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Review Article

Histopathology of Placentae in Pre-Eclampsia: A Review

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Abstract

Preeclampsia (PE) is a pregnancy related complex multisystemic disorder with a triad of symptoms including increased blood pressure, oedema, and proteinuria phenotypically observed after 20 weeks of gestation. The disorder worsens amongst the early onset patients PE (< 34 weeks). The placenta shares more responsibility for the cause of PE. The placenta is an essential organ for pregnancy and assists in the development of the fetus. It shares the same stress and strain to which the fetus is exposed. Any disease which affects the mother has a great impact on the placenta and also placenta acts as a future evidence of mother and fetus health. Therefore careful observation of histopathological changes can provide clinically useful information to pave the way for pathophysiology of PE. So the histopathological parameters like distal villous hypoplasia, accelerated villous maturity, increase in syncytial knots, immature villi, chorangiosis, fibrin deposition, infarction, and calcification are evident in histopathological observations of PE placentae.

Keywords: Histopathology of placenta, Pre-eclampsia, Distal Villous Hypoplasia, Chorionic Villi, Villous maturity.

Introduction

The placenta is an essential organ that helps in the survival of the fetus.[1] It is the most authentic evidence of fetal health. The placenta records the anatomical to pathological structural events that occur during gestation.[2] It has induced immeasurable curiosity among obstetricians and pathologists, as there is a paucity of data to appreciate the "exclusively anatomical condition" of this complex organ in Preeclampsia (PE) pregnancy.[3]

Pathophysiology of Preeclampsia

PE is a multisystemic pregnancy related hypertensive syndrome that involves improper placental implantation, and vascular endothelial dysfunction. Hence PE is called a disease of theories. The pathogenesis of PE is indecisive and imprecise.[4] To understand the pathophysiology of PE, it was assumed to be a two-stage disease: Early and Late. The early-stage-I: decrease in cytotrophoblastic invasion of uterine spiral arterioles which leads to utero-placental vascular insufficiency. Late-stage-II: Due to the delicate placenta there will be an imbalance in soluble angiogenic factors that leads to systemic endothelial dysfunction and clinical outcomes of PE.[5] Early-onset PE which occurs before 34 weeks of gestation is related to fetal and maternal consequences like improper implantation of placenta categorized by placental lesions and diminished fetal development, whereas late-onset PE occurs after 34 weeks and much related to maternal factors like obesity, metabolic syndrome, dyslipidemia but not appreciated with fetal development.[6] In normal pregnancy during the implantation process the trophoblast enters the uterus and encourages spiral

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arteriole remodeling. This process assists in accommodating proper nourishment by increasing blood flow to the developing fetus. But in PE, the placenta is not properly implanted which leads to poor placental perfusion. This process leads to the failure of spiral arteriole remodeling and leads to hypoxic conditions in the placenta, oxidative stress, and further results in reduction of blood flow and affects the growth of developing fetus.[7]

Histopathological Changes in Placentae of Pre-Eclampsia

The placenta has more impact on the origin of PE. The placenta is a villous structure and helps in nourishment to fetus by a rich source of the vasculature. In PE decidual vessels are invaded by endovascular trophoblasts further leading to placental ischemia, which is the basis for placental toxemia. The elementary changes in placental anatomy significantly affect the physiological functions of placentae which is evident pathologically like placental infarcts, syncytial knots, and acute atherosclerosis which can be observed histopathologically.[8,9] In the microscopic examination, common and significant features in PE placentae are distal villous hypoplasia, villous necrosis, fibrin deposition, and decidual arterial hypertrophy. [10]

The gross placental changes like placental calcification, infarction, fibrin deposition, retroplacental haemorrhages are observed in PE placentae.

Histological changes of Placentae

There is no specific gold standard classification for placental lesions. But the placental lesions were explained in Amsterdam classification. [11] Out of that a few features are important. They are: Distal Villous Hypoplasia (DVH), Hypervascularity (HYV), Mature Villi (MV), Immature Villi (IV), Syncytial Knots (SK), and Necrosis (N) are generally observed in the PE placentae (Figure :1).

