Original Article

DOI: 10.7860/JCDR/2022/57330.16670

Histomorphometrical Study of Placental Villi in Preeclampsia: A Case-control Study

Pathology Section

SAUMYA GAUR[1], N SANGEETHA[2], SARANYA BAI[3]

ABSTRACT

Introduction: Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality. In this disorder, placental morphology and cellular arrangement are altered so that oxygen delivery from mother to foetus is greatly disturbed, which ultimately results in cellular oxidative stress. Morphological and histological changes are both indicative of the pathogenesis of maternal and foetal morbidity and mortality in women with preeclampsia.

Aim: To study the gross and histomorphometric features of placenta in patients with preeclampsia.

Materials and Methods: This case-control study was conducted from January 2017 to December 2017 at Jawaharlal Nehru Medical College Hospital in Belagavi, Karnataka, India. Total 120 placentas of preeclampsia patients (60) and normal controls (60) were studied, which were received at Pathology Department of the institute. Immediately after delivery, gross parameters were recorded. For histomorphometrical study, full-depth tissue samples of placenta were fixed in 10% neutral buffered formalin solution for 24-48 hours, and then they were processed by graded concentrations of alcohol and embedded in paraffin to make blocks. The 5 µm thick sections were cut and slides were stained with Haematoxylin and Eosin (H&E) and the sections were studied. Values were calculated by mean±SD using Students unpaired t-test and Chi-square test, p-value of <0.05 was considered as significant.

Results: The mean maternal age of the study participants was 23.93±4.40 years in preeclampsia group and 23.85±3.44 years in control group. The gestational age was 36.42±2.69 weeks in preeclampsia group and 38.20±2.11 weeks in control group, the difference was statistically significant. Other parameters such as neonatal weight, placental weight, placental thickness and placental diameter had statistically significant difference between both the groups. Morphological findings of placental terminal villi showed that the mean surface area was larger (2500.05±245 µm^2) in preeclampsia group compared to control group (1878.01±214.53 µm^2) and this difference was statistically significant.

Conclusion: The gross reduction of the preeclampsia placenta like decreased placental weight and diameter disturbs the normal placentation and pathologically these results in histological and morphometric changes in the placenta. Due to oxidative stress in preeclampsia placental morphology is altered.

Keywords: Gross, Histological, Oxidative stress, Placenta

INTRODUCTION

The placenta is an organ that plays a central role in pregnancy, but so far, it is poorly understood [1]. It has been described as a "diary of intrauterine life": it can elucidate many aspects of the processes during pregnancy [2]. Examination of placenta is important for both mother and infant as it can yield information which is important for management of disorders of both [3]. Two such disorders which can occur are preeclampsia and eclampsia- affecting the mother. The placenta, on the other hand, remains an underappreciated and mishandled surgical material [4]. Preeclampsia is a common complication of pregnancy, with a reported prevalence of 2-8 percent. Preeclampsia/eclampsia causes more than 50,000 maternal fatalities each year around the world [5]. Preeclampsia, which is lethal to both mother and foetus, has long been referred to as the "disease of hypotheses," but recent research has changed that perception. All indications and symptoms of this condition disappear when the placenta is delivered, according to previous observations. As a result, the placenta is the focus of the disease's genesis [6]. Preeclampsia and eclampsia are multisystem hypertension disorders that affect pregnant women. The neurological system is usually impacted in these women, and it is a substantial source of morbidity and death. Preeclampsia and eclampsia are not independent conditions in and of themselves, but are distinguished by their clinical signs [7].

Preeclampsia and eclampsia are the most prevalent and dangerous complications of pregnancy. They are most common in the middle to late stages of pregnancy. Pregnancy induced hypertension, proteinuria, and oedema are the three clinical symptoms used to make the diagnosis. Eclampsia is a serious degeneration of the organs that is accompanied by development of a convulsive state [8]. "Gestational blood pressure increases with proteinuria that develops after 20 weeks of pregnancy" is what preeclampsia is classified as. Preeclampsia is diagnosed by a systolic blood pressure of 140 mmHg or a diastolic blood pressure of 90 mmHg, as well as proteinuria of 0.3 g or more in a 24-hour urine sample.

