**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA**
**DOCTORAL SCHOOL**

# CLINICAL, MORPHOLOGICAL AND ULTRASONOGRAPHIC STUDY OF THE PLACENTA IN PREGNANCY ASSOCIATED WITH DIABETES

## DOCTORAL THESIS

## *ABSTRACT*

***Scientific coordinator***
**Professor Sabina BERCEANU, MD, PhD**

***PhD Student***
**Adrian Victor TETILEANU, MD**

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## GENERAL PART

## 1. GENERAL CONSIDERATIONS ON PREGNANCY ASSOCIATED DIABETES

Classification of diabetes in the general population is primarily based on etiopathogenesis and pathophysiological manifestations. Thus, type 1 diabetes is characterized by absolute insulin deficiency, and type 2 diabetes is defined by poor insulin secretion, insulin resistance or increased glucose production [1].

Pregnancy associated diabetes continues to raise major problems in both maternal-fetal medicine and obstetrics.

Different studies on the incidence of pregnancy-related diabetes have found that the number of pregnant women with undiagnosed diabetes prior to pregnancy is on an ascending curve [1-4].

In this chapter were systematized current informations related to: diagnostic elements of gestation associated diabetes, hypertensive disorders in diabetic pregnancy and obesity, dyslipidemia and the inflammatory component in pregnancy associated with diabetes.

## 2. MATERNAL-FETAL CONSEQUENCES OF THE DIABETES AND THE ROLE OF GLICEMIC CONTROL

Diabetes significantly interacts with gestation and can cause complications with important maternal health effects, both immediate and post-pregnancy.

DM represents, along with arterial hypertension, the most common health problems in pregnancy [5].

In this chapter I discussed current issues regarding diabetic retinopathy, diabetic nephropathy, diabetic ketoacidosis, diabetic neuropathy, preeclampsia, maternal infectious pathology, fetal growth abnormalities, premature birth, fetal death in utero, diabetic embryopathy and spontaneous abortion, congenital malformations, neonatal hypoglycemia, neonatal hypocalcaemia, respiratory distress syndrome, neonatal cardiomyopathy, polycythemia, hyperviscosity and neonatal hyperbilirubinemia, neonatal hypomagnesaemia, neurodevelopment and neurological dysfunctions as well as transmission of diabetes and abnormal glucose tolerance.

## 3. NORMAL AND ABNORMAL MORPHOLOGY ISSUES OF THE PLACENTAL STRUCTURE

Diabetic placenta is of particular interest, in the fact that placental damage may be, at least partly, responsible for the increased incidence of fetal complications occurring in DM complicated pregnancies [6].

Within this chapter I analyzed the following issues: differentiation of the placenta, placental structure, maternal vascularization modeling and trophoblastic invasion, growth and maturation of maternal-fetal interface. Next, I have structured current information on: the morphopathological examination of the placenta, its morphological examination techniques, the placenta macro and microscopic morphological anomalies, such as form and size anomalies, fibrin perivillous deposition, subchoronic fibrin deposition, villous tissue infarction, intervillous thrombi, thrombosis and placental hematoma, chorangiosis, placental calcifications, chorangioma, hyperadherent placenta but also particular aspects of diabetic placenta.

# SPECIAL PART

## 1. INTRODUCTION

The placenta is a morpho-functional complex with a central metabolic role in the gestation period. This is the critical organ responsible for facilitating the absorption of nutrients, the elimination of metabolites and the gas exchange between the mother and the fetus [7]. Also, the placenta synthesizes different hormones, regulates the transport of maternal nutrients to the fetus and facilitates maternal metabolic adaptations at various stages of pregnancy [8].

During pregnancy complicated with DM, the placenta suffers a number of pathological, functional and structural changes [9].

DM was correlated with rapid progressive microangiopathy and this, in turn, may be associated with capillary hypertension and changes in capillary permeability [10].

### *1.1. STUDY OBJECTIVES*

The main motivation for which I chose this study was that diabetes is the most common medical complication of pregnancy. The incidence of pregnancy-related diabetes has increased spectacularly over the past 10-15 years, this increasement being actually a consequence of the evolution of obesity epidemiology.