Microscopic observations of placentae with definition & characteristic features.

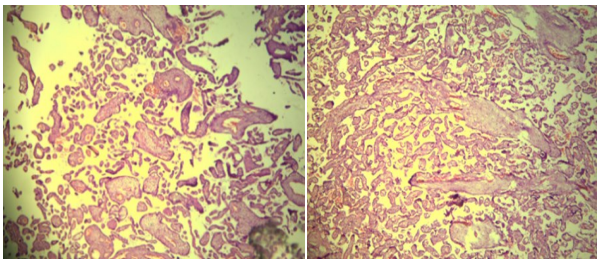

Figure 1: Distal Villous Hypoplasia (DVH) :A thin & broadly spaced out small distal villi.[11] Characterized by sparse, poorly developed distal villous tree with abnormally shaped, elongated, slender villi and widening of the intervillous space indicate that there is obstruction of decidual vessels.[12] (H&E 100X)

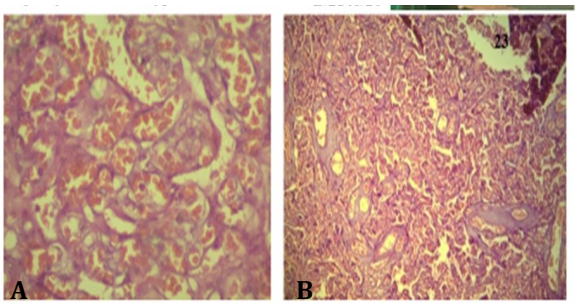

Figure 2: Hypervascularity (HYV) : HYV/ Chorangiosis is defined as villous hyper vascularity. In the terminal villi, excessive number of capillaries with intact basement membrane is observed.[13] A. (H& E 400 X) , B. (H&E 100 X)

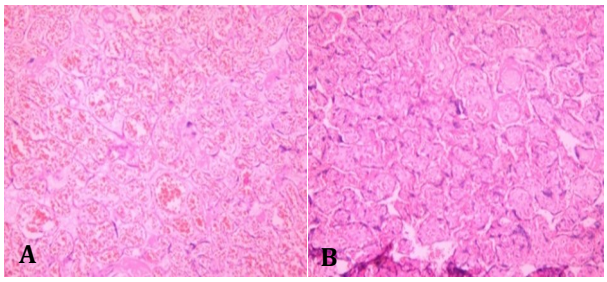

Figure 3: Mature Villi (MV) :MV are long, slender villi 80-150 µm in diameter with loose stroma, capillaries, and small vessels that can be differentiated from mid-gestation from peripheral ramifications of stem villi.[14] (H&E 100 X)

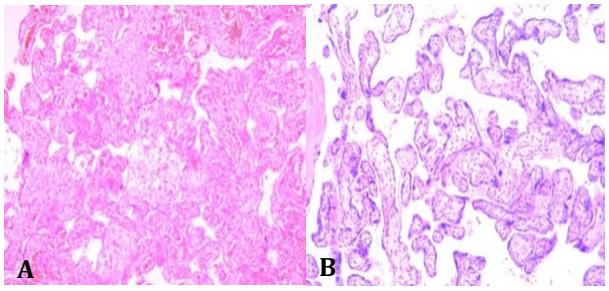

Figure 4: Immature Villi (IV) IV shows characteristic features like reticular arrangement of stroma with Hofbauer cells, arterioles, venules, and capillaries in the villous stroma are very small. The cytotrophoblastic layer is discontinuous whereas the outer syncytiotrophoblastic layer remains thick and continuous.[14] (H&E 100 X)

