.1)	3 (4.8)	1.00[2]	4 (8.5)	5 (5.6)	0.49[2]
Yes	31 (96.9)	60 (95.2)		43 (91.5)	85 (94.4)	
No						
Histolopathology related to maternal circulation malperfusion						
Decidual Vasculopathy	7 (21.9)	16 (25.4)	0.70	19 (40.4)	28 (31.1)	0.28
Yes	25 (78.1)	47 (74.6)		28 (59.6)	62 (68.9)	
No						
Accelerated Villous Maturity	4 (12.5)	10 (15.9)	0.77	3 (6.4)	5 (5.6)	1.00[2]
Yes	28 (87.5)	53 (84.1)		44 (93.6)	85 (94.4)	
No						
Intervillous Thrombi	6 (18.8)	8 (12.7)	0.54	7 (14.9)	14 (15.6)	0.92
Yes	26 (81.3)	55 (87.3)		40 (85.1)	76 (84.4)	
No						
Abruption	2 (6.3)	0 (–)	0.11	2 (4.3)	2 (2.2)	0.61
Yes	30 (93.8)	63 (100)		45 (95.7)	88 (97.8)	
No						
Infarct	8 (25.0)	8 (12.7)	0.13	7 (14.9)	11 (12.2)	0.66
Yes	24 (75.0)	55 (87.3)		40 (85.1)	79 (87.8)	
No						
Histopathology related to fetal circulation malperfusion						
Avascular Villi	1 (3.1)	3 (4.8)	1.00	2 (4.3)	8 (8.9)	0.49
Yes	31 (96.9)	60 (95.2)		45 (95.7)	82 (91.1)	
No						
Thrombosis	0 (–)	0 (–)	–	2 (4.3)	2 (2.2)	0.61
Yes	32 (100)	63 (100)		45 (95.7)	88 (97.8)	
No						
Histopathology related to infectious or inflammatory process						
Acute Chorioamnionitis	1 (3.1)	14 (22.2)	0.02	5 (10.6)	19 (21.1)	0.12
Yes	31 (96.9)	49 (77.8)		42 (89.4)	71 (78.9)	
No						
Acute Vasculitis	2 (6.3)	14 (22.2)	0.08	2 (4.3)	10 (11.1)	0.22
Yes	30 (93.8)	49 (77.8)		45 (95.7)	80 (88.9)	
No						
Funisitis	0 (–)	3 (4.8)	0.55	1 (2.1)	2 (2.2)	1.00
Yes	32 (100)	60 (95.2)		46 (97.9)	88 (97.8)	
No						
Villitis of unknown etiology	2 (6.3)	6 (9.5)	0.71	1 (2.1)	12 (13.3)	0.04
Yes	30 (93.8)	57 (90.5)		46 (97.9)	78 (86.7)	
No						
Infectious Villitis	0 (–)	0 (–)	–	1 (2.1)	1 (1.1)	1.00
Yes	32 (100)	63 (100)		46 (97.9)	89 (98.9)	
No						

Abbreviations: AGA, appropriate for gestational age, LGA, average for gestational age.

± 19.6). No significant differences were noted in the T2DM group. There is no significant difference of BMI between LGA and AGA groups in either T1DM or T2DM.

Placental histopathological changes are summarized in Table 2. Delayed villous maturation and villous vascularity changes are often seen in diabetic placentas. Villous vascularity changes include chorangiosis and chorangiomatosis. There are no significant differences seen in these two pathologies. There are no significant differences in placental pathology related to either maternal or fetal circulation malperfusion. Regarding infectious or inflammatory processes, the results revealed only 1 (3.1%) patient with chorioamnionitis in the T1DM LGA group, but 14 (22.2%) cases in T1DM AGA group (P = 0.02). The prevalence of villitis of unknown etiologies (VUE) was higher in T2DM population where 12 (13.3%) AGA placentas were reported to have VUE as compared to 1 (2.1%) in the LGA placenta (P = 0.04).

Pregnancy outcomes are listed at Table 3. The infants born in the T2DM AGA group had an average gestational age of 39 (23–40) weeks at delivery whereas in the T2DM LGA group the mean GA at delivery was 37 (33.3–39.0) weeks (P = 0.01). Birth weights of these infants were noted to be significantly higher in the T1DM LGA group (3883 ± 553) as compared to the T1DM AGA group (3299 ± 770; P = 0.0002). The results were similar in the T2DM group where the average neonatal weight was 3794 ± 584 in the LGA group and 3353 ± 763 in the AGA group (P = 0.0007).