The objective of the PhD research was to seek clinical correlations with influence on the pregnancy in general, and on the placental structure especially, in the pregnancy associated with T1DM, GDM and T2DM. The impact of maternal DM associated clinical conditions on placenta and fetal appendages was analyzed and subsequently correlated with the ultrasonographic, morphological, histological and immunohistochemical study of the placental structure.

## 2. MATERIAL AND METHOD

The retrospective and prospective PhD study was conducted between October 2016 and July 2018 on a group of 74 selected pregnant patients diagnosed with T1DM, GDM and T2DM.

The cases in the study groups were selected from the patients of The 2$^{nd}$ Obstetrics and Gynecology Clinic, Craiova County Emergency Clinical Hospital, Obstetrics and Gynecology Department, Emergency County Hospital Târgu Jiu, private practice of Obstetrics and Gynecology Office "Dr. Tetileanu Adrian" and the private practice of a Medical Obstetrics and Gynecology Center in Craiova.

Of the 74 patients in the study group, 37 (50%) were diagnosed with T1DM, 16 (21.6%) with GDM and 21 (28.3%) with T2DM.

All patients in the study group were Caucasian, with a mean age of 31 (20-42 years).

Monitoring from the point of view of the metabolic pathology of the patients in the study group was done through interdisciplinarity with the Diabetes, Nutrition and Metabolic Diseases Clinic, Craiova County Emergency Clinical Hospital.

### *2.1. CLINICAL STUDY*

Clinical characteristics and DM associated pathology were **(Table 1)**: HTA, PE, diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, urinary infections, mycotic vaginosis, obesity, infertility history.

**Table 1.** Clinical characteristics by diabetes type

| **DM associated conditions** | **T1DM N (%)** | **GDM N (%)** | **T2DM N (%)** | **T1DM + GDM + T2DM N (%)** |
|---|---|---|---|---|
| Maternal preexisting hypertension | 7 (18.91) | 2 (12.5) | 4 (19.04) | 13 (17.56) |
| Preeclampsia [1#] | 9 (24.32) | 3 (18.75) | 6 (28.57) | 18 (24.32) |
| Diabetic neuropaty | 3 (5.66) | - | 1 (4.76) | 4 (5.4) |
| Diabetic retinopathy | 5 (13.51) | - | - | 5 (6.75) |
| Diabetic nephropathy | 1 (2.7) | - | - | 1 (1.35) |
| Urinary infections | 16 (43.24) | 6 (37.5) | 10 (47.61) | 32 (43.24) |
| Candida vulvovaginitis | 19 (51.35) | 7 (43.75) | 8 (38.09) | 34 (45.94) |
| Obesity | 7 (18.91) | 2 (12.5) | 5 (23.8) | 14 (18.91) |
| History of infertility | 11 (29.72) | 4 (25) | 4 (19.04) | 19 (25.67) |
| **Singleton pregnancy** | 34 (91.89) | 15 (93.75) | 18 (85.71) | 67 (90.54) |
| **Twin pregnancy [2#]** | 3 (8.1) | 1(6.25) | 3 (14.28) | 7 (9.45) |
| **Macrosomia** | 15 (40.54) | 2 (12.5) | 7 (33.33) | 24 (32.43) |
| **IUGR** | 7[2#] (18.91) | 1[3#] (6.25) | 4[4#] (19.04) | 12 (16.21) |
| **Birth weight (g)** | **T1DM N (%)** | **GDM N (%)** | **T2DM N (%)** | **T1DM + GDM + T2DM N (%)** |
| | 3735 (± 995) | 3920 (± 1045) | 3810 (± 685) | 3821 (± 908) |
| **Gestational age at birth (weeks)** | 37.4 (± 1.9) | 38.2 (± 1.3) | 38.5 (± 1.6) | 38 (± 1.6) |

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, T1DM - Type 1 Diabetes Mellitus (pregestational diabetes), GDM - Gestational Diabetes Mellitus, IUGR - intrauterine growth restriction, [2#] 4 cases of selective IUGR and 3 cases of non-selective IUGR in dichorionic-diamniotic twin pregnancy, [3#] selective IUGR

### *2.2. ULTRASONOGRAPHIC STUDY*

US obstetrical assessment included fetal morphology and biometrics as well as placental, umbilical cord and amniotic fluid assessment, maternal-fetal Doppler profile and, in the case of multiple pregnancies, diagnosis of chorionicity and amnioticity **(Table 2)**.

