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Review Article

Morphological and histological variations of human placenta in pregnancies affected with preeclampsia and gestational diabetes – A review

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ABSTRACT

The placenta is a transitory organ that is situated between the mother and the foetus. This vital organ which has nutritional, endocrine and immunologic functions so as to maintain pregnancy and promote fetal development. Several factors are related to the proper functioning of the placenta including foetal and maternal blood flow, appropriate nutrients, expression and function of receptors and transporters, and also the morphology of the placenta itself. Gestational hypertension and gestational diabetes are among the most frequent obstetric disorders during pregnancy. Pregnancies complicated with one or both of these disorders are also associated with adverse consequences for the mother and infant (both acute and long-term). Preeclampsia being one of the toxemias of pregnancy is a condition of increased blood pressure accompanied by proteinuria, edema or both. Various changes like increased syncytial knots, cytotrophoblastic cell proliferation, villous stromal fibrosis and fibrinoid necrosis was observed in placenta from preeclamptic cases. Diabetes mellitus can be defined as a chronic disorder marked by high blood glucose levels and a disruption in fat and protein metabolism. In pregnancies affected by diabetes mellitus also several changes occur like placental size, increased glycogen deposits, increased volume of intervillous space and terminal villi, fibrinoid areas, and glycogen deposits compared to others.
All these changes may result in functional changes in this organ thus limiting the wellbeing of the developing foetus. Therefore, this review as a whole gives an overview of morphological changes at macroscopic and histological levels seen in the placenta from gestational diabetes and preeclampsia.

1. Introduction

Placenta – the discoid structure which is the most important organ of intrauterine life can never be defined appreciably. It is incomparable with other organs for its diversity of functions that it performs during differentiation & maturation of all other organs, systems etc.[1] Placenta is believed to be formed from elements of membrane surrounding the developing foetus & endometrium. The two components of placenta – fetal & maternal, interacts well with each other in a healthy pregnancy. Endometrium which is the maternal component of human placenta undergoes remarkable transitions and forms the decidua in early stage of pregnancy.[2]

Placental function includes integration of signals between the mother and the foetus to match foetal demand with the maternal nutrient supply.[3] The five layered diffusion barrier between the fetal & maternal circulation helps in exchange of gases & other substances and at the same time separates the mother and foetal blood.[2] Both structure and function of the placenta keeps changing during the entire course of pregnancy.[4] Even though human placenta is haemochorial, at certain early stages of pregnancy it acts as choriovitelline placenta in terms of

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physiological functions but never develops morphologically same.[1]

Placenta turns out to be the only indicator to know about the foetal environment adequacy. It can provide insight about what had happened with this dynamic organ inside a mother's womb and also foresee the life of a particular foetus.[5] Normal placental development is essential for normal foetal growth.[6]

Placenta is considered as the source of preeclampsia.[7] Preeclampsia is one of the hypertensive (high blood pressure) disorders of pregnancy. It is a major cause of maternal and perinatal mortality (number of stillbirths and deaths of new born in the first week of life) and morbidity.[6] The disease resolves itself after delivery which points out the major role of placenta in this.[7]

The failure of maternal arteries that supply the placenta undergoes certain physiological adaptations as that of normal pregnancy which ultimately provides sufficient placental perfusion. This is a common pathological feature of preeclampsia.[8] Preeclampsia can be both early and late onset. If the preeclampsia is late onset, it can be a maternal disease rather than a placental disease and it can also cause minimal morphological changes in placenta.[6]

In normal pregnancies, trophoblastic cells invade the wall of spiral arteries which then evolves into large channels which carry large amounts of blood to the intervillous spaces. This invasion starts at the time of 16–20 weeks of gestation and thus the muscularis layer of spiral arteries gets destroyed. It is then completed by 24 weeks' time. These changes do not occur in patients with preeclampsia. The vessels here fail to dilate and also respond to vasomotor influences. During the later course of pregnancy, the spiral arteries fail to accommodate the required increase in blood flow according to the increase in metabolic demand of the feto placental unit. Thus, the placental dysfunctioning clinically manifests as preeclampsia.[9]

The two familiar serious consequences of preeclampsia include fetal growth retardation and intrauterine fetal death. The precise etiology of these two still remain unclear.[10]

Diabetes Mellitus (DM) in pregnant women can be categorized into two. Clinical diabetes also termed as pregestational diabetes (women who are previously diagnosed with type 1 or type 2 diabetes) and gestational diabetes which is defined as any degree of glucose intolerance with commencement during pregnancy.[11,12]

