Comparative study of placenta acute fetal distress and diabetes associated with pregnancy

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Abstract
The authors analyze the main histopathological changes of placentas from pregnancies ended with fetal distress at birth and the tasks associated with diabetes. The parallel between the two types of placentas not trying to prove the existence of pathognomonic lesions. Are set out both the similarities between the two titles of placentas lesions (such as changes in microcirculation and so on) as well as particular aspects. The authors analyze a group of 19 pregnant women hospitalized in Obstetrics and Gynecology Clinics of Emergency County Hospital of Craiova, Romania, in September 2010–September 2011, who were born and who were diagnosed with diabetes. In the same period, were studied 21 pregnant women whose pregnancy ended with the birth of a child with fetal distress. Such were identified as placental lesions suggestive of fetal distress as diverse etiology of placental vascular changes and the placenta in pregnancy associated diabetes as immaturity and vascular edema and fibrinoid changes and glycogen stores. The authors have proposed to highlight some lesions suggestive of two groups of diseases but independent groups were analyzed and conclusions were drawn after discussing results. This study is justified by insufficient knowledge of the causes that lead to fetal distress regardless of its etiology. In conclusion, the authors mention both placenta’s common changes as specifically changes of the placenta for each type of disorder.

Keywords: placenta, fetal distress, diabetes.

Introduction
During the first half of pregnancy, trophoblast tissue is key to suffer the deepest changes, while extensive angiogenesis and vascularization occur in the second half of pregnancy the endothelium becomes more important now based processes although some overlap of the two phenomena. This period is also accompanied by extensive vascular remodeling and vascular stabilization [1, 2]. Term placenta histological presents a large number of chorial and syncytial knots. In these nodes, syncytiotrophoblast nuclei are arranged in clusters among themselves leaving thin areas cytoplasm lacking nuclei [3]. In other news, more and more data support the idea of long-term consequences of intrauterine growth restriction. There are authors who believe that these people have a higher propensity to develop metabolic syndrome later including type 2 diabetes. There is the idea that “malnutrition” intrauterine concomitant with increased insulin resistance leads to pancreatic β-cell loss and a predisposition to adult diabetes [4].

This study attempts to analyze changes in the placenta during pregnancy both finished with fetal distress of various etiologies as well as in pregnancy associated with diabetes.

Its usefulness derives from the impossibility of establishing an effective therapeutic behavior in the absence of mechanisms intimate knowledge encountered in these disorders.

Materials and Methods
The histopathological study it was composed of a group of 19 pregnant women hospitalized in Obstetrics and Gynecology Clinics of Emergency County Hospital of Craiova, Romania, in September 2010–September 2011, who were born and who were diagnosed with diabetes. In the same period, were studied 21 pregnant women whose pregnancy ended with the birth of a child with fetal distress. In eight cases, overlapped a syndrome of intrauterine growth restriction but in 13 cases did not have any clinical information on the etiology of that suffering.
We selected the material for the study from the following medical papers:
- clinical observation sheets pregnant;
- sheets observation of infants;
- ledgers of birth;
- ledgers surgery protocols;
- histological preparations and newsletters with histopathological results of fetal annexes.

### Study material

The material studied was the parts macroscopic and histological adnexal tissue fragments.

The study was prospective cases including pregnant and diagnosed with diabetes admitted to hospital during the preparation of the paper.

### Histological processing of tissue fragments

Placental tissue fragments were subjected to conventional histological processing techniques (including fixation and paraffin) and then serial sections were made from each block.

For placentas from pregnancies with acute fetal distress, we used Hematoxylin–Eosin staining and then we used the technique of immunohistochemistry with CD34 antigen (×100).

For placentas of tasks associated with diabetes, the first section was stained with the usual classical method (Hematoxylin–Eosin). The following two sections were stained with PAS and Alcian Blue technique. Histopathological aspects were selected Olympus CX31 microscope using the eyepiece with magnification of ×4. For image acquisition, we used an optical plane chromatography corrected objectives with magnification of ×10.

The most suggestive images were made by a Live View Pro digital camera. Then, we put them on the computer by Analysis Pro software and Photo Canvas Lite v. 1.1 ACDSee 4.0 software.

