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Research Article

A Histopathological Study of Placental Changes in Pregnancies Complicated by Preeclampsia

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ABSTRACT
Background: Placenta is a vital organ and the most accurate record of the infants prenatal experience. Preeclampsia is a serious complication encountered during pregnancy. Preeclampsia affects approximately 5–10% of all pregnancies regarding for almost 15% of pregnancy associated deaths, placing both mothers and babies at increased risk of adverse health outcomes. The conventional treatment to manage the preeclampsia is with anti-hypertensive drugs, bed rest and early delivery, which may lead to further complications. In this regard, safer alternative interventions like music therapy and yoga are emerging as promising strategies for the healthcare community. In the present study, the histopathological changes in the placentae of preeclamptic pregnancies were studied after giving interventions of music listening and *yoga* therapy for duration of 14 days in the third trimester of pregnancy.
Materials and Methods: A quasi-experimental study was carried out among hospitalized preeclamptic pregnant women (n=75), and normotensive controls (n=25) from the antenatal ward of Yenepoya Medical College Hospital, Mangalore, India. Preeclamptic patients were assigned into three experimental groups, group 1 music listening (n=25), group 2 *yoga* therapy (n=25) and group 3 preeclamptic control groups (n=25) using non-randomisation. Patient's blood pressure (BP), both systolic (SBP) and diastolic blood pressure (DBP), were measured before and after giving the intervention in the study groups. Placentae were collected after delivery for evaluating the histopathological changes in the study groups.
Results: There was a reduction in basement membrane thickening in 37% in the placental samples of preeclamptic music listening group and a reduction in 25% of placentae of preeclamptic *yoga* therapy group as compared with preeclamptic controls. There was a reduction of stromal fibrosis in 50% of placentae of preeclamptic *yoga* therapy group as compared with preeclamptic controls.
Conclusion: The villous and stromal pathology of placentae between preeclamptic study groups and normotensive control pregnant women were statistically significant. In contrast, no statistically significant differences were found in villous and stromal pathology among the preeclamptic study groups.

Keywords: Blood Pressure, Conventional Therapy, Instrumental Soothing Music, Yoga Therapy, Preeclampsia.

BACKGROUND

Placentation in normal pregnancies

Placentation and trophoblast invasion of the maternal tissue includes two processes: first is vascularisation, which commences a foeto-placental vascular network, and second is intrusion of the maternal spiral arteries by the cytotrophoblasts or endovascular trophoblasts [1]. At the time of implantation, trophoblastic cells differentiate into cytotrophoblasts and syncytiotrophoblasts. The cytotrophoblasts form the extravillous trophoblasts, which invade the decidua, the inner third of the myometrium and the spiral arteries. The extravillous trophoblasts influence remodelling of the spiral arteries by causing loss of the elastic lamina, most of the smooth muscle cells, and replacing the endothelial cells, thus transforming a high-resistance, low-flow vascular system into a low-resistance, high-flow type, necessary for normal foetal growth [2]. Therefore, the cytotrophoblasts, epithelial in nature, restore the endothelial cells and in the process, the epithelial-like receptors are replaced with maternal adhesion molecules such as vascular endothelial cadherin vascular adhesion molecule-1, platelet-endothelial cell adhesion molecule-1 (PECAM-1) and alpha-v beta-3

integrin (αVβ3 integrin) [3]. This possibly accounts for the prohibition of foetal rejection. Therefore, the trophoblasts take on the phenotype of endothelial cells and are in direct contact with maternal blood, but the maternal and fetal blood do not mix.

Placental vascular remodeling in preeclampsia

The pathophysiology of the disease is characterised as placental hypoperfusion and ischaemia, beginning from the implantation and early pregnancy. The most predictable morphological changes observed in the uteroplacental vasculature of preeclamptic women is the impaired vascular remodelling of the spiral arteries, produced by abnormal trophoblast interruption which takes place toward theend of the first trimester [4]. In preeclampsia, the cytotrophoblasts fail to mimic a vascular adhesion phenotype and their invasion is shallow, restricted to the superficial layer of the decidua. They fail to transform the maternal spiral arteries to high caliber capacitance vessels, and they remain small caliber resistance vessels. The failure in remodelling the placental bed in early pregnancy and the resulting placental ischaemia is proposed to lead to generation and release of some vasoactive substances into the maternal circulations which additionally act on the maternal endothelium. This is suggested to result in an endothelial cell disorder throughout the vasculature that leads to the multi-organ failure, which can be identified in preeclampsia [5,6].