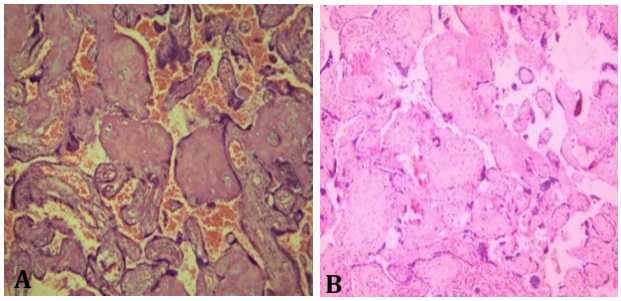

Figure 5: Syncytial Knots (SK): Poorly developed villous tree, and widening of the intervillous space, evidence for poor syncytiotrophoblast development. So syncytial knots are generally increased in PE.[15] (H&E 400 X)

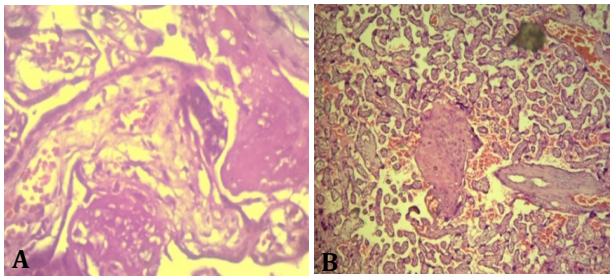

Figure 6: Necrosis (N): Normally 3% of mature villi in placentae show N.[12] More than 3% of the villi having N is seen in complicated pregnancies like PE. Among Intermediate villi - mature & immature villi and stem villi the N is more evident.[16] Small infarcts are insignificant. N more than 10 to 15% of the placental parenchyma is associated with intra uterine death.[17] A. (H&E 400 X) , B. (H&E 100 X)

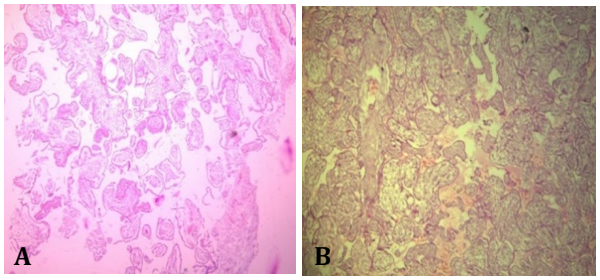

Figure 7: Crowding of villi (CV): CV is increased branching of villi that results in increased surface area for exchange. The increasing branching morphogenesis was observed in CV which is an indicator for hypoxic condition. [18]
A. (H&E 100 X) , B. (H&E 100 X)

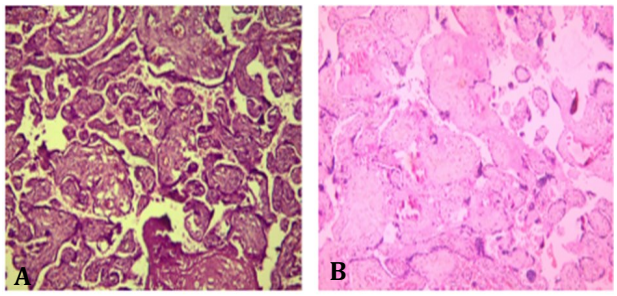

Figure 8: Avascular Villi (AV): The AV shows following characteristics: 2.5% or more of parenchyma affected, Lesion measuring 0.25 cm - 2 in multiple sections, or single foci. AV was observed in intrauterine growth retardation (IUGR), acute and chronic abnormalities, oligohydramnios, and maternal coagulation disorders.[19] (H&E 400 X)