### Results

#### Acute fetal distress

In acute fetal distress, most suggestive lesions are:

**Placental villous vascular density**

Morphometric measurements were performed intra-placental vascular density according to two criteria: type of villi and the placenta. Vascular density was quantified differently villi of grade I and II, where the coefficient between the levels of quantifying growth was 100 villous structures vasculare/mm² and third degree where growth coefficient between the levels of quantifying capillary was 500/mm².

**Villous vascular density in grade I and II**

Mean vascular density was higher in the villous placenta grade I and II of the peripheral than in the central placenta (Figures 1–4).

The average density values were placed inside the confidence intervals are concentrated most measurements, intervals also had the same position as the beaches of dispersion.

**Villous capillary density in grade III**

Beaches dispersion of capillary density values (from the lowest to the highest value determined) in the third degree villi both limits and different strains (Figures 5–8).

### Diabetes associated with pregnancy

In diabetes associated with pregnancy most suggestive lesions are:

**Villositary immaturity**

Shown signs of immaturity villositary were observed in all cases studied, particularly in the distal branches of the villositary tree. It should be emphasized that the distribution of immature appearance was a rather diffuse and synchronous length.

Some morphological elements defining focal abnormal development villositary, remember to increase the size especially at distal villi (chorionic intermediate and terminal), which creates the false impression of increased density and villositary (Figures 9–11).

In diabetic placentas, most times, one can observe the presence of a continuous syncytiotrophoblast consisting of two cell layers, typical villositary development in the first quarter of pregnancy, is another sign of abnormal development, delayed villous.

**Villositary edema**

Another anomaly villositary frequent in placenta parenchyma of diabetes is swelling. It is the accumulation of fluid in the interstitium villositary with intravillous cellular architecture disruption and replacement.

We have seen this kind of change, distribution distal villi length in all cases studied (Figures 9, 12 and 13).

Marked thickening of the basement membrane: All 19 cases studied showed focal thickening but generally small in scope, highlighted by specific staining mucopolysaccharides components. The phenomenon is significant in women with diabetes unbalanced placenta has a low intensity of diabetes well controlled and lacking in women without diabetes.

**Fibrinoid**

Anatomically speaking, two types of fibrinoid differ:
- fibrin (fibrinoid) perivillous surrounding more or less altered but still recognizable villosities;
- fibrinoid intravillos (subsyncytial fibrinoid, villositary fibrinoid necrosis) that affects the inside of villosity even from the beginning.

This type of fibrinoid or fill gaps in trophoblastic layer or encompass the entire chorionic villi or groups and new aspects captured in all cases.

These nodules grow in size, eventually replacing the villositary stroma (the appearance of “fibrinoid necrosis”). Initial syncytial intact can degenerate secondary or fibrinoid necrosis villository focal aspect was observed only in nine of the 19 placentas examined (Figure 14).

**Number of villositary capillaries**

Another morphological aspect also reported by studies in the literature of diabetic placentas also observed in the studied cases is the increasing of the number of villositary capillaries, the so-called “chorangiosis” and thickening of their walls.
**Glycogen deposits**

Glycogen PAS reactivity is stronger in diabetic placenta than in normal placentas. In the cases studied, PAS staining allowed us to identify, on the one hand, small clusters of PAS+ material located subsyncytially and, on the other hand, focal deposits located both in the thickened basement membrane and extracellular matrix especially terminal villous type (Figure 14).

![Figure 1 - Central placenta: minimum villous vascular density first and second degree (CD34 immunohistochemistry, x100).](image1)

![Figure 2 - Peripheral placenta: minimum villous vascular density of the first and second degree (CD34 immunohistochemistry, x100).](image2)

![Figure 3 - Central placenta: maximum villous vascular density first and second degree (CD34 immunohistochemistry, x100).](image3)

![Figure 4 - Placenta peripherals: maximum villous vascular density of the first and second degree (CD34 immunohistochemistry, x100).](image4)

![Figure 5 - Central placenta: minimum villous vascular density of third degree (CD34 immunohistochemistry, x200).](image5)

![Figure 6 - Placenta peripherals: minimum villous vascular density third degree (CD34 immunohistochemistry, x200).](image6)
Figure 7 – Central placenta: maximum villous vascular density third degree (CD34 immunohistochemistry, ×200).