Eclampsia is a disorder that occurs when a woman is pregnant and has convulsions [9,10]. Preeclampsia is characterised by generalised tonic-clonic seizures that occur during the third trimester, during birth, or during the puerperium in women who already have hypertension, proteinuria, and oedema. It is a leading cause of maternal and perinatal mortality and morbidity. Morphological and histological changes are both indicative of the pathogenesis of maternal and foetal morbidity and mortality in women with preeclampsia. Hence, this study would like to explore the gross and histomorphometric features of placenta for an early diagnosis of preeclampsia [11].

This study was done to study the gross and histomorphometrical features of placenta in preeclampsia for early identification of the condition and to understand the pathogenesis.

MATERIALS AND METHODS

This case-control study was conducted from January 2017 to December 2017 at Jawaharlal Nehru Medical College Hospital in Belgavi, Karnataka, India. Total 120 placentas of preeclampsia patients (n=60) and normal controls (n=60) recieved in the Pathology Department were studied. The study protocol was approved by the Institutional Ethical Committee (MDC/DOME/37 dated 17.10.2016).

Inclusion criteria: Specimens of placenta of preeclampsia patients were selected as cases; specimens of placenta of normal patients with normal blood pressure and no proteinuria were selected as controls.

Exclusion criteria: In both control and preeclampsia groups, patients suffering from diabetes mellitus, obesity, severe anaemia (Hb-6g%) and eclampsia or any other systemic or endocrine disorder were excluded.

Sample size calculation: The sample size was calculated using the formula:

$$n=\frac{2(Z_\alpha+Z_\beta)^2\ (S_1^2+S_2^2)}{(X_1-X_2)^2}$$

Control- X_1=470 S_1=75

Preeclampsia- X1=401 S_2=111

α=0.05 β=0.2

Z_α=1.96 Z_β=0.84

$$n=\frac{2\ (1.96+0.84)^2\ ((75)^2+(111)^2)}{(470-401)^2}$$

n=60

Therefore, 120 placentas (60 each from mothers with preeclampsia and without preeclampsia [controls/normal]) were included in the study.

Study Procedure

Total 60 placentas were collected from normotensive pregnant patients (controls), and the remaining 60 were obtained from patients whose pregnancies were complicated by Preeclampsia (PE), which was defined as a blood pressure of ≥140/90 mmHg with protein values of ≥300 mg in the 24-hour urine or a protein concentration of 1 g/L on two occasions at least 6 hours apart [1]. Immediately after the delivery, the umbilical cord was clamped; membranes were trimmed and blood clots were removed. The placental weight, thickness and diameter were recorded.

For histological study, full depth tissue samples of placenta were fixed in 10% neutral buffered formalin solution for 24-48 hours and then they were processed by graded concentrations of alcohol and embedded in paraffin to make blocks. The 5 µm thick sections were cut and slides were stained with hematoxylin and eosin and sections were studied.

Histological and morphometric parameters were assessed using pentahead (Olympus bx41) microscope. Images were obtained by jenoptik subra (camera). The software used was Progres. Microsoft word and Excel were used to generate graphs, tables etc.

In each group the following parameters were studied, gross parameters such as maternal age (yrs), gestational age (wks), neonatal weight (g), placental weight (g), placental thickness (cm), placental diameter (cm). The weight of the placenta was measured using an electronic weighing scale, placental thickness and diameter with measuring scale. Histological parameters such as-stem villi: arteriosclerotic blood vessel, fibrosis, lumen obliteration, smooth muscle hypertrophy, thrombus formation; Calcification in per villus fibrin, intervillus fibrin. Terminal villi characteristics such as vascularity, syncytial knots, fibroid necrosis, villous stromal fibrosis. Morphometrical parameters such as surface area (µm^2), villi density (per10 HPF), villi diameter (µm), blood vessel density (per 10 HPF), blood vessel diameter (µm), syncytial knot density (per 10 HPF), syncytial knot diameter (µm), vasculosyncytial membrane thickness (µm).

Per villus fibrin and intervals fibrin (in stem villi), fibrinoid necrosis (in terminal villi), villi density, blood vessel density, syncytial knot density were assessed in 10 high power fields and mean derived. To assess surface area, villi diameter, blood vessel diameter, and syncytial knots diameter and vasculosyncytial membrane thickness 50 terminal villi were counted in random fields.

