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Morphologic and ultrasound survey in type 2 diabetic placenta

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Abstract

The aim of this study is to establish morphological, histological and ultrasonographic (US) correlations in the placenta of type 2 diabetes. This is a multicenter case-control study conducted on a lot of 21 selected cases diagnosed with type 2 diabetes, analyzed over a two year period. The clinical characteristics of the patients in the study group are represented by the average age of 34 years and diabetes associated with preeclampsia, hypertension, diabetic neuropathy, urinary infections, obesity or history of infertility. All the patients in the study group are Caucasian. US assessment of placental characteristics in our series revealed increased placental thickness from the second trimester and placentomegaly at the end of the third trimester. Immature appearance of placenta has been observed. Gross analysis of maternal and fetal surfaces of the placentas revealed basal plate and subchorionic fibrin depositions, placental infarction or intervillous thrombosis. Preconceptional glycemic control and its support during gestation are essential for pregnancy outcome. US findings have as a background the morphological changes. From morphological perspective there is about a combination of anomalies, otherwise unspecific which, in terms of association with various comorbidities could define a placental diabetic pattern.
Keywords: *pregestational diabetes, hypertension, placentomegaly, pathology, diabetic pattern*

Introduction

The placenta is a transitory structure that serves an impressive array of different functions, such as selective forward transport of nutrients and gases to the fetus and reverse transport of metabolic waste from the fetus to maternal blood flow[1,2].

Maternal diabetes mellitus (DM) is linked to increases in morbidity and mortality in the embryonic, fetal and perinatal periods[3].

DM complicates pregnancy with different combinations of fetal growth abnormalities either in the sense of significant growth, or on the contrary to diminishing and restricting fetal weight[1,4].

Moreover, in an environment of abnormal metabolism, the placenta which is the sole source of oxygen and nutrients for the fetus, affects the fetal development[1].

DM has been linked to accelerated microangiopathy and this in turn, may be associated with capillary hypertension and changes in capillary permeability[3].

Lopa and contributors showed that the placenta represent a complex vascular system allowing the interpenetration between maternal and fetal vascular systems[5].

Throughout gestation the increasing requirements of the growing fetus are associated with continuous adaptations in structure and functional capacity of the maternal-fetal interface[3].

The association of DM with pregnancy has a steadily increasing prevalence due to increasing frequency in the general population of type 2 DM, as well as risk factors for its occurrence, such as obesity, sedentary lifestyle or hypercaloric diets[6-8].

It was showed that trophoblast together with endothelium represent important factors in oxygen transfer in whom the growth and maturity of maternal vessels depend on it[5,9].

Another pathological plancental condition which determinate the abnormal uteroplacental boold flow showed to become evident by placental infarction, abruption or villous changes[10-13].

Any type of gestational hyperglycemia can cause maternal-fetal complications such as fetal demise, spontaneous abortion, macrosomia, various fetal malformations, neonatal hypoglycemia, preeclampsia or intrauterine growth restriction[6,14].

In the case of pregnancies with type 2 (T2) DM, the placenta is exposed to a hyperglycemic condition in early stages, whereas in pregnancies with gestational diabetes, the placenta is affected only from the second or third trimester, much later in pregnancy[10].

Diverse biological or metabolic maternal abnormalities may have implications in terms of the dimensions of the placental structure, among which is also the DM. Placentomegaly is diagnosed by ultrasound (US) when the placental thickness is greater than 40 mm in the second trimester, or 60 mm in the third trimester of pregnancy[15].

The aim of this study is to establish morphological, histological and US correlations in the placenta of pregestational T2DM.

