New Various Histopathological Findings of the Placenta in Preeclampsia

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Preeclampsia represents a pregnancy-related disease which affects both the mother and the fetus. It's an important cause of materno-fetal morbidity and mortality. The placenta seems to be the main cause because after placental removal preeclampsia is no longer present. Placental examination is crucial and can reveal important information about this disease. After careful examination, besides the classic findings, new and uncommon histopathological aspects of the placenta in preeclampsia were described. A short observational study was performed which included placentas from preeclampsia complicated pregnancies. The various histopathological findings of the placenta in preeclampsia were evaluated according to gestational age.

Keywords: placenta, preeclampsia, pathology, atherosis

Approximately 10% of all pregnant women are affected by hypertension and according to the World Health Organization 16% of maternal deaths in developed countries are due to hypertensive disorders. These include: chronic hypertension, gestational hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension and eclampsia [1]. Among them, preeclampsia seems to be the most dangerous.

Preeclampsia is one of the primary causes of maternal morbidity and mortality, affects both the mother and the fetus [2]. It is defined as gestational hypertension with a BP >140/90mmHg after 20 weeks of gestation accompanied by proteinuria > 300mg/24 h in a patient who has no history of hypertension or renal disease [3-5]. The main risk factors for preeclampsia are: obesity, diabetes, extreme maternal ages, nulliparity, personal history of preeclampsia, race [6]. Multifetal pregnancy also exposes the mother to increased risk of preeclampsia [7].

The cause of preeclampsia is still incompletely elucidated but it is known to be related to placental insufficiency. Currently, there are some theories which partially explain its etiology: placental ischemia, the autoimmune theory and the genetic theory [8].

The diagnosis is mainly clinical and must be taken into consideration when high blood pressure, edema and proteinuria appear. The mean arterial pressure (MAP) should be calculated { MAP = [SP + 2DP]/3 } because an increase of 20mmHg represents an alarm sign and a value over 100mmHg is abnormal [9, 10].

The placenta is a temporary, unique organ, which can only be found in pregnancy [11]. It represents the interface between the mother and her fetus and its normal development and function are crucial for the outcome of a normal pregnancy [12, 13].

Most physicians fail to recognize the importance of examining the placenta, for it can serve as an objective indicator of maternal and fetal wellbeing throughout pregnancy. Abnormal placentas may raise a question mark upon the fetal current health status as well as it can serve as a prognostic factor on a future pregnancy.

Its development begins with the blastocyst implantation and is delivered with the fetus at birth. Early in pregnancy the villi cover the whole surface of the chorion, but by the end of the third month chorion frondosum forms the normal placenta and its location can now be established by ultrasound. In the second trimester the placenta has almost the same weight as the fetus but by term the ratio is 1:6 or 1:5, with a round placenta, measuring 17-20 cm in diameter and 2-3 cm in thickness [12, 14, 15].

We can talk about placenta even in the absence of the embryo, but we cannot have an embryo without a placenta. There are many related illnesses secondary to placenta. During pregnancy the placenta can suffer during development, implantation and functioning. The placenta should always be carefully examined after delivery and if there are abnormal findings, then it should be sent for further histopathological examination [16].

Term placenta histological presents a large number of chorionic and syncytial knots. In these nodes, syncytiotrophoblast nuclei are arranged in clusters among themselves leaving thin areas cytoplasm lacking nuclei [17, 18].

Preeclampsia can induce certain placental abnormalities. Firstly, the placenta can fail to develop properly and remains small compared to gestational age. Secondly, there might be an alteration in its function, independent of weight, due to reduced blood flow. The typical vascular lesion found in placentas affected by

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hypertension is called acute atherosis. It can be seen in the intramiometrial part of the spiral arteries and decidua parietalis [13, 16, 19].

Experimental part

The purpose of this retrospective study was to investigate the histopathological and therapeutical aspects of placental lesions as well as their concurrence with preeclampsia in a series of cases investigated and treated at Prof. Dr. Panait Sîrbu Hospital in Bucharest, Romania in collaboration with Pathology Department of University Emergency Hospital Bucharest. Placentas from 6 pregnancies complicated by preeclampsia were identified prenatally according to the following criteria:

Hypertension occurred after 20 weeks of gestation; blood pressure over 140/90mmHg together with proteinuria (0.3g/24h or + + on urinalysis).

All pregnancies ended in caesarean section.

After delivery, the placentas were weighed and examined starting with the maternal surface. Full-thickness samples were taken from the central areas and were embedded in paraffin. Tissue collection was obtained after the informed consent of all patients. The evaluation and the sampling method was standardized.

