Rom J Morphol Embryol 2022, 63(1):99–104 ISSN (print) 1220–0522, ISSN (online) 2066–8279 doi: 10.47162/RJME.63.1.09

ORIGINAL PAPER

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Maternal obesity and placental pathology in correlation with adverse pregnancy outcome

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Abstract

Maternal obesity is associated with increased maternal and fetal morbidity and mortality, with an increased risk of gestational diabetes mellitus (GDM) and preeclampsia (PE). This prospective study histopathologically analyzes the placentas obtained from 34 pregnant obese women studied between October 2016 and May 2020. The 10 cases of term placentas from obese pregnancies with GDM and the 12 cases with PE were examined by the Hematoxylin–Eosin (HE), Masson's trichrome (MT) and Periodic Acid–Schiff–Hematoxylin (PAS–H) classical stainings, and by the immunohistochemical evaluation and compared to placentae from uncomplicated term obese pregnancies (12 cases). We did not meet placental histopathological (HP) abnormalities that we could classify as characteristic only for the state of obese pregnancy, but we did find placental changes associated with PE and GDM, in the context of obese pregnancy. In the case of association with PE, there were common lesions, manifested by intra- and perivillous fibrinoid deposition, calcification, and placental infarction area, to which were added numerous syncytial knots. In the case of obese pregnancy associated with GDM, we found, in addition to common placental lesions of obesity, intravillositary vascular edema and in the terminal villi appearing chorangiosis. This study revealed a number of HP changes that occur in maternal obesity, even in uncomplicated obese pregnancies. A characteristic of obese pregnancies associated with PE was the presence of numerous syncytial knots, and in obese pregnancies associated with GDM, the most common HP lesion was placental chorangiosis. Certainly, we cannot conclude that these HP lesions are specific to a particular pathology, but they belong primarily to the status of maternal obesity.

Keywords: obesity, pregnancy, preeclampsia, gestational diabetes mellitus, pathology.

Introduction

Obesity is currently a global health problem and the prevalence of obesity during pregnancy is increasing. In the United States, the incidence of obesity during pregnancy varies from 18.5% to 38.3%, while in the most European countries, the prevalence of obesity is lower, about 15% [1, 2].

Pre-pregnancy obesity is associated with increased maternal and fetal morbidity and mortality, with an increased risk of gestational diabetes mellitus (GDM), preeclampsia (PE), fetal macrosomia, and late stillbirth during pregnancy [3]. It was noted that the offspring have an increased risk of developing obesity and metabolic syndrome [4], thus continuing the negative consequences of obesity in the next generation. Unfortunately, the mechanisms that determine these adverse outcomes are not yet well known.

The placenta probably mediates these complications, the consequence of obesity on placental function including the placental production of hormones and the transport of nutrients to the fetus [5]. Studies on the human placenta have shown an increased maternal inflammatory response in obese pregnancy, demonstrated by increased levels of circulating proinflammatory cytokines [interleukin-6 (IL-6)] and the presence of higher levels of placental proinflammatory cytokines [6].

Pathological analysis of the placenta is important in trying to find the underlying causes of pregnancy complications in obese women, because not much is known about the placental histopathological (HP) appearance of pregnancies with obesity, with or without adverse pregnancy outcome.

Aim

This study aimed to assess the correlation between PE and GDM and patients' body mass index (BMI) and assessed if obesity influences the fetal growth development. Another purpose was to signal the placental structural changes associated.

Patients, Materials and Methods

This was a prospective cohort study on singleton pregnancy in obese or overweight women. Term placentas from complications with obese pregnancies, GDM (10 cases) and PE (12 cases), were examined and compared to placentae

from uncomplicated term obese pregnancies (12 cases). The 34 cases were studied between October 2016 and May 2020. The study took place in the Clinic of Obstetrics and Gynecology, Filantropia Municipal Clinical Hospital, Craiova, Romania. Maternal obesity was defined as BMI >30 kg/m^2, reported to the first prenatal visit, in the first trimester. BMI was calculated according to the standard formula (kg/m^2), and patients were grouped according to the classification of the *World Health Organization* (WHO): normal BMI (≤24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30.0 kg/m^2). All pregnancies were singleton and term pregnancies (defined as >37 weeks gestation).