Methods

This multicenter case-control study has been conducted on a lot of 21 selected cases diagnosed with T2DM. The above mentioned group of pregnant women with

Table 1 Clinical characteristics of the patients

Associated conditions	T2DM – n (%)
Maternal preexisting hypertension	4 (19.04)
Preeclampsia [1]*	6 (28.57)
Diabetic neuropathy	1 (4.76)
Urinary infections	10 (47.61)
Candida vulvovaginitis	8 (38.09)
Age (years)	34.5 (± 7.5)
Obesity	5 (23.8)
History of infertility	4 (19.04)
Singleton pregnancy	18 (85.71)
Twin pregnancy [2]*	3 (14.28)
Macrosomia	7 (33.33)
IUGR [3]*	4 (19.04)
Birth weight (g)	3810 (± 685)
Gestational age at birth (weeks)	38.5 (± 1.6)

*T2DM - Type 2 Diabetes Mellitus (pregestational diabetes), n - number of cases, [1]*Preeclampsia - blood pressure <140/90 mmHg at the first prenatal visit (1st trimester); hypertension and proteinuria (>0.3 g protein/24h) after 20 gestational weeks, y - years, IUGR - intrauterine growth restriction, [2]* 2 cases with IVF, [3]*1 case of selective IUGR in dichorionic-diamniotic twin pregnancy.*

Table 2 US assessment of the placenta

Placental US findings		T2DM (n = 21)
Location n[1]* (%)	Uterine fundus	6 (28.57)
	Anterior (± lateral)	7 (33.33)
	Posterior (± lateral)	7 (33.33)
	Praevia	1 (4.76)
Thickness[4]* n (%)	24-28 gw[2]* >40 mm	4 (19.04)
	29-31 gw[2]* >45 mm	6 (28.57)
	32-34 gw[2]* >50 mm	7 (33.33)
	35-39 gw[2]* >55 mm	12 (57.14)
Echotexture n[1]* (%)	Homogeneous	17 (80.95)
	Inhomogeneous	4 (19.04)
Immature appearance n[1]* (%)	G[3]* at >26 gw	5 (23.8)
	G1[3]* at >32 gw	7 (33.33)
	G2[3]* at >35 gw	9 (42.85)

*[1]*n - number of cases, [2]*gw - gestation weeks, [3]*G - Grannum score, [4]* measured at the widest diameter in the sagittal plane*

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DM were selected and studied over a two year period (January 2016 - December 2017).

The clinical characteristics of the patients in the study group are represented by the average age of 34 years (27-42 years) and DM associated with preeclampsia, hypertension, diabetic neuropathy, urinary infections, Candida vulvovaginitis, obesity or history of infertility. All the patients in the study group are Caucasian (Table 1).

US assessment of the cases in the study group has been performed both via 2D technique, 3D or tomographic US imaging, as well as spectral, color or power Doppler (Voluson 730 Pro, Voluson E6, Voluson E8 Expert, US machines, equipped with RAB4-8L, RAB4-8D and RIC5-9-D US probes, GE Healthcare and Samsung H60 ultrasound system equipped with CV1-8AD transducer, Samsung Medison).

Obstetrical US assessment included fetal morphology (fetal head, central nervous system, fetal face, thorax, cardio-vascular and respiratory systems, abdomen and pelvis, digestive system, kidneys, urinary tract and genital organs, spine and fetal skeleton) and biometry, as well as placental (location, thickness, echotexture, volume, immature appearance), umbilical cord (number of vessels, insertion, coiling, diameter) and amniotic fluid evaluation (amniotic fluid index), maternal-fetal Doppler profile and in the case of multiple pregnancies, the diagnosis of chorionicity and amnionicity (placental location, T sign, lambda sign, interfetal membrane, biometry or morphology discordance).

The macroscopic analysis of the specimens included the placental weight and the number of umbilical cord blood vessels, also looking for subchorionic fibrin depositions, basal plate fibrin deposition, placental infarction, intervillous thrombi or placental calcifications.

The placenta specimens resulting after birth were fixed in 10% buffered neutral formalin, processed by paraffin embedding and Haematoxylin and Eosin staining.