METHODOLOGY

Aim

To investigate the histopathological changes in the placentae of preeclamptic study groups and compare with the placentae of preeclamptic control group and normotensive control group.

Inclusion Criteria

Selection of Preeclamptic Patients

Women aged 18-40 y, weighing 45-85 kg, diagnosed with preeclampsia if they had systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg, measured on two or more occasions, at least 4 h apart, after the 20th week of gestation, with proteinuria. Proteinuria is defined as an increase in the urine dipstick value of 1+ or (≥300 mg/dL) on two separate occasions, at least 6 h apart [7,8].

Selection of normotensive control group

Control subjects were normotensive women, aged 18-40 y, weighing 45-85 kg, who are healthy, and have had no miscarriages or preeclamptic pregnancies before the index pregnancy (age and weight matched) [9].

Exclusion criteria

Patients with hearing loss or difficulty in using headphones, physically challenged, illiterate, chronic hypertension, diabetes mellitus, jaundice, anaemia, multiple pregnancy, renal disorder and cardiac disorders associated with pregnancy were excluded from this study [10].

Sample size

Preeclamptic cases (n=75) and normotensive controls (n=25). Sample size was computed using the software Gx power, using a prevalence of preeclamptic patient as 5%.[39] Minimum samples required is 75 with effect size 0.1; Level of significance is 5% and power is 80%.

Procedure of intervention: Group 1 - music listening (n=25)

The group 1 received a single session of soothing instrumental music for 60 min each day in the evening (4-5 pm) for 14 days along with conventional therapy. The participants were given the freedom to choose the music according to their preference, from the set of soothing instrumental music tracks provided. The music was given to them with the help of headphones connected to an ipod. The patients were asked to lie down quietly, and not to involve in any other activities. The given music was without lyrics and consists of track of songs, each songs of duration of 15- 30 min. The songs were played at a comfortable listening volume of 50–60 dB in a quiet environment with soft lighting throughout the intervention.

Procedure of intervention: Group 2 - yoga therapy (n=25)

The group 2 (n=25) received a single session of *yoga* techniques included *tadasana, katiparivartanasana, ujjayi pranayama, basic vipassana meditation and shavasana*for 60 min each day in the evening (4-5pm) for 14 days along with conventional therapy. The one hour *yoga* therapy included three cycles of above mentioned yoga poses. The intervention was carried out in a room with quiet environment and moderate lighting.

Preeclamptic Control Group, No Intervention But With Standard Medical Treatment (N=25)

Collection of Placentae

A total of 32 placentae, of gestational age between 34-40 weeks, were collected from the Department of Obstetrics and Gynaecology, Yenepoya Medical College, Mangalore. The placentae were collected immediately after delivery from the study groups. The placenta along with the cord were tagged with number and preserved in neutral buffered formalin (10%). All the specimens were tagged with number discs for the purpose of identification.

Placentae from the study groups

Placentae were collected from the study groups as follows:

- Group 1: Preeclamptic music listening group (n=8)
- Group 2: Preeclamptic yoga therapy group (n=8)
- Group 3: Preeclamptic control group (n=8)
- Group 4: Normotensive control group (n=8)

Histopathological study of placentae in study groups

Histopathology- Steps [11]

Collecting samples

The placentae were collected immediately after delivery from the study groups. The collected placenta was washed under running tap water.

Fixation

The placenta along with the cord were tagged with number and preserved in neutral buffered formalin (10%).

Grossing

After fixation, tissue samples need to be properly trimmed to reach the adequate size and orientation of the tissue. The placenta was grossed by swiss-roll technique. Transverse cuts were made through the maternal surface at a distance of 1-2 cm in bread loaf manner. From each placenta four samples of size 1 cm ×1 cm × 0.5 cm were taken for microscopic examination; one from the central part and one from the peripheral part of both maternal and foetal surfaces. Placed the tissues into cassettes and covered with a lid on the cassette. Each cassette was labelled with a permanent ink and stored in a fixative container.