STATISTICAL ANALYSIS

Values were calculated by mean±SD. For Gross parameters and morphometrical parameters, statistical association was obtained by student's unpaired t-test. For per villus fibrin, intervals fibrin, fibrinoid necrosis and vasculosyncytial membrane thickness, Chi-square test was used to obtain the p-value (p-value of <0.05 was considered to be significant). Statistical Package for the Social Sciences (SPSS) version 20 was used for statistical analysis.

RESULTS

The mean maternal age of the study participants was 23.93±4.40 years in preeclampsia group and 23.85±3.44 years in control group. The gestational weeks was 36.42±2.69 weeks in preeclampsia group and 38.20±2.11 weeks in control group, the difference was statistically significant. Other parameters such as neonatal weight, placental weight, placental thickness and placental diameter had statistically significant difference between both the groups [Table/Fig-1].

Parameters	Preeclampsia	Control	p-value
Maternal age (yrs)	23.93±4.40	23.85±3.44	0.9081
Gestational age (wks)	36.42±2.69	38.20±2.11	0.0001
Neonatal weight (kg)	2.03±0.28	2.73±0.20	0.0001
Placental weight (gms)	456.92±125.79	526.75±95.59	0.0008
Placental thickness (cm)	3.46±0.90	2.82±0.87	0.0001
Placental diameter (cm)	15.01±2.28	16.25±2.33	0.0038

[Table/Fig-1]: Clinical and gross parameters assessed in preeclampsia and control groups.

The stem villi characteristics such as arteriosclerotic blood vessels were seen in preeclampsia group (40). Fibrosis, lumen obliteration, smooth muscle hypertrophy, thrombus and calcification were all high in numbers in preeclampsia group as compared to control group [Table/Fig-2].

Parameters	Preeclampsia	Control	p-value
Arteriosclerotic blood vessel	40	1	0.0001
Fibrosis	60	36	0.0001
Lumen obliteration	58	31	0.0001
Smooth muscle hypertrophy	59	38	0.0001
Thrombus	36	9	0.0001
Calcification	2	1	0.5589

[Table/Fig-2]: Histological changes of placenta in Stem Villi in Preeclampsia and Control groups.
values presented as n

The histological parameters such as perivillous fibrin, intervillous fibrin and fibrinoid necrosis showed significant difference between preeclampsia and control group [Table/Fig-3]. Morphological findings of placental terminal villi showed that the mean surface area was larger (2500.05±245 µm^2) in preeclampsia group compared to control group (1878.01±214.53 µm^2) and this difference was statistically significant [Table/Fig-4]. Morphometric findings of the placental terminal villi assessed through villi density, blood vessel density and syncytial knot density showed statistically significant difference between the two groups [Table/Fig-5]. The microscopic findings of the placental villi are shown in the figures below [Table/Fig-6-10].

Parameters	No. per 10 HPF	Preeclampsia	Control	p-value
1. Perivillous Fibrin (Stem Villi)	0-2	0	47	0.0001
	3-5	10	13	
	6-8	50	0	
2. Intervillous Fibrin (Stem Villi)	0-2	0	17	0.0001
	3-5	2	43	
	6-8	26	0	
	9-11	32	0	

3. Fibrinoid Necrosis (Terminal Villi)	0-2	0	1	0.0001
	3-5	0	8	
	6-8	13	51	
	9-11	36	0	
	>11	11	0	

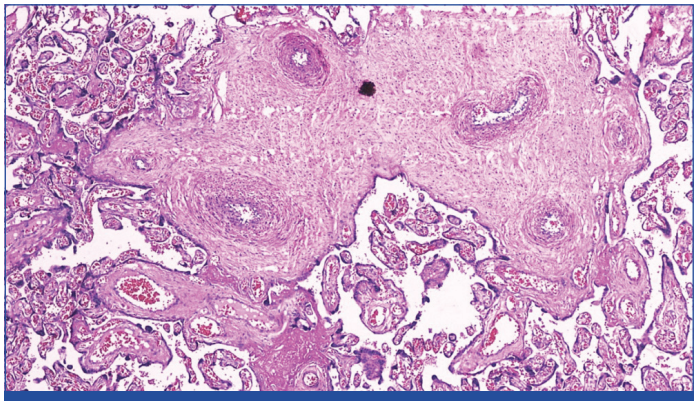
[Table/Fig-3]: Comparison of Histological parameters between Preeclampsia and Control groups (per 10 HPF).