The research meets the conditions of the ethical guidelines and legal requirements, and was approved

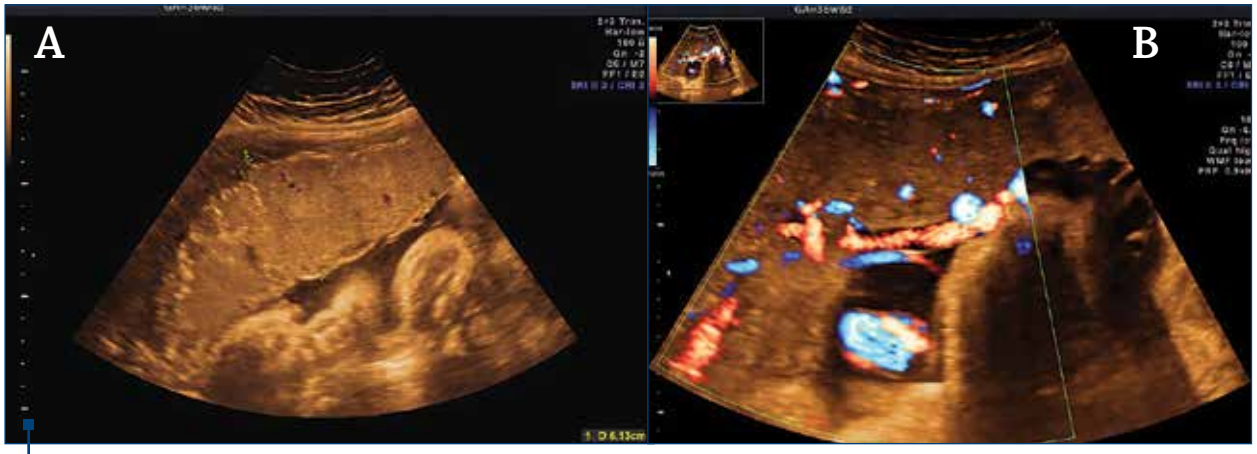

Figure 1.A). *US at 36(+4) gestational weeks in a T2DM pregnancy demonstrating a 61.3 mm thick placenta - placentomegaly.* ***B).*** *US at 36(+6) gestational weeks in a T2DM pregnancy demonstrating thick appearance of placenta and velamentous cord insertion*

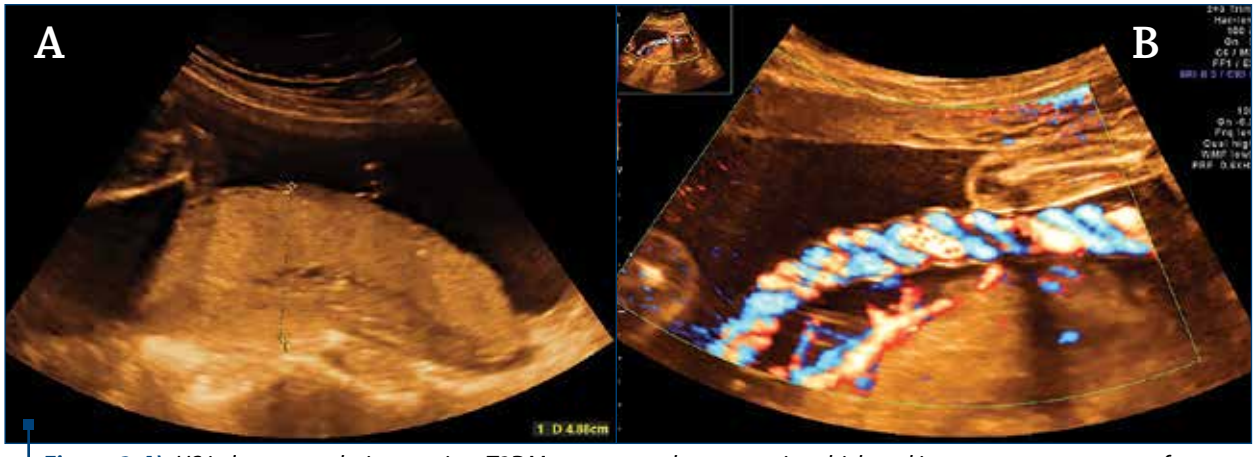

Figure 2.A). *US in late second trimester in a T2DM pregnancy demonstrating thick and immature appearance of placenta (G0).* ***B).*** *US in the third trimester demonstrating excessive cord coiling in a T2DM pregnancy*