Tissue Processing

The goal of pre-embedding is to infiltrate tissue samples with paraffin and replace water content of the tissue by this wax material. Paraffin was used as a supporting material before sectioning. Histology grade paraffin wax has a melting point around 56 or 57°C, a temperature that does not alter the structures and key morphological characteristics of tissues. The tissues were processed in an automated tissue processor.

Embedding

Once tissue samples were infiltrated by paraffin, they were removed from the cassettes, and carefully positioned inside a metal base mold. This step is critical as correct orientation of the tissue is essential for accurate microscopic evaluation. The mold was filled with melted paraffin and then immediately placed on a cooling surface.

Sectioning

The objective of this step is to cut 4–5 µm-thick sections of the paraffin blocks. The paraffin block was mounted on the microtome holder. Sections were cut as a ribbon and were floated on a water bath maintained at 45°C to stretch the paraffin section. A standard microscope glass slide was placed under the selected tissue section and removed from the water bath. Tissue sections were then allowed to dry, in a thermostatic laboratory oven at 37°C. The slides were stored in dry boxes at room temperature for the staining procedure and for immunohistochemistry slides were stored at 4°C to minimise antigen loss.

Staining

Staining Procedure

Deparaffinization was done by immersing the slides with tissue in 2 changes of xylene for 10 min each, then rehydrated with descending grades of alcohol of 95% and 70% for 2 min each. The tissues were then washed in distilled water. The tissues were dipped in Harris haematoxylin solution for 8 minutes and then washed in running tap water for 5 min. The tissues were dipped in 1% acid alcohol for 30 sec followed by washing in running tap water for 1 minute. The tissue was blued in saturated lithium carbonate solution for 30 sec followed by a wash in running tap water for 5 min. After that the sections were dipped in eosin-phloxine solution for 1 minute. Then dehydrated the sections through 95% alcohol, 2 changes of absolute alcohol for 5 minutes each. The sections were cleared in 2 changes of xylene for 5 min each and mounted with disterene dibutyl phthalate xylene (DPX).

Evaluation of Histopathological Changes In the Placental Tissue of Study Groups

The microscopic study of the placenta was carried out utilising a set of standard criteria for villous and stromal pathology. For studying these criteria eight random low power

microscopic fields were chosen and villi were counted in each field and final average was taken to observe the presence of the following parameters [12].

Villous lesions

- Cytotrophoblastic proliferation >20%
- Syncytial knots >30%
- Basement membrane thickening >3%
- Vasculo-syncytial membrane ≤5%
- Fibrinoid necrosis >5%

Stromal pathology

- Areas of stromal fibrosis >10%
- Intervillous fibrinoid deposition >5%
- Presence of narrowing of intervillous space
- Presence of calcified areas

The microscopic findings observed in the placenta from preeclampsia cases were compared with that of normal placenta with special reference to cytotrophoblastic cell proliferation, syncytial knots, basement membrane thickening, vasculo-syncytial membrane, fibrinoid necrosis, villous stromal fibrosis, intervillous fibrinoid deposition, narrowing of the intervillous space and calcified areas. The histopathological findings observed in the placentae of groups 1 and 2 were compared with group 3 and group 4.

Statistical analysis of the data

- The SPSS 23.0 for windows software package was used to analyse data.
- The chi-square Fisher's exact test was used to compare cross-tabulated data.
- Statistical significance was defined at $p<0.05$ and all p-values were two - sided.

RESULTS

Histopathological study of placentae in the study groups

The histopathological features in the placentae such as presence of cytotrophoblastic cell proliferation, syncytial knots, basement membrane thickening, fibrinoid necrosis, villous stromal fibrosis, intervillous fibrinoid deposition, narrowing of the intervillous space, calcified areas and absence of vasculo-syncytial membrane were seen in the placentae of preeclamptic study groups (Fig.1 a, b and c) and compared to the placentae of normotensive control group (Fig.1 d).