**Table 2.** Obstetrical US assessment

| | |
|---|---|
| **Fetal morphology** | ▪ Fetal head, CNS<br>▪ Fetal face<br>▪ Thorax, cardio-vascular and respiratory systems<br>▪ Abdomen and pelvis, digestive system, kidneys, urinary tract and genital organs<br>▪ Spine and fetal skeleton |
| **Fetal biometry** | ▪ BPD, OFD, HC, AC, FL, HL, TL, EFW (BPD-HC-AC-FL) |
| **Placental assessment** | ▪ Location<br>▪ Thickness<br>▪ Echotexture<br>▪ Volume<br>▪ Immature appearance/ Grannum score |
| **Umbilical cord** | ▪ Number of vessels<br>▪ Insertion<br>▪ Coiling<br>▪ Diameter |
| **Amniotic fluid** | ▪ Amniotic fluid index<br>▪ Echogenity |
| **Maternal-fetal Doppler profile** | ▪ UA<br>▪ MCA<br>▪ Uterine artery |
| **Twins** | ▪ Placental location,<br>▪ T sign/ lambda sign<br>▪ Interfetal membrane<br>▪ Biometry or morphology discordance |
| CNS - central nervous system, BPD - biparietal diameter, OFD - occipitofrontal diameter, HC - head circumference, AC - abdominal circumference, FL - femoral length, HL - humeral length, TL - tibial length, EFW - estimated fetal weight, UA - umbilical artery, MCA - middle cerebral artery | |

## *2.3. MORPHOLOGICAL STUDY*

### 2.3.1. Morphological macroscopic study

The macroscopic analysis of tissue samples included placental weight, number of umbilical cord blood vessels, measurement of diameter, direction and coiling, or location of insertion in the placental disc.

Analysis of placental, maternal and fetal surfaces was performed after gentle washing of these with sterile water to remove potential artefacts. The macroscopic anomalies that were sought were: perivillous fibrin deposition, subchoronic fibrin deposition, placental infarction, placental basal plaque massive fibrin deposition, subcoronic thrombosis, intervillous thrombosis, placental calcifications.

### 2.3.2. Morphological microscopic study

After completion of the macroscopic study, longitudinal placental sections of 2-5 cm thick were pre-fixed in 10% neutral formaldehyde solution at ambient temperature, subsequently included with paraffin after the histopathological protocol.

### 2.3.3. Immunohistochemical study

**Table 3.** Immunohistochemical panel of antibodies

| **Antibody** | **Company** | **Clone** | **Antigenic exposure** | **Secondary antibody** | **Dilution** | **Labeling** |
|---|---|---|---|---|---|---|
| **Anti-CD34** | Dako | Clone QBE nd 10 | Citrate | Monoclonal Mouse Anti-Human CD34 Class II | 1:50 | Endothelial cells of small blood vessels |
| **Anti-TGFβ** | Santa Cruz Biotechnology | sc-398 | Citrate | Rabbit Polyclonal IgG | 1:50 | Induction factor for cellular transformation |
| **Anti-PCNA** | Dako | Clone PC10 | Citrate | Monoclonal Mouse Anti-Proliferating Cell Nuclear Antigen | 1:100 | Cells in division in the late G1 or S phase |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Anti-CD68** | Dako | Clone KP1 | Citrate | Monoclonal Mouse Anti-Human CD68 | 1:100 | Macro-phages |

## 3. RESULTS

The US examination of the placental characteristics, revealed an increase in placental thickness in the second trimester, especially in GDM cases (56.25%), with significant increases in placental thickness in the first half of the third trimester, both in GDM (75%), and in the case of T1DM or T2DM, more than half of the cases (58.1%) presenting placentomegaly at the end of the third trimester in the whole study group **(Table 4)**.