Table 3 Gross analysis of the placenta and umbilical cord

Macroscopic analysis of the placenta and umbilical cord specimens		T2DM (n = 21)
Placental weight (g) 1*		644.5 (± 139.7)
Basal plate fibrin deposition		6 (28.57)
Subchorionic fibrin depositions		5 (23.8)
Placental calcifications		3 (14.28)
Placental infarction		3 (14.28)
Intervillous thrombi		2 (9.52)
Trivascular umbilical cord n²* (%)		20 (95.23)
SUA³* n²* (%)		1 (4.76)
Umbilical cord diameter (cm)		1.5 (± 0.3)
Twist direction n²* (%)	Left	15 (71.42)
	Right	6 (28.57)
Twisting n²* (%)	Normal	14 (66.66)
	Excessive	6 (28.57)
	Lack	1 (4.76)
Cord insertion n (%)	Central/pericentral	15 (71.42)
	Marginal	4 (19.04)
	Velamentous	2 (9.52)
Meconium staining		2 (9.52)

¹ g- without attached umbilical cord or membranes, ²*n - number of cases, ³*SUA - single umbilical artery*

by each Ethical Committee of the Universities of Medicine and Pharmacy from Romania. Informed consent was obtained from every patient included in the study.

Results

The US assessment of placental characteristics in our T2DM series revealed increased placental thickness even from the second trimester, with significant increases in placental thickness in the first half of the third trimester, with more than half of the cases (57.14%) presenting placentomegaly at the end of the third trimester (Table 2) (Figure 1, A and B).

Placental location by US has been predominantly at the uterine fundus and anterior or anterolateral (61.9%), followed by posterior or posterolateral localization (33.3%). Also, the homogeneous placental ecostructure was found in most cases (80.9%) (Table 2) (Figure 2, A and B).

Immature appearance of placenta has been observed since the second trimester, such that during the third trimester, this finding increased progressively, exceeding 42% towards the end of the third trimester (Figure 2, A and B).

Gross analysis of the placentas and umbilical cords, has shown that the placentas of women with T2DM are heavier, compared to standard medians in unaffected pregnancies, in our study with an average of 644.5 g. In our group we identified one bivascular umbilical cord singleton pregnancy as an isolated anomaly (Table 3).

According to these findings, we noticed an increased diameter in the umbilical cord compared to standard medians, but also an incidence of 4.76% lack of cord twisting, or 28.57% excessive coiling (Figure 3A).

Abnormal cord insertion has been found in 19.04% cases including 1 multiple pregnancy (Figure 3B).

Macro analysis of maternal and fetal surfaces of the placentas revealed a significant occurrence of the basal plate fibrin deposition (28.57%) (Figure 4A) and also subchorionic fibrin depositions, with an incidence of 23.8% (Figure 4B).

Other macroscopic findings that have also been observed in our group are the placental calcifications, placental infarction (both 14.28%), and intervillous thrombi (9.52%) (Table 3).

The most common pathologic finding in our series has been fibrinoid necrosis, in 66.6%. Intervillous fibrosis is another placental observation in our group, in a 52.3% cases. Focal hyaline degeneration was recorded in 57.1% of the analyzed placentas (Table 4).

Figure 3.A). *Excessive cord twisting and umbilical cord diameter of 1.7 cm in a T2DM pregnancy.* ***B).*** *Velamentous cord insertion, with the fetal vessels running through the membranes, unprotected by Wharton's jelly in the emerging segment of the placental disk in a T2DM singleton pregnancy.*