Parameters	Preeclampsia	Control	p-value
Surface area (μm^2)	2500.05±245	1878.01±214.53	0.0001
Villi diameter (μm)	43.25±3.30	41.25±2.36	0.0002
Blood vessel diameter (μm)	10.53±1.44	10.32±1.14	0.3950
Syncytial Knot diameter (μm)	19.83±1.41	20.06±1.15	0.3298
Vasculosyncytial membrane thickness (μm)	2.28±0.28	2.34±0.28	0.3080

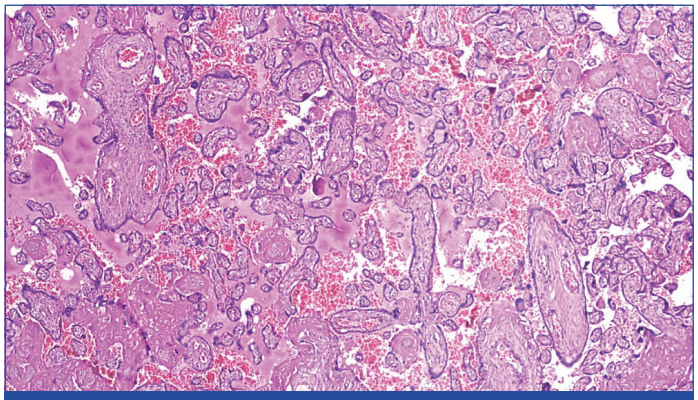
[Table/Fig-4]: Morphometric findings of placental terminal villi in Preeclampsia and Control groups.

Parameters	Preeclampsia	Control	p-value
Villi density	21.48±1.83	18.85±1.43	0.0001
Blood vessel density	20.50±1.00	24.05±1.34	0.0001
Syncytial knot density	16.78±2.42	8.95±0.79	0.0001

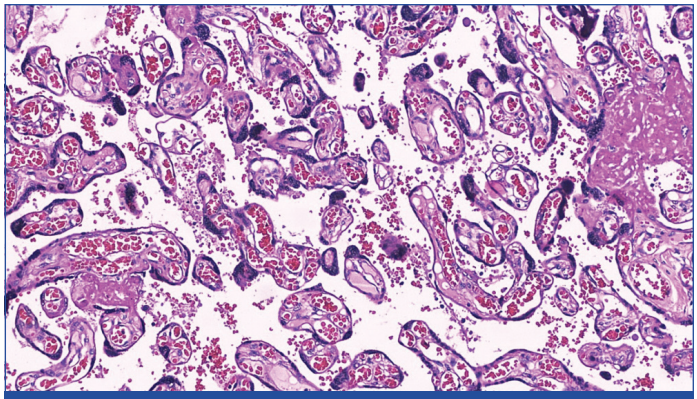
[Table/Fig-5]: Density of placental terminal villi (per ten HPF) in Preeclampsia and Control groups.



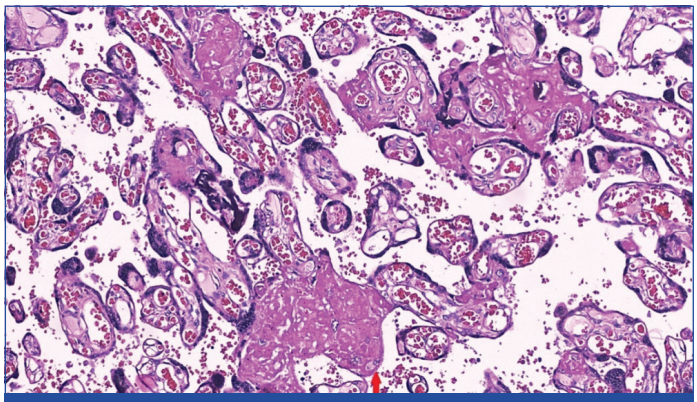
[Table/Fig-6]: Photomicrograph showing smooth muscle hypertrophy of vessels and fibrosis of stem villi in preeclampsia (H&E; x100).