**Table 4.** US assessment of the placenta in diabetic pregnancy

| **Placental US findings** | | **T1DM (N = 37)** | **GDM (N = 16)** | **T2DM (N = 21)** | **T1DM + GDM + T2DM (N = 74)** |
|---|---|---|---|---|---|
| **Location N (%)** | Uterine fundus | 10 (27.02) | 5 (31.25) | 6 (28.57) | 21 (28.37) |
| | Anterior (± lateral) | 12 (32.43) | 3 (18.75) | 7 (33.33) | 22 (29.72) |
| | Posterior (± lateral) | 15 (40.54) | 7 (43.75) | 7 (33.33) | 29 (39.18) |
| | Praevia | - | 1 (6.25) | 1 (4.76) | 2 (2.7) |
| **Thickness* N (%)** | 24 - 28 gw > 40 mm | 8 (21.62) | 9 (56.25) | 4 (19.04) | 21 (28.37) |
| | 29 - 31 gw > 45 mm | 10 (27.02) | 12 (75) | 6 (28.57) | 28 (37.83) |
| | 32 - 34 gw > 50 mm | 13 (35.13) | 12 (75) | 7 (33.33) | 32 (43.24) |
| | 35 - 39 gw > 55 mm | 16 (43.24) | 15 (93.75) | 12 (57.14) | 43 (58.1) |
| **Echotexture N (%)** | Homo-geneous | 29 (78.37) | 14 (87.5) | 17 (80.95) | 60 (81.08) |
| | Inhomo-geneous | 8 (21.62) | 2 (12.5) | 4 (19.04) | 14 (18.91) |
| **Immature appearance / Grannum score** | G0 at > 26 sg | 8 (21.62) | 6 (37.5) | 5 (23.8) | 19 (25.67) |
| | G1 at > 32 sg | 11 (29.72) | 7 (43.75) | 7 (33.33) | 25 (33.78) |
| | G2 at > 35 sg | 15 (40.54) | 12 (75) | 9 (42.85) | 36 (48.64) |
| N - number of cases, * measured at the widest diameter in the saggital plane, gw - gestation weeks, G - Grannum score | | | | | |

Macroscopic analysis of the placentas and umbilical cords showed that placentas of women with diabetes were heavier compared with standard medians in unaffected pregnancies, in my study with an average of 641 g, the maximum median being reached in the GDM group (658 g), and the lowest in the T1DM group (621 g) **(Table 5)**.

**Table 5.** Macroscopic analysis of the placenta and umbilical cord

| **Gross analysis of the placenta and umbilical cord specimens** | | **T1DM (N = 37)** | **GDM (N = 16)** | **T2DM (N = 21)** | **T1DM + GDM + T2DM (N = 74)** |
|---|---|---|---|---|---|
| **Placental weight (g)*** | | 621.5 (± 138.9) | 658.3 (± 141.5) | 644.5 (± 139.7) | 641.4 (± 140) |
| Basal plate fibrin deposition N (%) | | 11 (29.72) | 3 (18.75) | 6 (28.57) | 20 (27.02) |
| Subchorionic fibrin depositions N (%) | | 9 (24.32) | 2 (12.5) | 5 (23.8) | 16 (21.62) |
| Placental calcifications N (%) | | 6 (16.21) | - | 3 (14.28) | 9 (12.16) |
| Placental infarction N (%) | | 2 (5.4) | 1 (6.25) | 3 (14.28) | 6 (8.1) |
| Intervillous thrombi N (%) | | 1 (2.7) | - | 2 (9.52) | 3 (4.05) |
| **Trivascular umbilical cord N (%)** | | 35 (94.59) | 16 (100) | 20 (95.23) | 71 (95.94) |
| **SUA N (%)** | | 2 (5.4) | - | 1 (4.76) | 3 (4.05) |
| **Umbilical cord diameter (cm)** | | 1.4 (± 0.3) | 1.5 (± 0.2) | 1.5 (± 0.3) | 1.4 (± 0.2) |
| **Twist direction N (%)** | Left | 26 (70.27) | 12 (75) | 15 (71.42) | 53 (71.62) |
| | Right | 11 (29.72) | 4 (25) | 6 (28.57) | 21 (28.37) |
| **Twisting N (%)** | Normal | 29 (78.37) | 12 (75) | 14 (66.66) | 55 (74.32) |
| | Excessive | 3 (8.1) | 1 (6.25) | 6 (28.57) | 10 (13.51) |
| | Lack | 5 (13.51) | 3 (18.75) | 1 (4.76) | 9 (12.16) |
| **Cord insertion N (%)** | Central/ pericentral | 33 (89.18) | 14 (87.5) | 15 (71.42) | 62 (83.78) |
| | Marginal | 3 (8.1) | 2 (12.5) | 4 (19.04) | 9 (12.16) |
| | Velamentous | 1 (2.7) | - | 2 (9.52) | 3 (4.05) |
| **Meconium staining** | | - | 1 (6.25) | 2 (9.52) | 3 (4.05) |
| * without attached umbilical cord or membranes, N - number of cases, SUA - single umbilical artery | | | | | |