Neonatal outcomes are summarized in Table 4. The fetal-to-placental (f/p) weight ratio was also noted to be lower in the T1DM LGA group (6.2 ± 0.8) as compared to the T1DM AGA group (7 ± 1.2; P = 0.001). The results were similar in the T2DM group where f/p weight ratio was 5.9 ± 1 in the LGA group and 7.0 ± 1.2 in the AGA group (P = 0.0001). While in both T1DM and T2DM the LGA group had a lower f/p ratio, in T2DM, there was a significant higher prevalence of f/p < 10^{th} percentile (which is usually regarded as low placental efficiency) in the LGA group (17/46 vs 4/90, P < 0.0001). In both T1DM and T2DM, the AGA group had significantly higher f/p > 90^{th} percentile (which is usually regarded as a marker of exhausted placental functional reserve).

In all groups no statistically significant difference in adverse pregnancy outcome was observed.

Table 3
Pregnancy outcomes.

Variable	T1 DM			T2 DM		
	LGA Placenta (n = 32)	AGA Placenta (n = 63)	p-Value	LGA Placenta (n = 46)	AGA Placenta (n = 90)	p-Value
GA at delivery	37.0 (34.0-39.0)	37.0 (26.0-40.0)	0.31	37.0 (33.3-39.0)	39.0 (23.0-40.0)	0.01
Median (min-max)	(37.0-36.0)	(39.0-36.0)		(38.0-37.0)	(39.0-37.0)	
IQR (Q3-Q1)						
Preeclampsia	8 (25.0)	17 (26.9)	0.84	13 (27.7)	13 (14.4)	0.06
Yes	24 (75.0)	46 (73.0)		34 (72.3)	77 (85.6)	
No						
PPROM (PPROM + PTL)	2 (6.3)	10 (15.9)	0.33	3 (6.4)	6 (6.7)	1.00
Yes	30 (93.8)	53 (84.1)		44 (93.6)	84 (93.3)	
No						
IUGR	0 (–)	2 (3.2)	0.55	0 (–)	2 (2.2)	0.55
Yes	32 (100)	61 (96.8)		46 (100)	88 (97.8)	
No						
IUFD	0 (–)	0 (–)	(–)	0 (–)	0 (–)	–
Yes	32 (100)	63 (100)		46 (100)	90 (100)	
No						
Adverse Outcomes*	17 (53.1)	33 (52.4)	0.91	28 (59.6)	61 (67.8)	0.35
No adverse outcomes	10 (31.3)	18 (28.6)		15 (31.9)	23 (25.6)	
1 adverse outcome	5 (15.6)	12 (19.1)		4 (8.5)	6 (6.7)	
2 or more adverse outcomes						

Abbreviations: AGA, appropriate for gestational age; GA, gestational age; IUFD, intrauterine fetal death; IUGR, intrauterine growth restriction; IQR, interquartile range; LGA, large for gestational age; PTL, pretern labor; PPROM, preterm premature rupture of the membranes; TI DM, type I diabetes mellitus, T2 DM, type II diabetes mellitus.
Adverse Outcomes*: Adverse outcomes were defined as birth before 37 weeks (preterm birth), preeclampsia, intrauterine growth restriction (IUGR, defined as estimated fetal weight below 10th percentile), intrauterine fetal demise (IUFD), or neonatal death.

4. Discussion

As previously discussed, placental weight increases with gestation age. It would be less meaningful to just compare the placental weight without considering the gestational age (GA). The classification of placenta into SGA, AGA and LGA considers the variable of GA and helps to compare placental weight more accurately. Previous studies of placental growth parameters such as volume and surface area, and histopathologies are well summarized by Huynh et al. [8].

Most studies of placental weight related to diabetic pregnancy were conducted more than three decades ago. There have been significant strides in our understanding of the management of diabetic pregnancy during the recent two decades. As such, it is necessary to relook at some placental parameters such as placental weight. Clarson et al. compared placental weight in pregnancies complicated with overt diabetes (preGDM), GDM and normal pregnancies and found no differences of

Table 4
Neonatal Outcomes.

Variable	T1 DM			T2 DM		
	LGA Placenta (n = 32)	AGA Placenta (n = 63)	p-Value	LGA Placenta (n = 46)	AGA Placenta (n = 90)	p-Value
1 min Apgar score	8 (25.0)	12 (19.1)	0.50	6 (12.8)	15 (16.7)	0.55
< 7	24 (75.0)	51 (80.9)		41 (87.2)	75 (83.3)	
≥ 7						
5 min Apgar score	0 (–)	1 (1.6)	1.00	3 (6.4)	3 (3.3)	0.41
< 7	32 (100)	62 (98.4)		44 (93.6)	87 (96.7)	
≥ 7						
Neonatal birth weight	3883 (553)	3299 (770)	0.0002	3794 (584)	3353 (763)	0.0007
Mean (std)	(4275-3488)	(3760-2890)		(4010-3460)	(3895-3095)	
IQR (Q3-Q1)						
Placental weight	633 (70)	471 (75)	< 0.0001	652 (74)	468 (80)	< 0.0001
Mean (std)	(659-590)	(522-423)		(693-597)	(528-439)	
IQR (Q3-Q1)						
Fetal to placental weight ratio	6.2 (0.8)	7.0 (1.2)	0.001	5.9 (1.0)	7.0 (1.2)	< 0.0001
Mean (std)	(6.8-5.7)	(7.7-6.2)		(6.6-5.3)	(7.8-6.3)	
IQR (Q3-Q1)						
F/P ratio rates - < 10	4 (12.5)	2 (3.2)	0.17[2]	17 (36.2)	4 (4.4)	< 0.0001[2]
Yes	28 (87.5)	61 (96.8)		30 (63.8)	86 (95.6)	
No						
F/P ratio rates - > 90	0 (–)	10 (15.9)	0.01[2]	0 (–)	11 (12.2)	0.02[2]
Yes	32 (100)	53 (84.1)		47 (100)	79 (87.8)	
No						
Macrosomia (BW > 4500)	2 (6.3)	2 (3.2)	0.60	6 (12.8)	3 (3.3)	0.06
Yes	30 (93.8)	61 (96.8)		41 (87.2)	87 (96.7)	
No						