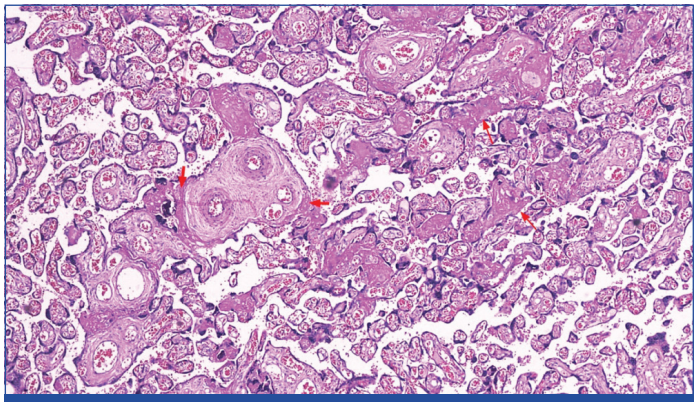
[Table/Fig-7]: Photomicrograph showing no smooth muscle hypertrophy of vessels and no fibrosis of stem villi in control (H&E; x100).



[Table/Fig-8]: Photomicrograph showing increased number of syncytial knots in preeclampsia (H&E; x100).



[Table/Fig-9]: Photomicrograph showing intervillous fibrin frequently seen in preeclampsia (arrow) (H&E; x100).



[Table/Fig-10]: Photomicrograph showing intervillous and per villous fibrin frequently seen in preeclampsia (arrow) (H&E; x100).

DISCUSSION

Preeclampsia affects 2-8% of all pregnancies and is a leading cause of maternal and perinatal morbidity and mortality worldwide [1]. The only known treatment of preeclampsia is delivery of the placenta, which suggests that placenta is the principal contributor to the pathogenesis of preeclampsia.

Preeclampsia results from widespread endothelial dysfunction due to higher levels of antiangiogenic factors and lower levels of proangiogenic factors released by the placenta. During early placental development, extra villous cytotrophoblasts of foetal origin invade the uterine spiral arteries of the decidua and myometrium. These invasive cytotrophoblasts replace the endothelial layer of the maternal spiral arteries, transforming them from small, high-resistance vessels into large-caliber capacitance vessels capable of providing adequate placental perfusion to nourish the foetus. In preeclampsia, this transformation is incomplete [12].

Therefore, widespread apoptosis of cytotrophoblast cells is the primary cause of preeclampsia [13,14]. Invasion of uterine spiral arterioles by trophoblasts is limited to the superficial portions of the decidua. About 30-50% of these arterioles in the placental bed escape trophoblastic remodeling [15,16]. The mean luminal diameter of uterine spiral arterioles in women with preeclampsia is less than one-third of the diameter of similar vessels from uncomplicated pregnancies [17]. And so, utero placental perfusion decreases, and as gestation progresses the placenta becomes ischaemic [18,19]. This results in foetal hypoxia as well as morphological and histological changes in the placenta, leading to preeclampsia. Hypoxia leads to a damaged maternal endothelium and restriction of placental growth.

In the present study, mean maternal age was 23.93±4.40 years which were higher compared to control group in which it was 23.85±3.44 years. This was in concordance with the study conducted by Sankar KD et al., [15] and Saleh RA and Dkhil MA [20]. However maternal age did not show statistically significant correlation in the present study and also in the study done by Saleh RA and Dkhil MA [20], but showed statistically significant correlation in the study done by Sankar KD et al., [15].

The mean gestational age in the present study was 36.42±2.69 weeks in preeclampsia which was lower than control group (38.20±2.11 wks) and this was in agreement with other similar studies [20,21]. Gestational age ($p<0.0001$) showed statistically significant association in the present study as well as in other studies. Possible explanation to this can be because reduced uteroplacental circulation causing foetal hypoxia.