The most common microscopic finding in my study series was fibrinoid necrosis in 72.97% overall, with no statistically significant difference between T1DM (72.97%) and GDM (81.25%), but relatively increased compared to T2DM (66.66%). Intervillous fibrosis is another placental microscopic finding in this study, in a 66.21% overall frequency, more common in the T1DM group (72.97%), compared to GDM (68.75%) and T2DM (52.38%) **(Table 6)**.

Chorangiosis was found in 50% of cases overall, with a significant difference in T1DM cases (56.75%) compared to GDM (37.5%), but comparable to T2DM (47.61%) **(Table 6)**.

**Table 6.** Microscopic placental pathology in diabetes associated pregnancy

| **Placental histopathological findings** | **T1DM (N = 37)** | **GDM (N = 16)** | **T2DM (N = 21)** | **T1DM + GDM + T2DM (N = 74)** |
|---|---|---|---|---|
| Fibrinoid necrosis N (%) | 27 (72.97) | 13 (81.25) | 14 (66.66) | 54 (72.97) |
| Intervillous fibrosis N (%) | 27 (72.97) | 11 (68.75) | 11 (52.38) | 49 (66.21) |
| Focal hyaline degeneration N (%) | 28 (75.67) | 9 (56.25) | 12 (57.14) | 49 (66.21) |
| Villous immaturity N (%) | 19 (51.35) | 13 (81.25) | 9 (42.85) | 41 (55.4) |
| Villous maturity N (%) | 18 (48.64) | 11 (68.75) | 8 (38.09) | 37 (50) |
| Chorangiosis N (%) | 21 (56.75) | 6 (37.5) | 10 (47.61) | 37 (50) |
| Nucleated fetal red blood cells N (%) | 13 (35.13) | 9 (56.25) | 7 (33.33) | 29 (39.18) |
| Calcifications N (%) | 12 (32.43) | 2 (12.5) | 5 (23.8) | 19 (25.67) |
| Lymphohistiocytic villitis N (%) | 6 (16.21) | 4 (25) | 3 (14.28) | 13 (17.56) |
| Placental infarctions N (%) | 3 (8.1) | 3 (18.75) | 2 (9.52) | 8 (10.81) |
| Syncitial nodes N (%) | 3 (8.1) | - | 2 (9.52) | 5 (6.75) |
| Villous hypermaturity N (%) | 3 (8.1) | - | 1 (4.76) | 4 (5.4) |
| Decidual vasculopathy N (%) | 1 (2.7) | 1 (6.25) | 3 (14.28) | 5 (6.75) |
| Phantom cells N (%) | 2 (5.4) | - | - | 2 (2.7) |

## 4. DISCUSSIONS

In this study, we included cases with T1DM, GDM and T2DM, analyzing the US and morphological changes occurring in the placenta, comparing them with each other, but also with the standard median of some parameters, where appropriate.