Figure 8 – Placenta peripherals: maximum villous vascular density third degree (CD34 immunohistochemistry, ×200).

Figure 9 – Determination of villosities distal diameters: villositary reticular stroma rich cell (left), villositary edema (bottom right), and extravillous fibrinoid; syncytial knots (HE staining, ×100).

Figure 10 – Terminal villosities trophoblast continuous cytotrophoblast cell layer present (HE staining, ×200).

Figure 11 – Mitosis of a cytotrophoblast cell (Alcian Blue staining, ×400).

Figure 12 – Villous edema, dilated stromal channels, the stromal Hofbauer cells (blue arrows) in the villositary interstitial hyaluronic acid (red arrows) (HE staining, ×100 – left; Alcian Blue staining, ×100 – right).
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Discussion

Acute fetal distress

About placental villous vascular density, since most cases of placental pathology were labeled as antepartum placental insufficiency syndrome, emerged assumption that poor functioning placenta could be determined by a quantitative modification of intra placental vascular structures [5].

About villous vascular density in grade I and II, dispersion beaches vascular density values (from the lowest to the highest value determined) had approximately the same extent in the central and peripheral placenta, slightly wider at the center of the placenta but the center was shifted to the left, to lower densities.

About villous capillary density grade III, the lower limit of capillary density range of central placenta was lower than in placenta and peripheral upper limit was higher, which led to a range of dispersion of villous capillary density in grade III placenta wider central.

However, the average density of capillaries in the villi of grade III placenta was higher in peripheral and a concentration range of cases more closely, as evidenced by the smaller standard deviation.

Microscopic morphometric measurements revealed the fact that parallel increase or decrease vascular density in the central and peripheral placenta, the villi of Levels I and II and in the third degree, or, in other words, placental vascular tree grows or regresses uniformly and harmonious [5].

Macroscopic and microscopic morphological examination of the placenta postpartum could identify changes that justify the existence of the syndrome of “placental insufficiency” macroscopic profile presence impregnations being either limestone or atrophic appearance (small placenta that is in proportion to fetal weight, even with normal appearance) or dystrophic appearance (“bacon”) and microscopic profile is shaped by the presence of villousitary structures.

May turgid and dense, the highlight of villositary larger spaces, finding it more difficult to cytotrophoblast, changes syncytiotrophoblast consisting of thinning to the presence of clusters (“nodes”) of syncytial cells and fibrillar collagen structures and clusters between chorionic highlighting.

Placental tissue mass, quantified morphologically by
fully possible. The modern means of investigation allow achieving fetal distress installation. Thus, low weight placentas determining weight can be one of the determinants of births [9].

Placental pathology was the main factor determining the subset of cases with intrauterine growth restriction, where response syndrome in two thirds of cases.

An interesting finding resulting from the analysis of correlation between morphological measurements placental macroscopic and microscopic level was that the probability that the vascular tree in the center of the placenta to be more dense is even greater as the placenta is greater (measured by determining the weight).

Late consequence of placental vascular changes of tasks completed with fetal distress at birth, can be including physical and psychological [4].

Mental health problems were found more frequently in children with intrauterine growth restriction. Impaired fetal circulation, as demonstrated by Doppler studies in combination with intrauterine growth restriction may be due to worsening cognitive function in adulthood [4].

**Diabetes associated with pregnancy**

Immature intermediate villi immaturity villosities defined by the presence of abundant stroma, loose reticular obvious channel containing Hofbauer cells. They predominate over the second trimester of pregnancy, persisting only in small nests within the center of lobules [6].

The most commonly reported change in the placenta of pregnant women with diabetes is relative immaturity of villi, even despite a nearly optimal metabolic control [7–9].

Morphometric measurements, quantitative values of diameters revealed distal villi located and the upper limit of normal 80 μm.

We also noticed the constant presence of syncytial knots, look identical to that encountered in fetal distress, but they must be interpreted with caution, are usually the result of cutting the incidence of villi in the context of congestion caused by increasing relative size of villi.

Presence Hofbauer cells is not specific and can be found in other pathological situations such as pregnancy placentas with maturation villositary delayed or premature births [9].