Placental weight in women with PE is directly proportional to neonatal birth weight. In the present study neonatal birth weight and placental weight were lower in preeclampsia compared to control groups and this was in concordance with other studies conducted by Sankar KD et al., [15] and Saleh RA and Dkhil MA [20]. In the present study, placental weight and neonatal weight showed statistically significant association among both groups. However, though the placenta adapts well to the hypoxic condition in preeclampsia, the compensatory changes that occur are insufficient. These compensatory changes cause inadequate placental mass and maldevelopment of placenta leading to placental dysfunction, which results in oxidative stress and chronic foetal hypoxemia [20].

In the present study, placental thickness was more in preeclampsia placentas compared to control placentas which was discordant with other studies conducted by Sankar KD et al., [15]. However, the present study showed statistically significant association (p-value-0.0001) between the two groups, whereas in the study conducted by Sankar KD et al., [15] no significant difference between the placental thickness was noted between the two groups. A few studies concluded that preeclampsia placentas were thicker in comparison with control placentas [18,19]. Raio L et al., [21] found that abnormally thick placentas have been correlated with adverse pregnancy outcome. Therefore, placental thickness contributes to the management of a foetus at risk.

In the present study, placental diameter was less in preeclampsia placentas as compared to control placentas and this finding was in agreement with other studies [21,22]. Placental diameter showed statistically significant association between the two groups in the present study, contrary to that observed in the study by Shankar KD et al., [15]. Decreased uteroplacental perfusion leading to foetal hypoxia could be the possible explanation for reduced placental diameter [18,19].

In the present study, stem villi of preeclampsia placentas showed more frequent arteriosclerotic blood vessels and fibrosis as compared to control placentas. These findings were in concordance with similar studies conducted by Sankar KD et al., [15] Saleh RA and Dkhil MA [20] and El Gelany S et al., [22]. In the present study as well as in other studies, arteriosclerotic blood vessels and fibrosis showed statistically significant association in preeclampsia and control groups.

Lumen obliteration was more frequent in blood vessels of stem villi in preeclampsia placentas when compared with control group placentas. This finding was in agreement with other studies conducted [18,19]. Lumen obliteration showed statistically significant association in the present study between both groups.

Smooth muscle hypertrophy in blood vessels of stem villi was a more frequent finding in preeclampsia placentas in comparison to control placentas. This was in concordance with other studies conducted by Sankar KD et al., [15] and Akhlaq M et al., [1]. A statistically significant association was observed in both preeclampsia and control groups in the present study as well as in the above-mentioned studies.

Thrombus formation and calcification were more frequent in blood vessels of stem villi in preeclampsia placentas as compared to control group placentas with statistically significant association for thrombus formation. These findings were in concordance with another study [1].

Vascularity, syncytial knots and villous stromal fibrosis were seen more frequently in preeclampsia placentas as compared to control group. This was in concordance with other studies conducted; vascularity was more frequent in preeclampsia cases compared to controls in a study conducted by Saleh RA and Dkhil MA [20] syncytial knots were more frequent in preeclampsia group as compared to control in a study done by Shankar KD et al., [15] Saleh RA and Dkhil MA [20] and Akhlaq M et al., [1]. Reduced foetal blood flow through the villi results in stromal fibrosis in toxemic cases. The mode of formation and the function of syncytial knots are still not clear, but they are considered to be a degenerative phenomenon, an ageing change, [13] a syncytial hyperplasia and also a response to trophoblastic ischaemia or hypoxia. Therefore, they are seen frequently in preeclampsia because of more hypoxia.

Perivillous fibrin and Intervillous fibrin deposition were more in number in preeclamptic placentas in comparison to control group placentas. These findings were in agreement with other studies [1]. Also, intervillous fibrin showed concordant results in the present study and in a study conducted by Sankar KD et al., [15]. Per villous and intervillous fibrin deposition showed statistically significant relation between the two groups in the present study. Fibrinoid necrosis lies beneath the syncytiotrophoblast and external to basement membrane. Increasing amount of this cellular eosinophilic material eventually forms a large fibrinoid nodule bordered by a few attenuated nuclei of syncytiotrophoblast, which virtually replaces the villous stroma. Fibrinoid Necrosis of terminal villi was seen more in preeclamptic placentas compared to control placentas with statistically significant correlation. This was in concordance with other studies [14,15]. Increased deposition of fibrinoid was initially thought to be due to elevated blood pressure but it is now believed that it is due to inappropriate immune response. About 3% of the normal placenta show fibrinoid necrosis. Increased deposition is seen in preeclampsia [15].