Preeclampsia or preexisting maternal hypertension, associated more frequently with T1DM than with GDM, are correlated with distinct placental morphological abnormalities that may predominate in T1DM over GDM and vice versa [11-14].

The association between diabetic pregnancy and preeclampsia, maternal hypertension or obesity is almost unanimously accepted, therefore, placental changes may reflect the influence of these abnormalities on its function and development.

Also, in the context of diabetes, hyperglycemia has been shown to have a pro-constrictive, pro-coagulant, pro-inflammatory, pro-angiogenic and vascular pro-permeability effect [15-18].

Daskalakis *et al.* have found a 40% incidence of chorangiosis in a series of 40 GDM placentas, while Huynh *et al.* identified this change in 38.1% of cases on a cohort of 126 GDM pregnancies, including women with preeclampsia [9, 19-21].

In the GDM group in my series, I found an incidence of 37.8% chorangiosis, including pregnant women with preeclampsia, which is comparable to the data presented above, but my research is limited by fewer cases. In this study, I observed the presence of chorangiosis in half of the cases, and villous immaturity in over 55% of the placenta.

In my study group, there were patients with inconstant glycemic control in the T2DM group, and moreover, there were two cases with poor glycemic control in the preconception. These aspects, correlated with the associated pathology, especially preexisting or pregnancy-induced arterial hypertension, obesity and preeclampsia, could explain the significant number of placental pathological findings in my series. Viewed as a whole, the hypertensive disorders, represented by pre-existing arterial hypertension and PE were identified in the entire series, respectively, with an incidence of 18.19% in the T1DM group and 12.5% in the GDM group, whereas PE had an incidence of 24.32 % in T1DM vs. 18.75% in GDM. Obesity was also a condition associated with both T1DM and GDM (18.91% vs. 12.5%).

There have been numerous studies of angiogenesis and vascular remodeling in diabetic placenta to date, but specific abnormalities can not be discussed, but rather a placental diabetic pathological pattern.

These data, as well as the data from this study, highlight the importance of both maternal and fetal US assessment throughout the diabetic pregnancy, especially during the second and third trimesters of pregnancy, and, on the other hand, confirm the importance of obtaining and maintaining an effective and constant glycemic control throughout pregnancy.

## 5. CONCLUSIONS

Diabetic placenta does not show specific changes, but different associations may represent a diabetic pathological pattern, influenced by associated conditions, especially preeclampsia, obesity, dyslipidemias and lack of euglycemia during pregnancy.

Maternal hypertensive disorders amplify the spectrum of morphological changes of the placenta.

Placental immaturity and villous capillary dysfunction are characterized by increased angiogenesis and vascular permeability.

Both in gestational diabetes, but especially in pre-gestational DM, the maternal-fetal interface undergoes morphological changes related in particular to placental immaturity and chorangiosis.

Ultrasound findings in diabetic placenta have as a background the morphological changes, which are based on abnormalities of placental angioarchitecture.

Maternal diabetes affects the maternal-fetal interface through placentomegaly in the second half of pregnancy, the role of the inflammatory component being essential.

Placentomegaly occurs due to parenchymal proliferation and villous vasculature, and can be considered a response to relative hypoxemia associated with the maternal diabetic environment.

The spectrum of placental morphological changes is dependent on glycemic or metabolic control, and management of associated conditions.

Maternal diabetes has a different impact on pregnancy depending on its type, namely pregestational diabetes, by early onset and longer duration may induce a wider spectrum of morphological changes compared to gestational DM.

The quality of maternal metabolic control, both preconceptional and during gestation, influences the rate of complications of pregnancy, especially those related to abnormal placentation.

Excessive dichotomic angiogenesis may be a representative feature of diabetic placenta.

The inflammatory response to the maternal diabetic condition involves the presence of macrophages and monocytes in the placenta, probably indicating the role of inflammation in the occurrence of structural changes in the maternal-fetal interface.

Euglycemia throughout pregnancy is an objective whose touch depends on maternal-fetal prognosis.

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