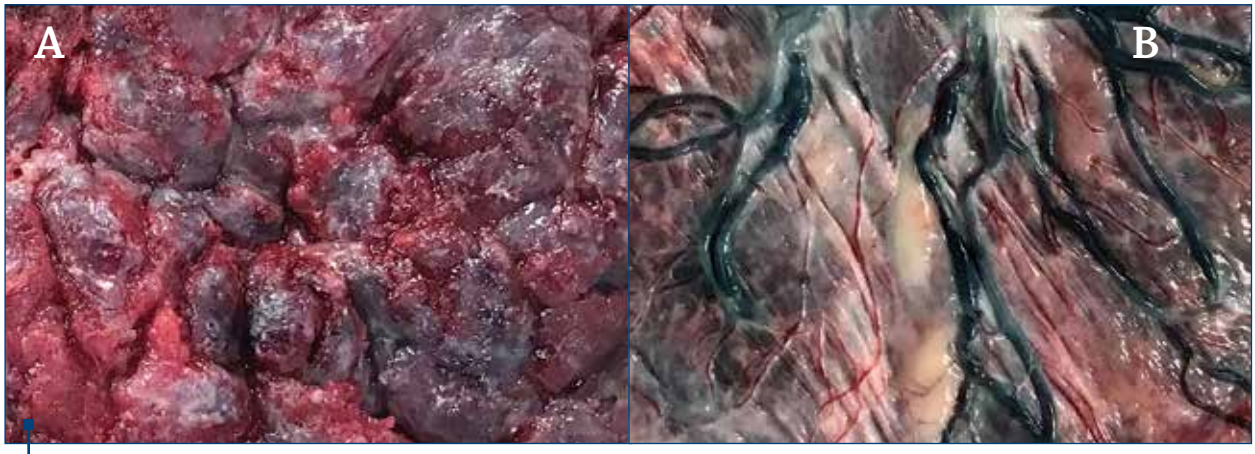

Figure 4.A). *Maternal surface of the placenta from a T2DM pregnancy demonstrating basal plate fibrin deposition, with a greyish - yellow appearance.* ***B).*** *Fetal surface of the placenta from a T2DM pregnancy demonstrating subchorionic fibrin deposition which is apparent as a laminated white plaque.*

With regard to the placental maturation deficiency, villous immaturity has been found in 42.8% of T2DM placentas.

On the other side, villous maturity has been recorded in 38% of the placentas in the study. Chorangiosis has been found in over 47% of cases.

The presence of nucleated fetal red blood cells was found in over 33%, placental calcifications were observed in 23.8% and lymphohistiocytic villitis in 14.2% of the cases. Placental infarctions and syncitial nodes were both detected in over 9% of cases, while villous hypermaturity in 4.7%. Decidual vasculopathy has been observed in 14.2% of the cases in our group. (Figure 5, A and B) (Table 4).

Discussion

Vasculogenesis of feto-placental vessels occurs in the first month of pregnancy, when stem cells in extra-embryonic mesoderm invade the developing chorionic villi[3,16].

In diabetic placenta, increased oxidative stress to the cell and the activation of protein kinase pathways, may create the basis for early damage in developing placental vessels[17].

In the diabetic environment the vascular dysfunction is characterized by increased angiogenesis and the preponderance of leaky vessels[5].

Leach et al. consider that maternal and fetal hyperglycemia may impact on placental vascular permeability[5].

Therefore, in diabetes the rise in blood glucose has several effects on the surrounding vasculature, and hyperglycemia has been shown to have a direct effect, acting as a pro-constrictor, pro-coagulatory, pro-inflammatory, pro-angiogenic and pro-permeability agent[18-24].

Huynh et al. observed that placentas complicated by T2DM have a greater incidence of maternal vasculopathy or decidual vasculopathy and placental infarctions[10].

On our case-control study, we observed the incidence of placental infarction at 9.52%, and decidual

Table 4 Placental pathology in T2DM

Placental histopathological findings	T2DM (n = 21)
Fibrinoid necrosis	14 (66.66)
Intervillous fibrosis	11 (52.38)
Focal hyaline degeneration	12 (57.14)
Villous immaturity	9 (42.85)
Villous maturity	8 (38.09)
Chorangiosis	10 (47.61)
Nucleated fetal red blood cells	7 (33.33)
Calcifications	5 (23.8)
Lymphohistiocytic villitis	3 (14.28)
Placental infarctions	2 (9.52)
Syncitial nodes	2 (9.52)
Villous hypermaturity	1 (4.76)
Decidual vasculopathy	3 (14.28)
Phantom cells	-