All women completed a questionnaire of demographic details, obstetric history, and pregnancy symptoms before the first consultation, and informed consent was obtained from the women who agreed to participate in this study. The study was conducted in full compliance with the ethical principles contained in the "Declaration of Human Rights" adopted in Helsinki, which are in accordance with the "Rules of Good Practice in Clinical Trials" and the legal regulations in force and with the Approval of the Ethics Committee of the University of Medicine and Pharmacy of Craiova. The statistical analysis was performed in the Department of Biostatistics, University of Medicine and Pharmacy of Craiova.

The placental tissues were sent to the Research Center for Microscopic Morphology and Immunology (University of Medicine and Pharmacy of Craiova) for HP analysis. The tissues were fixed in 10% neutral buffered formalin at room temperature (RT). After fixation, the tissue pieces included in solid paraffin blocks were sectioned to a thickness of 5 μm, using the HM350 microtome, equipped with a water-based transfer system (STS microM); the tissue sections were applied on single slides and on slides treated with poly-L-lysine and left to thermostat (37°C) for one day for drying. To highlight the microscopic elements, we applied the protocol for the classical histological stainings: Hematoxylin–Eosin (HE), Masson's trichrome (MT), Periodic Acid–Schiff–Hematoxylin (PAS–H), but also on the special immunohistochemical (IHC) ones.

For the IHC study, sections were collected on slides coated with poly-L-lysine and dried in a thermostat at 37°C for 24 hours. After this procedure, the sections were subjected to a classical protocol: deparaffinization, dehydration, rehydration, antigen unmasking by boiling the slides in a sodium citrate solution, pH 6, for 21 minutes (seven cycles of 3 minutes) in a microwave oven. The endogenous peroxidase blocking was performed by incubating the histological sections in 3% hydrogen peroxide for 30 minutes, at RT, followed by a wash in distilled water for 10 minutes and a wash in 1% phosphate-buffered saline (PBS) for five minutes. Afterwards, blocking the nonspecific sites followed by using 2% skim milk for 30 minutes. Subsequently, histological sections were coated with the primary antibody (Table 1) and introduced into the cold (4°C, for 18 hours). After 18 hours, the slides were left at RT (30 minutes), washed in PBS (3×5 minutes) and the secondary antibody was applied for one hour [mouse/rabbit immunoglobulin G (IgG) antibody, VC002-025, R&D Systems VisUCyte Horseradish peroxidase (HRP) Polymer], were washed again in PBS (3×5 minutes) and developed with 3,3'-Diaminobenzidine (DAB) (Dako). At the end, the nuclei were labeled with Hematoxylin, the slides were dehydrated in ethanol with increasing concentrations (70%, 90%, 96%, 100%) (×5 minutes each), clarified in xylene for 30–45 minutes and Canada conditioner slides were fitted.

Table 1 – ***Antibody used in this study***

Primary antibody	Producer	Clone	Antigenic unmasking	Secondary antibody	Dilution	Marking
Anti-CD34	Dako	QBEnd 10	Citrate, pH 6	Monoclonal mouse anti-human CD34 Class II	1:50	Small neoformation vessels

CD34: Cluster of differentiation 34.

Results

The maternal and neonatal characteristics of the 34 cases whose placentas were studied from a HP point of view (Table 2). We selected cases with similar characteristics to try to determine specific HP lesions. Regarding BMI, PE occurred mainly in obese women (>30 kg/m^2), and GDM in overweight women. We noticed that fetal birth weight, interpreted as mean ± standard deviation (SD), did not exceed 50 percentiles, the lowest weight being in cases with PE, which shows that in pregnancies associated with obesity there is some restriction or slowdown of fetal growth.

The present study revealed at the HP examination of the placental sections obtained from obese mothers, several changes of the placenta, which we tried to distribute according to the pathology presented: PE, GDM or pregnancies with normal evolution but associated with obesity.