Abbreviations: AGA, appropriate for gestational age; BW, birth rate; IQR, interquartile range; LGA, large for gestational age.

placental weight but significantly lower f/p ratio in the overt diabetes group [17]. Taricco et al compared pregnancies with GDM with normal control and found significantly higher placental weight and lower f/p ratio in GDM pregnancies [18]. This current study for the first time compared the histopathology and perinatal outcomes between LGA and AGA placentas in pregnancies complicated with preGDM.

Our study demonstrated that in pregnancies complicated with preGDM, approximately 25% are associated with LGA placentas, roughly half in number compared to the pregnancies with AGA placentas. In both T1DM and T2DM, LGA placentas are associated with higher neonatal weight, but lower f/p ratio, indicating that in pregnancies with preGDM, LGA placentas are associated with lower placental efficiency. This is further demonstrated by the significantly higher prevalence of f/p < 10^{th} percentile in LGA placentas in T2DM.

Between diabetic pregnancies associated with LGA and AGA placentas, there is no difference of maternal BMIs. There is no obvious difference of glycemic control testing results measured at early gestation, except higher post-prandial glucose level in the LGA group in T1DM. These results may suggest that outside of maternal BMI and glycemic control before and at early gestation, there are other factors influencing the placental growth. Since there are no obvious differences in maternal BMI and glycemic controls (except postprandial glucose level in T1DM) between the pregnancies associated with LGA and AGA placentas, the differences observed probably cannot not be contributed to maternal BMI or glycemic control at early gestations. Whether these differences can be attributed to the glycemic control during mid-late gestational stages cannot be answered by this study.

Histopathologically, there is more inflammatory response in the AGA group, i.e., more acute chorioamnionitis in the AGA group, statistically significant in the T1DM group but not in the T2DM group. There is more villitis of unknown etiology in the AGA group, statistically significant in the T2DM group but not in the T1DM group.

Acute chorioamnionitis is regarded as a marker of maternal inflammatory response while fetal vasculitis and funisitis are regarded as markers for fetal inflammatory response. Villitis of unknown etiology, a form of chronic villitis, is regarded an immune reaction. This current study found less acute chorioamnionitis in the T1DM group with LGA placenta and less VUE in the T2DM group with LGA placentas. Previously, Evers M et al reported no difference of villitis between AGA and LGA placenta groups in T1DM [11], consistent with our results in the T1DM. Villitis of unknown etiology (VUE) is known to be associated with a spectrum of adverse pregnancy outcome. One possible explanation of less VUE in the LGA placenta group in T2DM is that VUE is significantly associated with small for gestational age birth weight [19].

The result of no differences in histopathology related to villous development, villous vascular changes, maternal and fetal circulation suggest that LGA and AGA placentas are subject to the similar intrauterine environment and pathogenetic mechanisms of diabetic pregnancy. The difference in feto-placental weight ratio which is a marker for placental efficiency suggests that there may be morphometric or ultrastructural differences between two groups. The interface between maternal and fetal circulations in placenta consists of trophoblastic layer with basement membrane and villous capillary endothelium. The changes in volume density and surface density of different levels of chorionic villi including terminal, intermediate and stem villi may affect the placental efficiency. The thickness of this interface may affect placental efficiency, too. As reviewed by Huynh et al, previous study has found increased parenchymal volume in T1DM placentas compared to normoglycemic controls [8]. However, parameters such as volume density, surface density, and villous capillaries density have not been well studied in pregnancies with preGDM.

5. Conclusion

In conclusion, in our study population, about 25% pregnancies with preGDM have LGA placentas which are associated with lower placental efficiency. Otherwise there is no significant difference in other pregnancies and neonatal outcomes. The impact of this lower placental efficiency and clinical significance remains unknown. Future morphometric and ultrastructural studies may help further dissect the structural variation leading to the lower placental efficiency.

Conflict of interest

All authors have nothing to disclose.

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