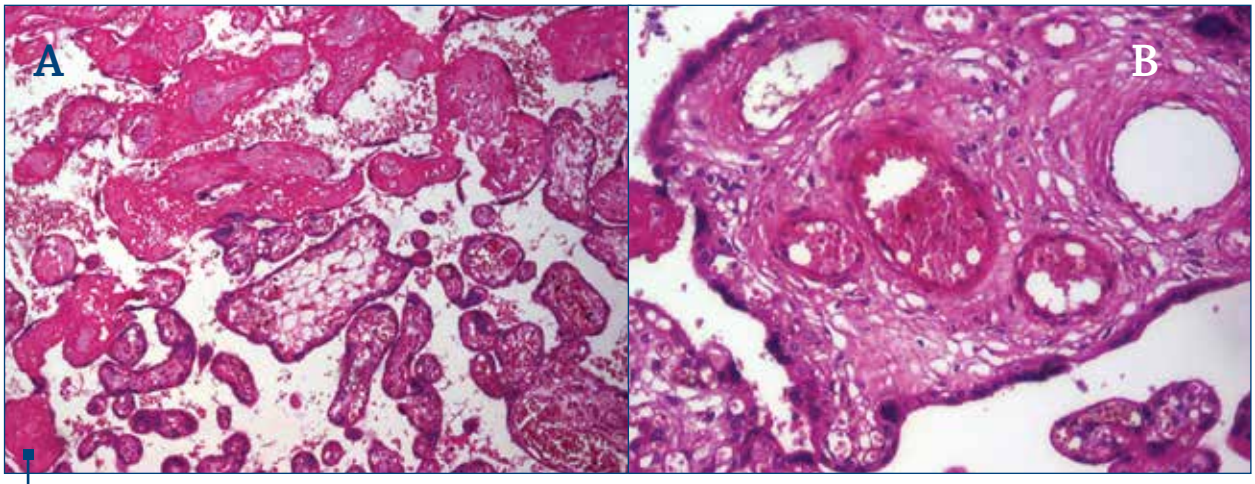

Figure 5.A). *Placental infarction, Haematoxylin - Eosin staining, x40.* ***B).*** *Villi with vascular stasis and sclerosis, Haematoxylin - Eosin staining, x100*

vasculopathy at 14.28%. Perhaps we could speculate that these data could vary in terms of effective glycemic control.

On the other hand, Roberts et al.[17], consider that the most well documented effects of maternal diabetes in pregnancy include chorangiosis, meaning increased villous vasculature, and placental villous immaturity, hence chorgangiosis could be a response to the relative hypoxemia due to the immaturity of the villi[25-29].

In this study we observed the presence of chorangiosis in almost half of the cases, and villous immaturity in over 40% of placentas.

In our study group we noticed pregnant women with T2DM who did not have constant glycemic control during pregnancy, even more, there were two cases with poor glycemic control in preconception. These aspects correlated with associated pathology, especially preexisting or induced pregnancy hypertension, obesity and preeclampsia, could explain the significant number of placental pathological findings in our series.

Hormann et al.[30] describe the notion of diabetic placentopathy, consisting of a combination of otherwise unspecific modifications, but present fairly consistent in the placenta of diabetic pregnancy, being represented by increased size and weight and villous immaturity[30, 31].

Generally non-hypertensive diabetic placenta has fewer changes compared to hypertensive diabetes[17, 32-37].

In this study, we found an association between T2DM and hypertensive disorders, meaning maternal preexisting hypertension (19.04%) and preeclampsia (28.57%), and a 23.8% maternal obesity association, which may explain the placental abnormalities found.

Conclusions

In T2DM, the amplitude of the placental anomaly spectrum is closely correlated with maternal glycemic control.

Associated hypertensive disorders amplify the spectrum of placental morphological changes. Preconceptional glycemic control and its support during gestation and perinatal period are very important elements for the outcome of diabetic pregnancy. US findings in diabetic placenta have as a background the morphological changes that are based on anomalies in angioarchitecture of the maternal-fetal interface. In pregnancy associated with T2DM we can talk about a combination of morphological changes, otherwise unspecific which, in terms of association with various comorbidities, especially hypertensive, could define a diabetic placental morphologic pattern. ■

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