In uncomplicated term deliveries from obese pregnancy, abnormal placental histopathology has been observed, but that may be an aspect of obese uncomplicated term pregnancies because it has been found in almost all obese pregnancies. Intra- and perivillous fibrinoid deposition, placental infarction, perilesional fibrinoid deposition, extravillous calcification were present, and at the level of the chorionic plaque we noticed fibrinoid deposition (Figure 1, A and B).

Table 2 – ***Maternal and neonatal characteristics***

	Uncomplicated term deliveries in obese pregnancy (*n*=12)	GDM in obese pregnancy (*n*=10)	PE in obese pregnancy (*n*=12)
Maternal characteristics			
Age [years]	28±3.96	27±4.05	28.5±4.38
BMI [kg/m^2]	28.45±7.42	29.20±5.84	33.15±7.42
Nulliparity [%]	83.33	60	83.33
Normal vaginal delivery [%]	25	10	10
C-section [%]	75	90	90
Fetal characteristics			
GA at birth [years]	38.4±1.39	38.25±0.85	38.1±1.10
Birthweight (percentile) [kg]	46±30.80	44±23.27	34±24.14
Apgar score at five minutes	9±0.51	9±0.63	8.5±0.96
SGA (<10 percentile) [%]	8.33	10	25
LGA (>90 percentile) [%]	0	0	8.33
AGA (10–90 percentile) [%]	91.66	90	66.67

AGA: Appropriate for gestational age; BMI: Body mass index; C-section; Caesarean section; GA: Gestational age; GDM: Gestational diabetes mellitus; LGA: Large for gestational age; *n*: No. of cases; PE: Pre-eclampsia; SGA: Small for gestational age.

We found no placental HP abnormalities that we could classify as characteristic only for the state of obese pregnancy, but placental changes associated with PE and GDM were found. In case of association with PE, common lesions were present, manifested by intra- and perivillous fibrinoid deposition, calcification, and placental infarction area, with perilesional, intravillous and pericotyledonary fibrinoid deposition (Figure 2, A and B).

To all these lesions were added the presence of syncytial knots, which are constantly present in the placenta at term, but increased syncytial knots are frequently associated with maternal vascular malperfusion, as occurs in PE (Figure 3, A–C).

At the level of the chorionic plaque, in the case of obese pregnancy associated with PE, we noticed a massive deposition of subchorial and intrachorial fibrinoid, as well as areas of chorial infarction (Figure 4, A–C).

In the case of obese pregnancy associated with GDM, we found, in addition to common placental lesions of obesity, intravillositary vascular edema, massive deposition of subchorial and subamniotic fibrinoids, perichorial and intercotyledonary calcification (Figure 5, A–C). In this context, in the terminal villi develop several branches from a single capillary, appearing a phenomenon of hypervascularity, known as chorangiosis. Chorangiosis appears to be a placental adaptation for better placental efficacy in GDM. CD34 cells with a positive immunoreaction were found in the endothelium of vascular tree villi in cases with GDM, for the appearance of chorangiosis (Figure 6, A–C).

In the IHC study performed, we also found a number of aspects that were common for placentas from obese women with associated PE and GDM: placental villi infarcted completely with absent vascular capillaries, perivillous calcification, placental cotyledons with extremely dilated blood vessels and edema (Figure 7, A–C).

This study found that HP examination of placentas obtained from obese mothers did not reveal placental HP abnormalities specific only to the state of obese pregnancy, but only placental changes associated with PE and GDM, associated pathologies that were followed.