Gestational Diabetes Mellitus represents nearly 90% of all pregnancies complicated by diabetes. DM during pregnancy induces a variety of placental abnormalities which affect both the development and function of the placenta. And the nature and extent of these abnormal changes depend on a number of factors including the quality of glycaemic control achieved during the critical periods in placental development.[11] These pathological changes in the placentae of diabetic mothers are either due to the direct effect of diabetic environment on the foetus or on the placenta as there would be disturbance in trophoblast invasion and dysfunction of glucose, lipid and amino acid transport as well as oxidative stress and inflammation associated with diabetic environment.[13]

During pregnancy diabetes may show different clinical pictures and cause various complications in the mother and the foetus such as fetal macrosomia, congenital malformations, intrauterine growth retardation, spontaneous abortions, hypoxia and polycythaemia with neonatal jaundice.[11,13,14] In GDM, when the intra-uterine environment for foetus becomes hostile, the placenta tries to exert its reserve capacity by changing its morphological structure, as well as some pathological changes occur that are compounded principally of some disturbances in its normal rate of maturation.[15]

Studies have shown that if there is adequate metabolic control, perinatal mortality would not be higher than general population. But macrosomia or large babies continue to be a problem in higher than average proportions of such cases.[11,13]

Thus, to improve the cognizance related to the pathophysiology in terms of a normal or an adverse pregnancy outcome, a broad evaluation of the placenta including clinical & pathological examination should be considered. For an appropriate description of any foetal malady, a proper observation of its placental condition is mandatory. Any case of a diseased foetus cannot be concluded without examining the placenta because it can possibly turn out to be a cause of the disease or even death.[16]

1.1. Literature search strategy and selection of studies

The search was conducted in PubMed, Science Direct and Google Scholar databases. Searches were performed considering the keywords: placenta, preeclampsia, diabetes, pregnancy. Filters such as year of publication was not used. The papers were selected according to the following eligibility criteria: a) articles on humans, b) studies that were performed in pregnant women with preeclampsia regardless of age, c) studies carried out in women who had gestational diabetes mellitus, d) studies which were carried out on the morphology and histology of the placenta affected by each of the disease. Similarly, the articles excluded were: a) studies carried out in animals, b) studies performed in placenta affected by any other conditions other than preeclampsia and gestational diabetes mellitus. Finally, the articles that met the inclusion criteria were considered for this review.

1.2. Search results

After the search, 26 articles met the inclusion criteria. Among them 4 of them explained the normal anatomy and importance of normal placenta, 9 of them evaluated

the morphological and histological changes of placenta in preeclampsia, 13 articles evaluated the morphology and histology of placenta affected with gestational diabetes mellitus. These articles were considering the similarity of the outcomes that were analysed in each of the study.

1.3. Data extraction

The data included in the articles were type of study, sample size, age of the pregnant women, changes that occurred in the placenta affected by the underlying disease and its comparison with the normal, duration of the study, effect of disease in the health of mother and foetus. The primary endpoint was considered by several parameters including morphological and histological such as weight, diameter, thickness, number of syncytial knots, stromal fibrosis, fibrinoid necrosis for both the conditions separately.

2. Discussion

Marked placental changes were noted in cases of both preeclampsia and diabetes. Various studies have confirmed it by morphometric, histological and immunohistochemical results.

Examination of placenta is extremely important in understanding the pathophysiology of preeclampsia. Careful gross and histological evaluation, along with clinical pathologic correlation, could be useful to identify the underlying causes and recurrence risks also.

2.1. Alterations of placenta in preeclampsia

Examination of pre-eclamptic placentae revealed significant decrease in morphological parameters such as weight, diameter, thickness, volume and cotyledon number. The decrease in these values was mainly because of insufficient blood supply due to preeclampsia.[9,10,17,18] Whereas an increase in values was observed in the presence of gross infarction and calcification. Thrombotic occlusion of maternal uteroplacental blood vessels could be the cause of infarction in pregnancies complicated by preeclampsia. Presence of infarction can also be related to low birth weight and intra uterine death of foetus as well. Infarction which leads to placental insufficiency can also be a cause for both foetal and maternal morbidity and mortality. Intra uterine death and low foetal weight were noticed among cases with more placental calcification.[10,17,18] On the other hand, significant increase in number of syncytial knots, areas of fibrinoid necrosis, areas of calcification, and areas of hyalinization was seen in preeclamptic placentae. A significant increase in syncytial knot formation in placental villi indicates disturbance in the hormonal factors, which can lead to alterations in the morphometry of placenta resulting in pregnancy induced hypertension in the mother and to low birth weight in the new born.[5,17–19] Fibrinoid necrosis and hyalinization leads to placental insufficiency and ultimately to foetal growth retardation.[5,17,18,20] Cytotrophoblastic cellular proliferation, syncytial knot formation and fibrin plaque formation in greater amount is seen in preeclamptic placenta.[17,18]

Table 1: Morphological alterations in human placenta from pregnancies affected with preeclampsia