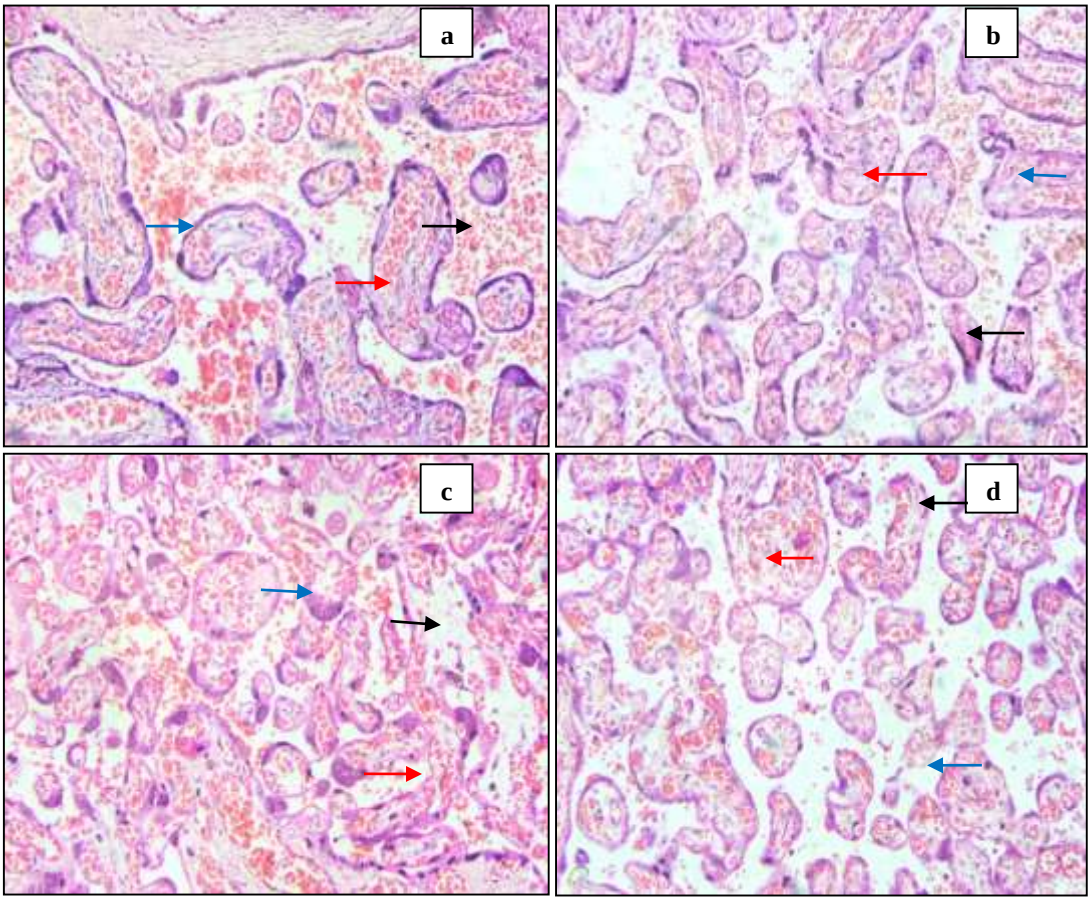

Fig. 1 Histopathological Features in the Placentae of the Study Groups

Placental villi of study groups, (a) Preeclamptic music intervention group; (b) Preeclamptic yoga therapy group; (c) Preclamptic controls; (d) Normotensive controls, showing syncytial knots (red arrow); Cytotrophoblasts (black arrow); Vasculo-syncytial membrane (blue arrow), Olympus magnus microscope, 20x, Scale bar=100µm.

Wide spectrums of villous lesions were observed in preeclamptic cases as compared with normal placentae (Table 1). The villous lesions were attributed to the decreased maternal uteroplacental blood flow in preeclampsia due to maternal vasospasm and placental insufficiency.