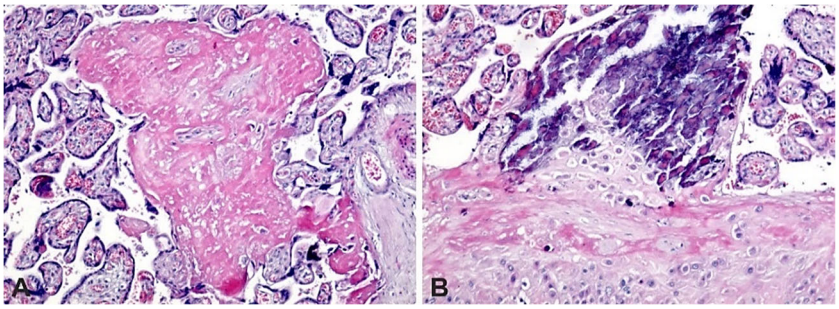

Figure 1 – ***Placental structural analysis in obese pregnancy: (A) The presence of intra- and perivillous fibrinoid deposition (intense pink), small areas of extravillous calcification and the area of massive placental infarction that included several terminal placental villi, with perilesional fibrinoid deposition; (B) The presence of intra- and perivillous fibrinoid deposition (intense pink color), massive area of extravillous calcification (pink-purple color), perichorial and fibrinoid deposition in the structure of the chorionic plaque. HE staining: (A and B) ×100. HE: Hematoxylin–Eosin.***

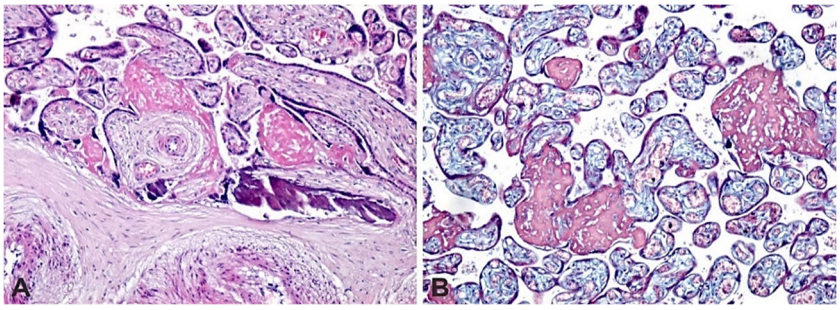

Figure 2 – ***Placental structural analysis in obese pregnancy associated with preeclampsia: (A) Intra- and perivillous fibrinoid deposition (intense pink color), extravillous calcification and placental infarction areas, with perilesional, intravillous and pericotyledonary fibrinoid deposition; (B) Intra- and perivillous fibrinoid deposition (red), small areas of extra- and intravillous calcification and old placental infarction, with perilesional fibrinoid development. HE staining: (A) ×100. MT staining: (B) ×100. HE: Hematoxylin–Eosin; MT: Masson's trichrome.***

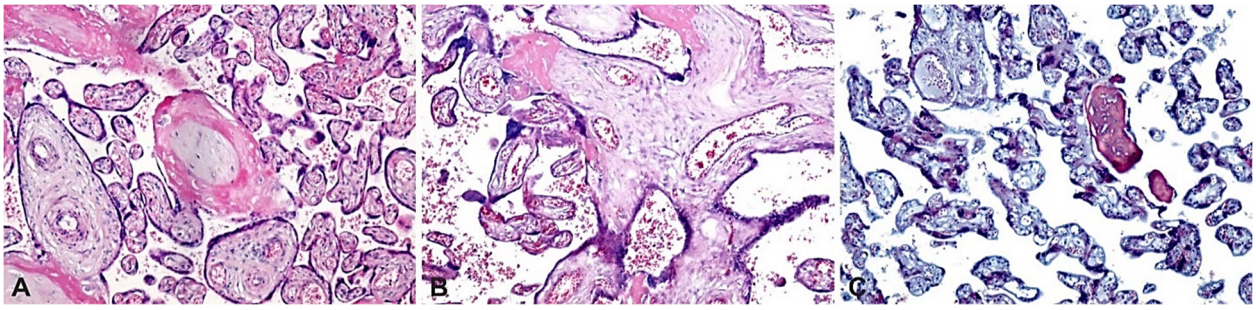

Figure 3 – ***Placental structural analysis in obese pregnancy associated with preeclampsia: (A) Intra- and perivillous fibrinoid deposition (intense pink), small areas of extravillous calcification, old placental infarction, with perilesional fibrinoid development and syncytial knots; (B) Intra- and perivillous fibrinoid deposition (intense pink), small areas of extravillous calcification; the presence of syncytial knots and intervillous extravasation was identified; (C) Intra- and perivillous fibrinoid deposition (intense pink) and the presence of small syncytial knots. HE staining: (A and B) ×100. MT staining: (C) ×100. HE: Hematoxylin–Eosin; MT: Masson's trichrome.***