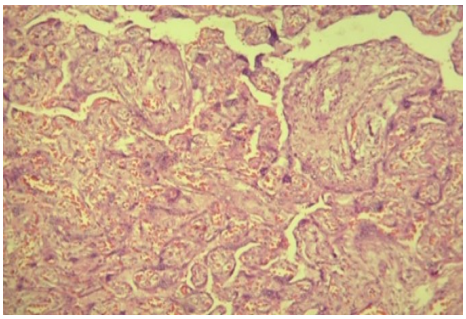

Figure 9: Accelerated Villous Maturation (AVM): AVM defined as the presence of small or short hypermature villi for gestational period and usually accompanied by an increase in syncytial knots and considered to reflect maternal vascular malperfusion. With earlier and more severe type of maternal vascular malperfusion, premature placentae show distal villous hypoplasia, characterized by lack of mature, intermediate and terminal villi. The histologic indicator for AVM is an alternating pattern of villous crowding and paucity (low power examination). AVM is defective remodelling of the spiral arterioles which leads to malperfusion of the placenta, causing damage to the syncytiotrophoblast, and hypoxia.[20] (H&E 400 X)

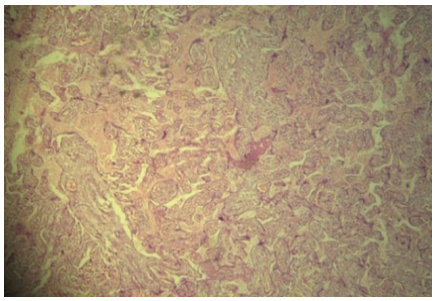

Figure 10: Delayed Villous Maturation (DVM):DVM defined by the presence of a monotonous villous population (at least 10 such villi) with centrally placed capillaries and decreased vasculo-syncytial membranes, recapitulating the histology of early pregnancy and involving 30% of one full-thickness parenchymal slide. [20] H&E 100X

Discussion

Lessons from various observers a birds eye view:

It is known fact that pathophysiology of PE is still unclear. As such no gold standard methods have been adopted to follow in PE but in 2014 Amsterdam Placental Workshop Group criteria a classification was initiated. Based on that classification it was grouped as placental vascular process, placental inflammatory-immune processes, and other placental processes. A few of them were considered in this review.[21]

On gross examination loss of placental weight indicates presence of red infarcts. Microscopic examination reveals distal villous hypoplasia, villous necrosis, and decidual arterial hypertrophy which are common and significant findings especially in PE placentae.[10] on pregnancy consequences in relation to placental histopathology in PE women a review for 10 years was conducted. In that study, they selected the PE women who had first-time PE and repeated PE in their second pregnancy. The maternal vascular malperfusion lesions, placental weight, neonatal outcomes were compared. These features are more significant in repeated (second) PE pregnancy than the first pregnancy with PE.[21] In a case-control study on Babylon pregnant women, studied on morphological and histopathological features of placentae, the morphological features include placental weight and measurements of placentae (shape, size, length, etc.) which are significant when compared to normal women. The histopathological features like the number of syncytial knots, trophoblastic basement membrane thickening, cytotrophoblastic cell proliferation, areas of fibrinoid necrosis, hyalinisation, calcification , and areas of infarction were significant in PE.[17] There are a lot of differences in data because different parameters were followed, as well as the study design and methodology adopted, inclusion & exclusion criteria followed in their studies. By comparing with blinding and unblinding studies there is inconsistency in results. In an unblinded review, the villous lesions were 11.6% and 48.2% in normal and PE pregnancies respectively with an odds ratio (OR) of 7.59. In blinded studies, the villous lesions observed were 18.5% and 42.0% in normal and PE pregnancies respectively with an OR of 4.28. In blinded studies, the incidence of both placental villous and vascular histopathological lesions was higher in PE than in normal pregnancies. Greater differences are reported in unblinded studies. Despite the higher probability (point prevalence) of finding abnormal placental pathology in pregnancies with PE, placental lesions are not specific to the diagnosis of PE.[22] In a single tertiary care hospital study including 10 years review performed by Bustan-Nahumson et al. on PE subjects by observing the maternal age groups along with maternal characteristics, fetal outcomes, and placental histopathology like syncytial knots, placental infracts, and calcification. Based on the maternal age the subjects were grouped into 3: group 1: < 27 years; group 2: 27-35 years; and group 3: >35 years. In the late-onset of PE that is >35 years of maternal age significant changes were observed in histopathology of placentae.[23] The histopathological assessment of placentae like infarcted areas, calcified areas, and marginal insertion of the umbilical cord in the PE women show a significant increase in value ($p>0.01$) The morphology of placentae also shows significant changes like smaller in size, weight, volume, area, thickness, diameter, circumference and fetoplacental ratio than normal placentae.[24] Based on mild or severe PE, ischemic placentae had shown significant changes in the degree of placental infarction which is inversely proportional to fetal birth weight. But with other parameters like placental calcifications, stromal oedema, stromal fibrosis, and syncytial knots were not statistically significant.[25] A original study performed in Japan by Tataeishu et al., on the pathological changes in the 107 placentae of early and late-onset PE. The observations include that hypoxic placentae show infarctions at different areas in placentae with an increase in DVH, and SK.[26]