Histopathological findings were compared with 6 other normal placentas. Inclusion criteria for control cases were normal blood pressure and no proteinuria. Exclusion criteria for the control were: diabetes mellitus, obesity, severe anemia and infection.

All specimens were processed using the conventional method of paraffin embedding and hematoxylin and eosin staining. The embedded placental specimens were initially sampled from areas with obvious macroscopic lesions: hyalinization, calcification, areas of infarction and also areas with significant hemorrhage. The selected areas for sampling were in the proximity of the umbilical cord insertion. After 24 h fixation with buffered 10% formalin and after proper paraffin embedding, 2µm thick sections were subsequently stained with haematoxilin and eosin and examined entirely using a light microscope.

Results and discussions

Several aspects were found after examining different placentas coming from preeclampsia-affected pregnancies.

The most common lesions were areas of necrosis and alterations in decidual vascularization. These appear secondary to insufficient intervillous circulation. Additional findings were: placentas smaller than normal for gestational age. The surface area, villous diameter and blood vessels were smaller than in a normal placenta. The samples were also darker than normal, due to hemoconcentration.

Case No. 1: 35 weeks of gestation with preeclampsia. The fetus is alive after C-section delivery (fig. 1).

Case No. 2: 26 year old female, 27 weeks of gestation complicated with preeclampsia and ended in stillbirth.

Discreet inflammatory infiltrate in the decidua basalis beneath the Nitabuch fibrinoid. Focal oedema of the chorionic villi. Hematoxylin-eosin staining - ob. 100X (fig. 2).

Case No. 3: 33 weeks of gestation, preeclampsia. The fetus is alive after C-section delivery.

The placental villi appear hypervascular extensive fibrinoid deposits within the intervilozitar space and dystrophic calcifications. Discrete hyalinosis of the villous blood vessels. Syncytiotrophoblast with Tenney - Parker type alterations (multiple syncytial nodules). These changes are consistent with hypoperfusion and hypoxia.

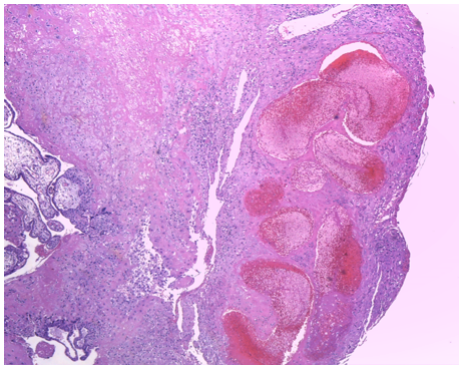

Fig. 1. Gross appearance: placental weight[g]: 327; placental thickness[cm] 1,26; placental diameter[cm] 12,70; placental surface area[cm^2] 156,4; vili diameter[mm] 0,07; blood vessel density/area [mm^3] 21,60

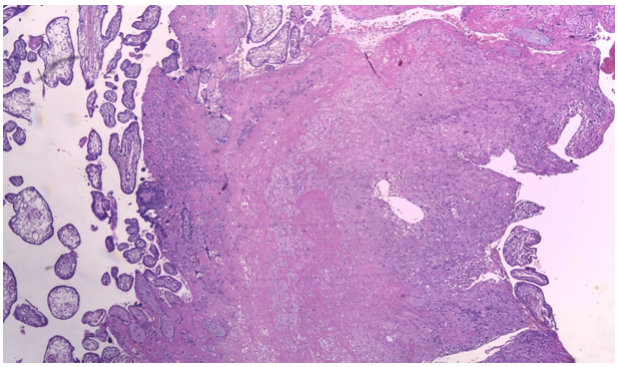

Fig. 2. Gross examination: placental weight[g]: 210,6; placental thickness[cm] 0,98; placental diameter[cm] 10,60; placental surface area[cm^2] 124,4; villi diameter[mm] 0,05; blood vessel density/area [mm^3] 18,40.

Hematoxylin-eosin staining - ob. 100X (fig. 3).