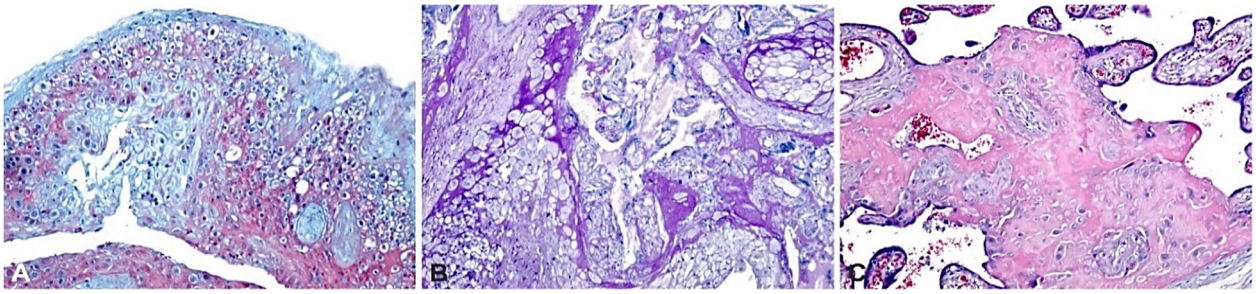

Figure 4 – ***Chorionic plate structural analysis in obese pregnancy associated with preeclampsia: (A) Chorionic plaque with fibrinoid deposit (red areas) and small areas of chorionic infarction; (B) Area of massive deposition of subchorial and intrachorial fibrinoid (intense pink), small areas of perichorial calcification; (C) Intra- and perivillous fibrinoid deposition (intense pink), small extravillous calcification areas, and the subchorial fibrinoid deposition area that includes chorionic plaque cells. MT staining: (A) ×100. PAS–H staining: (B) ×100. HE staining: (C) ×100. HE: Hematoxylin–Eosin; MT: Masson's trichrome; PAS–H: Periodic Acid–Schiff–Hematoxylin.***

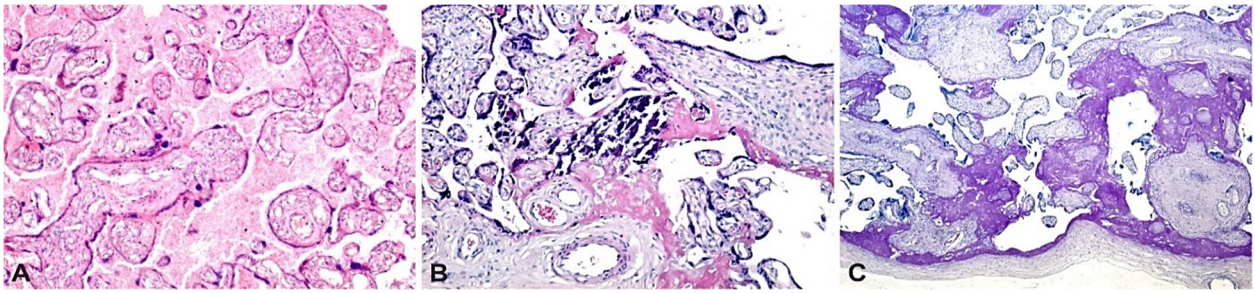

Figure 5 – ***Placental structural analysis in obese pregnancy associated with gestational diabetes mellitus: (A) Intra- and perivillous fibrinoid deposition (intense pink), small areas of extravillous calcification and intense extravillous hemorrhagic process with areas of intravillous vascular edema; (B) Intra- and extravillous fibrinoid deposition, with massive area of central villous calcification and small areas of perivillous calcification; (C) Area of massive deposition of subchorial and subamniotic fibrinoid (intense pink), small areas of perichorial and intercotyledonary calcification. HE staining: (A and B) ×100. PAS–H staining, ×100. HE: Hematoxylin–Eosin; PAS–H: Periodic Acid–Schiff–Hematoxylin.***