Distal Villous Hypoplasia: A study conducted by Tateishi et al., Gunasena et al., Stark et al., mentioned that in early-onset PE there was evidence of increase of distal villous hypoplasia especially in placental hypoxic conditions.[26, 27,28] Stark et al., in their study observed that placental weight and DVH are inversely proportional to each other.[28] Decidual arteriopathy results in a reduction of the blood flow to the placental villus that in turn leads to distal villous hypoplasia.[10]

Necrosis: Kambale et al., Sahay et al., Nahar et al., Shams et al studied fibrinoid necrosis in PE placentae they found 47% to 80% necrosis is highly significant in PE mothers.[29,30,31,32]

Hypervascularity: Kiran et al., studied HV in anaemic PE women. The study revealed that HV is prominent with increased incidence of anaemia. 33 Chauhan et al., in his review revealed that 3% of HV is evident in PE women. 34 Srinivasan et al., observed that in terminal villi HV is more significant.[35]

Matured Villi: Jaiman et al., and Ezeigwe et al., in their observations mentioned that accelerated villous maturation was significant in PE and especially in IUD cases and in severe PE.[36,37] A twin study piloted by Jaiman et al., observed that there was defective villous maturation due to hypoxia.[38] Morgan et al., in their study observed in terminal villi there was significant hyper maturity.[39] Egbor et al., in their study noticed about villous vasculature and morphology are significantly changed in the early onset PE. But in terminal villi no significant changes were noticed in early onset. In late onset PE villous vasculature is not at all affected. But in late onset PE complication is of fetal growth retardation were noticed that in intermediate and terminal villi more significant changes in villous vasculature was observed.[40] Schweikhart et al., in their study observed 33% of villous mal-development and in PE 60% of villi were evident with hyper-maturity.[41]

Immatured Villi: Jaiman et al., Wang et al., Stoz et al., in that study observed that retarded maturation of villi is significant in PE.[36.42.43] Jaiman et al.,, also observed IV was 44% prominent in fetal death due to PE.[36]

Syncytial Knots: Ezeigwe et al., observed there is no significant difference in syncytial knots.[37] Gunasena et al, and Morgan et al., and Rogers et al., observed that there was significant increase in SK of PE placentae.[27,39] Tateishi et al., & Salam et al., in their interpretations that the early PE is associated with more aggressive histological changes and increased SK reflecting placental ischemia in early onset PE.[26,44,45]Stark et al., piloted a study and his research work revealed that there is an inversely proportion to placental weight and SK which was more evident in early-onset PE.[28] Increased syncytial knots are formed by an imbalance between the production and shedding of villous syncytiotrophoblast in PE placentae. Increased syncytial knots with increasing gestational age assist in evaluating villous maturity.[10]

Avascular Villi: Kaur et al .,in their study observed significant avascular villi in PE.[46] Chauhan et al., in their findings mentioned 6% of AV villi were observed in PE placentae.[34] Mehendale et al., in their work found the reason for AV was due to placental ischemia. [47]

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