In normal placentas, together with villositary maturation, the barrier between maternal and fetal blood flows is reduced by the thinning of syncytiotrophoblast, thus reducing the cytotrophoblast, the decrease of mean villositary diameter and fetal capillary apposition at villosity surface [6].

The significant increase of microvillosity surface density and focal thickening of microvillosity surface at syncytiotrophoblast level (the same as the placenta of fetal distress) is constantly accompanied by the presence of numerous Langhans cells (cytotrophoblasts) in which there was identified a significant mitotic activity (an aspect found only in diabetes placentas) [10, 11].

Vilozitar edema was observed in placenta from diabetes, more obvious forms of gestational diabetes and those less well-controlled diabetes [12].

Is regarded as having pathological significance, especially in premature tasks and is considered one of the causes of fetal ischemia, mechanism encountered mainly in fetal distress. Its etiology is still unclear.

Marked thickening of the basement membrane becomes visible syncytiotrophoblast obviously been described in various pathological situations, one of them being the maternal diabetes.

This thickening is the result of mucopolysaccharides storage, which can be evidenced by intense staining Alcian Blue at pH 2.5 and it might be due to alterations vilozitar trophoblastic activity, such as high or low turnover secretion of basement membrane molecules, known as constituents of the basement membrane are produced by secretion of its [7, 13].

Unusual chorionic capillary densification increased with hypercellularity stroma – “chorangiosis”. Some authors consider increasing the number of capillaries vilozitare a sign indicative of chronic hypoxic changes also cause acute fetal distress.

Diabetic microangiopathy placental microcirculation changes to inscribe on line systemic, specific diabetes. Microvascular complications (retinal damage, nephropathy, transient cerebral ischemia, or peripheral arterial disease) are specific to the disease [14–16].

Both systemic and placental diabetic microangiopathy does not have a particular aspect generated by therapeutic practice. Both during pregnancy and outside it, there may be administered metformin and insulin as hypo-glycemic medication. There could not be noticed any differentiated aspects of the microvascularity neither during pregnancy nor in general pathology [17].

About fibrinoid, disseminated deposits of fibrinoid material in the intervillosity space and/or the villositary tree is a common phenomenon in term placenta.

Intra- or extra-villositary excess fibrinoid deposits may be considered pathological phenomena that are often incompatible with normal fetal development [18].

About glycogen deposits, according to some authors, placental histological changes are mainly due to metabolic disorders that lead to the accumulation of carbohydrates and lipids in the placenta.

Accumulation of carbohydrates, particularly glycogen, somewhat paradoxical since in other maternal organs decreases glycogen content in diabetes was identified using histochemical stain specific for glycogen (PAS staining) [3, 19].

There is a study, which analyzed the histological changes observed in placentas of pregnancy associated with diabetes [3]. The group studied by Indian researchers studied 30 cases and in general, the morphologically parameters were similarly with the parameters evaluated in our study. Observations the two studies were similarly in general [3, 20].

**Conclusions**

Common issues:

- Increasing the number of capillaries met the placenta of fetal distress so acute as well as in the diabetic may be a consequence of chronic hypoxic changes;
- “Syncytial knots” that can make clusters of villi are constantly present in both types of placentas;
• Increasing surface density of microvillocities are typical for diabetic placenta occur in placentas from pregnancies fetal distress;

• The villositary edema is regarded as having pathological significance, especially in premature tasks and is considered one of the causes of fetal ischemia, mechanism encountered mainly in fetal distress is very suggestive of diabetic placenta.

Particular aspects:

• Pathogenesis of placental changes is still far from being fully understood but there is a general opinion that the extent and degree is not only depending on the severity and duration of maternal diabetes but also depends on the degree of metabolic control during pregnancy.

• It is also true that, in diabetes, systemic changes microvascularization are more important than changes in placental microvascularization. Relatively short time interval, the task may be the reason that these changes are less extensive;

• Parallel increase or decrease vascular densities in central and peripheral placenta, the villi of levels I and II and in the third degree, or, in other words, placental vascular tree grows or regresses evenly balanced even if the task is completed with pain fetal.

Contribution Note

All authors have equally contributed to this work.

References


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