Morphological parameters	Change (In preeclampsia)	Reference article number
Weight	Decreased	10,17,18
Diameter	Decreased	9,10,17
Thickness	Decreased	9,17
No of cotyledons	Decreased	9,17
Infarction	Increased	10,17,18
Calcification	Increased	17,18

Table 2: Histological alterations in human placenta from pregnancies affected with preeclampsia

Histological parameters	Change (In preeclampsia)	Reference article number
Syncytial knots	Increased	5,17–19
Stromal fibrosis	Increased	5,6,17,18
Fibroid necrosis	Increased	5,17,18,20
Cytotrophoblast proliferation	Increased	17,18
Calcification	Increased	17,18
Villous hyalinization	Increased	17,18

Histological alterations in human placenta from pregnancies affected with preeclampsia

Histological alterations in human placenta from pregnancies affected with preeclampsia

2.2. Alterations of placenta in gestational diabetes

Studying the gross features of the placentas from pregnancies affected by diabetes mellitus, showed there was a difference in the size and the placenta were larger and also they weighed more compared to non-diabetic group. This is mainly because of the compensatory hyperplasia that occurs due to fetal macrosomia.[11,13,15]

Diabetic placentas revealed several morphological abnormalities when stained with H and E. Some diabetic placentas have an increased number of villous capillaries and dilated blood vessels. Numerous vessels were also congested in many villi, resulting in an increase in blood flow.[12,21] Fibrinoid, a cellular eosinophilic homogeneous substance, was found in both extra villous and intravillous tissues. Within the villous stroma, a fibrinoid develops in the sub trophoblastic region and eventually takes over the whole villous stroma. This form of fibrinoid either covers the trophoblastic layer's gaps or encompasses all chorionic villi or clusters of villi.[11,13,21,22]

Table 4: Histological alterations in human placenta from pregnancies affected with gestational diabetes

Histological parameters	EFFECT (In GDM)	Reference article number
Syncytial knots	Increased	[13] 19, 22, 23, 24
Stromal fibrosis	Increased	[13] 19, 22, 23
Fibroid necrosis	Increased	[11,13] 17, 19, 22, 24
Crowding of villi	Increased	22, 23
Villous edema	Increased	[12,13,21,22] 19, 22, 23, 24
Thickening of basement membrane	Increased	[11] 17, 22, 23

In diabetic women, PAS showed a thickening of the syncytiotrophoblast basement membrane. The reactivity of glycogen PAS in diabetic placentas was higher than in normal placentas.[11,12,21]

Van Gieson staining of diabetic placenta sections reveals the presence of fibrin and fibrosis in the chorionic villi, as shown by the h and e, Mallory's trichome stains.[12,21]

Despite near-optimal metabolic management, relative villous immaturity is the most often documented alteration in the placenta of pregnant women with diabetes. The occurrence of syncytial knots was also noted in the study, although they should be viewed with care because they are generally the result of the villi splitting in the setting of congestion induced by their rising relative size.[13,21,22] Also, in another study, When comparing the placentas of diabetes patients to normal placentas, histological research indicated higher syncytial knots in 80 % of the cases. The presence of multiple cell populations in the villous stroma, notably in the secondary and stem villi, was another morphological trait that allowed the investigators to detect villous immaturity. Furthermore, the formation of an indented border on the villous stem has been detected, indicating that the trophoblastic layer has been lost and replaced with extra villous fibrinoid. However, stromal fibrosis was also seen in few patients examined.[13,23] All diabetic placentas had thickening of the trophoblastic basement membrane. In all diabetic placentas, villous stromal fibrosis was considerably enhanced, and villous edema was also detected and there was more crowding of villi, and regions of glycogen and lipid accumulation were found to be substantially higher than in normal placentas.[13,23]

Table 3: Morphological alterations in human placenta from pregnancies affected with gestational diabetes

Morphological parameters	Effect (In GDM)	Reference article number
Weight	Increased	11,13–15,24,25
Diameter	Increased	13,15,24
Thickness	Increased	13,15,24
Volume	Increased	14,15,25
No of cotyledons	Increased	11,13,15,24

3. Conclusion

The placenta is an organ that allows foetal growth and development. The physiological conditions in a normal pregnancy lead to healthy new-borns. Any defect in the structure of the placenta along with metabolic alterations result in defective foetal growth and development and causes a negative new born outcome. There is still limited information addressing the impact and relevance of the changes observed in the placenta from GDM and preeclampsia. It is unclear which morphological and histological changes are due to the pathophysiology and which are compensatory adaptations to the disease.[10,26]

A better understanding of these abnormalities can change our medical assistance during the pregnancy in future.[20] Thus more precise intervention strategies should be devised that can contribute to effective management of the condition which will help to bring down the fetal and maternal mortality and morbidity.[17]

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