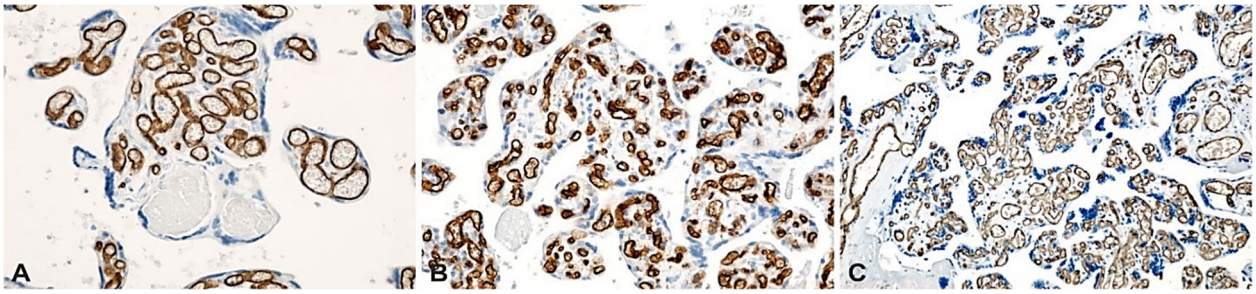

Figure 6 – ***Placental structural analysis in obese pregnancy associated with gestational diabetes mellitus. The basement membrane of the capillary endothelium was immunohistochemically labeled in brown: (A) Placental villi with chorangiosis (>10 intravillous capillaries) and the presence of minor intravillous infarcts; (B) Placental villi with chorangiosis; (C) Placental villi with the presence of normal looking intravillous capillaries and the area of placental villi with chorangiosis. Anti-CD34 antibody immunomarking: (A–C) ×200. CD34: Cluster of differentiation 34.***

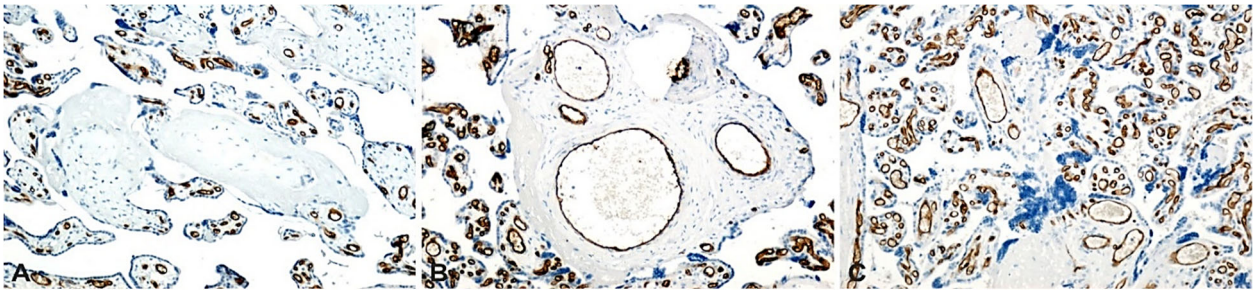

Figure 7 – ***Placental structural analysis in obese pregnancy associated with gestational diabetes mellitus and preeclampsia. The basement membrane of the capillary endothelium was immunohistochemically labeled in brown: (A) Placental villi with the presence of normal-looking intravillous capillaries and placental villi with total infarction, with absent vascular capillaries; (B) Placental villi with the presence of normal-looking intravillous capillaries and placental cotyledons with extremely dilated, edematous blood vessels; in the dilated vessels, there is a decrease in the thickness of the vascular endothelium; (C) Placental villi with the presence of intravillous capillaries, with normal appearance and placental villi with total infarction, which do not have intravillous vascular capillaries; the presence of perivillous calcification areas was identified. Anti-CD34 antibody immunomarking: (A–C) ×200. CD34: Cluster of differentiation 34.***

Discussions

The placenta is a unique extraembryonic organ that is present only during pregnancy and is responsible for fetal intrauterine development [7]. The HP study of the placenta may reveal aspects of fetal intrauterine life, which promises a clarification of the "mysteries" that cause adverse pregnancy outcome in several maternal pathologies, including obesity.