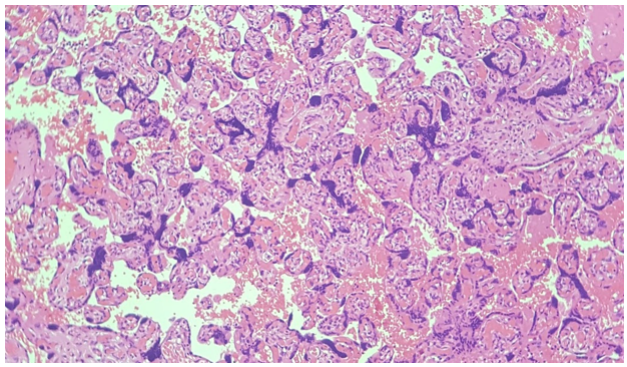

Fig. 3. Gross examination: placental weight[g]: 316; placental thickness[cm] 1,28; placental diameter[cm] 11,60; placental surface area[cm^2] 146,2; vili diameter[mm] 0,07; blood vessel density/area [mm^3] 22,30.

Case No. 4: 22 year old female, 23 weeks of gestation, severe hypertension, proteinuria. The pregnancy ended in abortion (fig. 4).

Case No. 5: 31 year old female, 32 weeks of gestation, preeclampsia, stillbirth.

The intervilozitar space is significantly narrowed by the extensive accumulation of fibrinoid . The vessels suffered hyalinization , some chorionic villi are necrotic (villous-shadow appearance). Syncytiotrophoblast hyperplasia is distinguished (Tenney - Parker type alterations) and focal dystrophic calcifications. Hematoxylin- eosin staining - ob. 100X (fig. 5).

Case No. 6: 21 year old female, severe preeclampsia, 30 weeks, placenta praevia and uterine rupture.

Normal placenta cases - macroscopic exam revealed: mean placental weight (g): 510; mean placental thickness

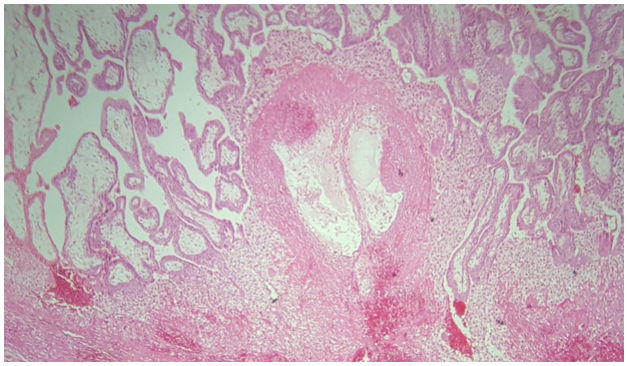

Fig. 4. Acute atherosis of a vessel from the decidua basalis. Degeneration and fibroid necrosis of the vascular wall, Hematoxylin- eosin staining, ob. 100X

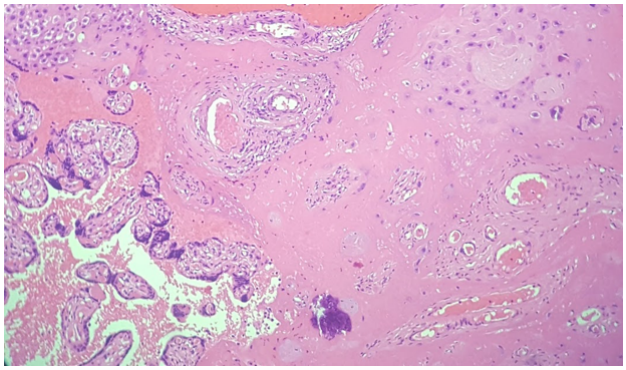

Fig. 5. Gross examination: placental weight[g]: 298; placental thickness[cm] 1,18; placental diameter[cm] 11,20; placental surface area[cm^2] 126,4; vili diameter[mm] 0,07; blood vessel density/area [mm^3] 20,40

(cm) 1.86; mean placental diameter (cm) 18.90; mean placental surface area (cm^2) 256.2; mean vili diameter (mm) 0.08; mean blood vessel density/area (mm^3) 24.80 (fig. 6).

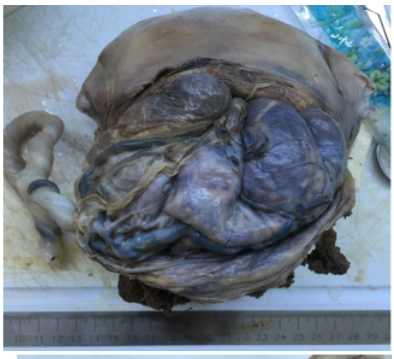

Fig. 6. Gross appearance of a complete uterine rupture with separation of the uterine wall and partial expulsion of the placenta.

In normal placentas, the villous structure is composed of a central connective tissue core covered by trophoblastic cell layers. Each villous has many fetal capillaries and were separated by intervillous spaces. Disturbance of maternal blood flow in pregnancy is known to be interfering with fetal development, but how specific or severe this interaction is it's still controversial and difficult to establish.