Table 1: Comparison of histopathological characteristics in the placentae of preeclamptic study groups with normotensive control group

Histological Features (per LPF)	Percentage Present/ Absent	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)	Group 4 (n=8)	p-value
Cytotrophoblastic Cell proliferation						
	≤ 20%	1 (12.5)	3 (37.5)	3 (37.5)	8 (100)	0.001*
	> 20%	7 (37.5)	5 (62.5)	5 (62.5)	0	
Syncytial Knots						
	≤ 30%	0	0	0	5 (62.5)	0.002*
	> 30%	8 (100)	8 (100)	8 (100)	3 (37.5)	
Basement membrane thickening						
	≤ 3%	5 (62.5)	6 (75.0)	3 (37.5)	8 (100)	0.032*
	> 3%	3 (37.5)	2 (12.5)	5 (62.5)	0	
Vasculo-syncytial membrane						
	≤ 5%	5 (62.5)	6 (75.0)	7 (87.5)	0	0.0004*
	> 5%	3 (37.5)	2 (25.0)	1 (12.5)	8 (100)	
Fibrinoid necrosis in villi						
	<3%	1 (12.5)	0	1 (12.5)	5 (62.5)	0.126
	3-10%	3 (37.5)	5 (62.5)	3 (37.5)	2 (25.0)	
	>10%	4 (50.0)	3 (37.5)	4 (50.0)	1 (12.5)	
Stromal fibrosis						
	1-10%	3 (37.5)	6 (75.0)	2 (25.0)	7 (87.5)	0.031*
	>10%	5 (62.5)	2 (25.0)	6 (75.0)	1 (12.5)	
Intervillous Fibrinoid Deposition						
	< 5%	5 (62.5)	5 (62.5)	3 (57.5)	8 (100)	0.047*
	5-10%	3 (37.5)	3 (37.5)	5 (62.5)	-	
Narrowing of the intervillous space						
	Present	3 (37.5)	3 (37.5)	4 (50.0)	-	0.13
	Absent	5 (62.5)	5 (62.5)	4 (50.0)	8 (100)	
Calcified areas						
	Present	8 (100)	8 (100)	8 (100)	6 (75.0)	0.053

Absent	0	0	0	2 (25.0)

*All values are expressed as frequency with percentage in parenthesis. Group 1: Preeclamptic music intervention, Group 2: Preeclamptic yoga thrapy, Group 3: Preeclamptic controls, Group 4: Normotensive controls, LPF: Low power field, Statistical test used: Fisher's exact probability test. Level of significance: *Significant (p<0.05), Non significant (p>0.05*

Histopathological study of placentae in preeclamptic music listening and *yoga* therapy groups with preeclamptic controls

Comparison of the histopathological features in the placentae of preeclamptic intervention groups with preeclamptic control group are given in Table 2. Although there was a reduction in villous lesions and stromal pathology in preeclamptic music listening and preeclamptic *yoga* therapy group with preeclamptic controls but was not statistically significant. There was reduction in the severity of stromal fibrosis and intervillous fibrinoid deposition in preeclamptic *yoga* therapy group. There was a reduction in basement membrane thickening in 37% of the placental samples of preeclamptic music listening group and of 25% of the preeclamptic *yoga* therapy group as compared with preeclamptic controls. There was an increase of vasculo-syncytial membrane in 25% of the placentae of preeclamptic music listening group as compared with preeclamptic controls.

Table 2: Comparison of Histopathological Features in the Placentae of Preeclamptic Intervention Groups with Preeclamptic Control Group

Histological	**Percentage**	**Group 1**	**Group 2**	**Group 3**	**p-value**
Features	Present /	(n=8)	(n=8)	(n=8)	
(per LPF)	Absent				
Cytotrophoblastic					
cell proliferation					
	≤ 20%	1 (12.5%)	3 (37.5%)	3 (37.5%)	0.47
	> 20%	7 (87.5%)	5 (62.5%)	5 (62.5%)	
Syncytial Knots					
	≤ 30%	0	0	0	1.00
	> 30%	8 (100%)	8 (100%)	8 (100%)	
Basement membrane					
thickening					
	≤ 3%	5 (62.5%)	6 (75%)	3 (37.5%)	0.23
	> 3%	3 (37.5%)	2 (25%)	5 (62.5%)	
Vasculo-syncytial					
membrane					
	≤ 5%	5 (62.5%)	6 (75%)	7 (87.5%)	0.37
	> 5%	3 (37.5%)	2 (25%)	1 (12.5%)	
Fibrinoid necrosis in villi					
	<3%	1 (12.5%)	0	1 (12.5%)	0.71
	3 -10%	3 (37.5%)	5 (62.5%)	3 (37.5%)	
	>10%	4 (50%)	3 (37.5%)	4 (50%)	
Stromal fibrosis					
	1 - 10%	3 (37.5%)	6 (75%)	2 (25%)	0.10