This prospective study evaluated the HP findings of the placentas of obese mothers both with the association of PE and GDM, and a pregnancy with obesity without any associated pathology. Our observations showed a significant increase in the frequency of intra- and perivillous fibrinoid deposition, fibrinoid deposition that was also present in the chorionic plaque, and placental infarction that included several terminal placental villi. As reported by some studies and authors, this lesion is due to increased muscle layer of the vessels, which causes a stasis of maternal blood in the intervillous space, which leads to a coagulation reflex [6, 8]. In their study, Jarmuzek *et al*. [9] showed that placental HP lesions in GDM pregnancies show some typical features, such as villous immaturity, villous fibrinoid necrosis, chorangiosis, and increased angiogenesis, but the authors point out that the type of lesion depends on how early the pathology set in [9].

The classical definition of chorangiosis refers to the marked increase in the number of vessels (>10 capillaries in more than 10 villi in several areas of the placenta) from non-infarcted and non-ischemic placental areas [10–13].

Suzuki *et al*. [14] appreciate that chorangiosis is a compensatory response to the status of chronic hypoxia associated with common conditions, including GDM and PE, facilitating vascular remodeling to adapt to low oxygen intake [15].

Redline [16] also reported that chorangiosis could be the hallmark of delayed villous maturation, which occurs in placentas from obese pregnancies, due to increased insulin resistance and hypoxia [16]. An independent factor for hypoxia is fetal hyperinsulinemia, which is associated with maternal obesity [17]. Probably that is why in our analysis we identified GDM-associated obese pregnancy as being associated with placental chorangiosis much more frequently than PE-associated obese pregnancy.

Another element in our study of the placental lesion found in placentas from obese pregnancies, was syncytial knots, which was more common in obese pregnancies associated with PE. Syncytial knots increase with increasing gestational age (GA) and assess villous maturity. But a high increase in syncytial knots may call into question maternal vascular malperfusion, which may be associated with adverse pregnancy outcomes, including PE and small for gestational age (SGA) in newborns [18, 19].

Syncytial knots are a feature of pregnancy associated with PE, as previous studies have shown, with numerous syncytial knots being combinations of reduced perfusion [20–22]. According to Burton *et al*. [23], the presence of oxidative stress and the generation of reactive oxygen species could underlie abnormal vascular remodeling and the appearance of increased syncytial knots [21]. As we mentioned, in our study we found an increase in syncytial knots especially in cases with obese pregnancies and associated PE, but we also found this HP lesion in cases with GDM or uncomplicated obese pregnancies, but less frequently. These findings are in accordance with other studies [24–26].

All the placental changes determined chorionic villi changes and in histoarchitecture and chorionic villi function with serious consequences on vascular, procoagulant status and areas with reduced blood flow [27, 28], having significant influence in the fetal outcome [28], with consequences on trophoblastic vascularization [29].

Conclusions

This study revealed a number of HP placental changes that occur in maternal obesity, reflecting the adaptability of this unique organ for fetal protection. Even in uncomplicated pregnancies, maternal obesity can cause characteristic changes in placental histology. Thus, in uncomplicated obese pregnancies we can find increase in fibrinoid deposition, and placental infarction that included several terminal placental villi, intravillous vascular edema. A characteristic of obese pregnancies associated with PE was the presence of numerous syncytial knots, and in obese pregnancies associated with GDM, the most common HP lesion was placental chorangiosis. We cannot conclude that these HP lesions are specific to a particular pathology, but they may be primarily related to maternal obesity status.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

Microscopic images have been acquired in the Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania (Manager: Laurenţiu Mogoantă, Professor, MD, PhD).

Authors' contribution

Maria Carmen Tabacu and Anca-Maria Istrate-Ofiţeru equally contributed to this article.

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Received: July 10, 2021

Accepted: August 20, 2022