In preeclamptic patients' placentas abnormal changes were described. In 1945 Hertig was the first who described the pathologic changes of preeclampsia in the spiral arterioles at the site of implantation.

Preeclampsia is a frequent and potentially lethal pregnancy complication for women and also for the offspring. Women who develop preeclampsia also develop a long-term enhanced risk of cardiovascular disease and premature death. Also, women developing preeclampsia and cardiovascular disease may have common risk factors, which are unmasked by pregnancy. In preeclampsia, lipid deposition and fibrinoid necrosis within the walls of the maternal uterine arteries leading to the placenta, named spiral arteries, regularly occurs. These vascular lesions resemble early stages of atherosclerosis and are named acute atherosis and are believed to regress after delivery. The mechanisms that trigger atherosis in preeclampsia are largely unknown, but are related to the impaired vascular remodeling of the spiral arteries in the first half of pregnancy. One conspicuous feature of these atherosclerosis-like lesions may be partly linked to the invasion of trophoblasts by specialized fetally derived placental cells [20].

Furthermore, placental atherosis is usually accompanied by other histopathological alterations such as chronic mononuclear perivascular inflammatory infiltrate along with increased fibrin depositions, placental villi necrosis, areas of dystrophic calcifications and infarctions and discrete, ubiquitous presence of reactive Hofbauer cells. These lesions found in patients with preeclampsia can lead to fetal death, small-for-gestational age, spontaneous preterm labor/premature prelabor rupture of membrane, and spontaneous mid-trimester abortion.

It is suggested that most of these findings are related to low oxygenation secondary to impaired perfusion. However, hypoxia may not be a major feature of the abnormal vascular remodeling but rather the generation of reactive oxygen species [21]. It is also known that syncytial knots can be induced in vitro by either hypoxia or oxidative stress [22].

Placental insufficiency is another term often used in connection with placental malperfusion and is sometimes defined as a reduction of placental exchange. It is a most difficult term to define precisely. We prefer to specify the pathological lesions that are present rather than to embrace them all in the imprecise terminology of *placental insufficiency*. As such we reported the presence of atherosis as a primary sign of preeclamptic induced modification. Also, the predominance of clustered, knotted terminal villi, with increased branching angiogenesis, referred to as Tenney-Parker changes are highly suggestive for preeclampsia related placental modification. This abnormality is suggestive of uteroplacental hypoxia. We also observed an increased intra- and intervillous fibrinoid deposits and intervillous edema, retroplacental hematoma with surrounding areas of infarction and microcalcification. These are also signs of malperfusion. We compared our findings with other published data and the results were analogous. Preeclampsia can be easily suspected in the placenta both after microscopic and macroscopic examination. Abnormal placentation cause mal-development of the placenta and is reflected in dysfunction. In placentas from preeclampsia cases we found less surface areas, smaller vili diameters, and reduced blood vessel densities. It is well known that normal morphology of the placenta is important for oxygen changes between mother and fetus [20, 22].

The constellation of placental findings, however, is also

seen in the syndrome of lupus anticoagulant, systemic lupus, occasionally in coagulation disorders, and even without underlying maternal disease. The fact that the same pattern of placental lesions occurs in different disorders suggests that there is a common thread in the underlying pathophysiology of these disorders. However, the pathophysiology of these disorders is still not fully understood [23].

Placental examination should always be performed in complicated pregnancies and all abnormal placentas should be referred for further histopathological examination.

Conclusions

Preeclampsia is a life-threatening condition which ceases only after delivery. The main aspects of a preeclamptic placenta are decidual arteriopathy, infarcted and ischemic areas, abruption placentae, Tenney-Parker changes.

As we can see morphological and histological changes in placenta such as reduced weight, thickness, and diameter, decreased blood vessel density are correlated with preeclampsia.

Standard histopathological examination of the placenta in abnormal pregnancies would be helpful. A better understanding of the process underlying spiral artery atherosis in pregnancy may cast a new light on the development of preeclampsia which may further lead to new therapeutic options.

References

1.HASSAN, M., BEGUM, M., HAQUE, S.M.Z., JAHAN, N., YASMEEN, B.H.N., MANNAN, A., ET AL. North Int Med Coll J. **6,** no 2, 2015, p. 57.