In the present study, villous surface area was higher in preeclamptic placentas compared to control group with statistically significant association. This finding was concordant with the study conducted by Mukherjee R [23]. This can be explained by qualitative assessment of villous vascularity which concludes that preeclampsia is associated with increased branching of villi that could result in increased surface area for exchange [23]. This was predicted as an adaptive response to reduced oxygen delivery supporting the hypothesis that hypoxia resulting from reduced oxygen delivery increases branching morphogenesis [15]. However, this was discordant with the study conducted by Sankar KD et al., [15]. Terminal villi diameter was increased in the present study in preeclamptic placentas compared to control placentas. This was in agreement with the study conducted by Mukherjee R [23]. This finding showed statistically significant correlation in the present study as well as in the other study. This can be explained as a compensatory response to oxidative stress.

In the present study, blood vessel diameter was more in placentas of preeclamptic cases in comparison to that of control cases, which was contrary to the study done by Sankar KD et al., [15] where it was almost equal between the two groups. Syncytial knot diameter and vasculosyncytial membrane thickness were reduced in the present study in preeclampsia placentas compared to control group placentas. On the contrary, these were increased in other study also [20]. The reason for this could be that they compared and quantified the above mentioned parameters in large numbers of terminal villi, contrary to the present study.

In the present study, villi density was more in preeclampsia than control group placentas with statistically significant relation and this

was consistent with other studies conducted [20]. Increased villi density could be because of repeated sprouting of the intermediate villi into terminal villi, so as to compensate for the placental maldevelopment and dysfunction.

Blood vessel density was decreased in the present study in preeclampsia placentas in comparison to control group placentas. This finding was in agreement with other study [21]. Villi density showed statistically significant association in the present study as well as in the other study. This could be explained by fibrinisation along with the stenosis and apheresis of the stem villi. The reduced blood vessel lumen found in the stem villi and maturing intermediate villi fail to replicate and build a network into terminal villi. This causes complete absence of capillaries in the terminal villi in most areas of placenta, leading to the formation of avascular villous. Therefore, the resultant decreased perfusion causes oxidative stress [18].

In the present study, there was increased syncytial knot density in preeclamptic placentas when compared to control placentas with statistically significant relation. This was in concordance with studies conducted by Sankar KD et al., [15] and El Gelany S et al., [22]. Numerous syncytial knots are the result of reduced perfusion.

Limitation(s)

This study is limited by its cross-sectional nature and relatively small sample size. Future studies with large sample size are recommended in order to establish a clear association and assess the various parameters involved.

CONCLUSION(S)

Due to oxidative stress in preeclampsia, placental morphology is altered. The gross reduction of the preeclampsia placenta, like decreased placental weight and diameter disturbs the normal placentation and pathologically this result in histologic and morphometric changes in the placenta. Morphology of stem villi like more frequent arteriosclerotic blood vessels, fibrosis, lumen obliteration, smooth muscle hypertrophy, thrombus, calcification, per villus and intervals fibrin and fibrinoid necrosis, syncytial knots of terminal villi are indicative of pathogenesis of preeclampsia, and thereby are a cause of increased foetal and maternal morbidity and mortality in women with preeclampsia.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Chengalpattu, Tamil Nadu, India.
2. Associate Professor, Department of Pathology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Chengalpattu, Tamil Nadu, India.
3. Assistant Professor, Department of Pathology, ACS Medical College and Hospital, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. N Sangeetha,
Associate Professor, Department of Pathology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Madhuranthagam,
Chengalpattu, Tamil Nadu, India.
E-mail: sangeethanagalingam86@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 01, 2022
- Manual Googling: May 11, 2022
- iThenticate Software: Jun 24, 2022 (22%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Apr 27, 2022**
Date of Peer Review: **May 13, 2022**
Date of Acceptance: **Jun 30, 2022**
Date of Publishing: **Jul 01, 2022**