2.IVAN, M.V., PETRE, I., VLAICU, B., APOSTOL, A., TESLOIANU, D., MUNTEANU, M., COSTACHESCU, R., MOLERIU, L.C., FULGER, L. Rev. Chim. (Bucharest), **69**, no. 5, 2018, p. 1260

3.KINTIRAKI, E., PAPAKATSIKA, S., KOTRONIS, G., GOULIS, D.G., KOTSIS, V. Horm. **14,** no 2, 2015, p. 211.

4.POWER, C.E., LEVINE, R.J., KARUMANCHI, S.A. Circulation. **123,** no 24, 2011, p. 2856.

5.SERBAN, D., CRISAN, C., SERBAN, C., MICU SERBU, I.B., KUNDANI, N., POROCH, V., SHARMA, A., BUCIU, V., HORHAT, I.D., SAS, I., BIRIS, M., RATIU, A. Rev. Chim. (Bucharest), **69**, no. 5, 2018, p. 1204

6.LYELL, D.J., LAMBERT-MESSERLIAN, G.M., GIUDICE, L.C. Prenatal screening, epidemiology, diagnosis, and management of preeclampsia. Clin Lab Med. **23,** no 2, 2003, p. 413.

7.VADUVA, C.C., CONSTANTINESCU, C., TENOVICI, M., VADUVA, A.R., NICULESCU, M., DITESCU, D., ALBU, C.C., ALBU, D.F. Rom J Morphol Embryol. **57,** no 3, 2016, p. 1089.

8.TOTH, G., CRAINA, M., STELEA, L., CITU, C., NEAMTU, R., FOGOROSSY, A., MOLERIU, R.D., BARDAN, R., PETRE, I., SUSAN, R., CHEVERESAN, A., SUCIU, N. Rev. Chim. (Bucharest), **69**, no. 12, 2018, p. 3457

9.WRIGHT, D., AKOLEKAR, R., SYNGELAKI, A., POON, L.C.Y., NICOLAIDES, K.H. Fetal Diagn Ther. **32,** no 3, 2012, p. 171

10.PARK, H. J., SHIM, S.S., CHA, D.H. J Mol Sci. **16,** no 8, 2015, p. 17952.

11.BRAILA, A.D., GLUHOVSCHI, A., NEACSU, A., LUNGULESCU, C.V., BRAILA, M., VIRCAN, E.L., COTOI, B.V., GOGANAU, A.M. Rom J Morphol Embryol. **59,** no 1, 2018, p. 187.

12.BURTON, G.J., JAUNIAUX, E. Am J Obstet Gynecol. **213,** Suppl. 4, 2015, p. 6. DOI: 10.1016/j.ajog.2015.07.050.

13.SILASI, M., COHEN, B., KARUMANCHI, S.A., RANA, S. Obstet Gynecol Clin North Am. **37,** no 2, 2010, p. 239.

14.HUPPERTZ, B. J Clin Pathol. **61,** no 12, 2008, p. 1296

15.NELISSEN, E.C.M., VAN MONTFOORT, A.P.A., DUMOULIN, J.C.M., EVERS, J.L.H. Hum Reprod Update. **17,** no 3, 2011, p. 397.

16.GORDIJN, S. J. (2009). On perinatal pathology: aspects of perinatal autopsy, placental pathology and classification of perinatal mortality. 2009, Groningen: s.n., p. 176.

17.TEWARI, V., TEWARI, A., BHARDWAJ, N. Asian Pac J Tropical Dis, **1,** no 1, 2011, p. 1.

18.GHEORMAN, V., GHEORMAN, L., IVANUª, C., PANA, R.C., GOGANAU, A.M., PATRASCU, A. Rom J Morphol Embryol. **54,** no 3, 2013, p. 505.

19.ROBERTS, J.M., ESCUDERO, C. Pregnancy Hypertens. **2,** no 2, 2012, p. 72. doi: 10.1016/j.preghy.2012.01.001

20.SANKAR, K.D., BHANU, P.S., RAMALINGAM, K., KIRAN, S., RAMAKRISHNA, B.A. Anat Cell Biol. **46,** no 4, 2013, p. 285. DOI: 10.5115/acb.2013.46.4.285.

21.BURTON, G.J., WOODS, A.W., JAUNIAUX, E., KINGDOM, J.C.P. Placenta. **30,** no 6, 2009, p. 473

22.HEAZELL, A.E.P., MOLL, S.J., JONES, C.J.P., BAKER, P.N., CROCKER, I.P. Placenta. **28,** Suppl A, 2007, p. 33. DOI:10.1016/j.placenta.2006.10.007

23.BAERGEN, R.N. Manual of Pathology of the Human Placenta, Second Edition, Springer New York Dordrecht Heidelberg London, 2011, section V, P. 325.

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