	> 10%	5 (62.5%)	2 (25%)	6 (75%)	
Intervillous Fibrinoid					
Deposition					
	< 5%	5 (62.5%)	5 (62.5%)	3 (37.5%)	0.52
	5-10%	3 (37.5%)	3 (57.5%)	5 (62.5%)	
Narrowing of the					
intervillous space					
	Present	3 (37.5%)	3 (37.5%)	4 (50%)	0.77
	Absent	5 (62.5%)	5 (62.5%)	4 (50%)	
Calcified areas					
	Present	8 (100%)	8 (100%)	8 (100%)	1.00
	Absent	0	0	0	

*All values are expressed as frequency with percentage in parenthesis. Group 1: Preeclamptic music intervention, Group 2: Preeclamptic yoga thrapy, Group 3: Preeclamptic controls, LPF: Low power field, Statistical test used: Fisher's exact probability test. Level of significance: *Significant (p<0.05); Non significant (p>0.05).*

DISCUSSION

Histopathological features in the placentae of preeclamptic study group with normotensive control group

Pregnancies complicated by preeclampsia are echoed in the placenta both macroscopically and microscopically. Although the placenta adapts well to the hypoxic condition in preeclampsia, the compensatory changes that occur are insufficient. These compensatory changes cause maldevelopment and insufficient placental mass, causing placental dysfunction that leads to oxidative stress and chronic foetal hypoxemia. The present study revealed that microscopic features like cytotrophoblastic cell proliferation, syncytial knots and villous stromal fibrosis are significantly increased in placenta from preeclampsia cases as compared to placenta from normal term pregnancy.

Cytotrophoblastic proliferation

In the present study, 71% of preeclamptic placentae showed cytotrophoblastic proliferation of greater than 20% in the villi, while all the cases of the normotensive control group fell within the normal range of villi with cytotrophoblastic cells (<20%). Fox, (1970), reported that the cytotrophoblastic hyperplasia was seen strikingly in placenta of women suffering from preeclampsia and eclampsia syndrome and its presence could be associated with high incidence of foetal hypoxia and intra-uterine death. He suggestsed that if the syncytiotrophoblast suffers ischaemic damage, the cytotrophoblast proliferation was a repair pheneomenon which was designed to evaluate placental functional efficiency. Thus, the degree of cytotrophoblastic hyperplasia is related to the severity of ischaemia [13].

Syncytial knots

In the present study, all the placentae of preeclamptic pregnancies showed syncytial knots of greater than 30% and in the placental villi of normal pregnant women, syncytial knots were less than 30%. Syncytial knots were seen with increased frequency in last weeks of pregnancy and more villi show these changes in preeclampsia. It is an indication of excessive aging due to disease state causing placental insufficiency. It is also proposed that the protein of the basement membrane is secreted by cytotrophoblastic cells, and excessive proliferation of these cells leads to excessive production of basement membrane material [13].

Basement membrane thickening

The incidence of villi showing a thickened basement membrane of more than 3% in the villous population is regarded as abnormal and is a common feature of placentae from preeclampsia. None of the placentae from the normotensive control group showed undue basement membrane thickening, while the incidence of basement membrane thickening in the placentae of preeclamptic group was 41%.

Genset, (1992), reported that cytotrophoblastic hyperplasia and excessive syncytial knot formation are seen in hypertensive disorders of pregnancy, which is a result of reduction of perfusion of the placenta [14].

Stromal fibrosis

In the present study, stromal fibrosis of greater than 10% was present in 54% of preeclamptic placentae and in normal placentae stromal fibrosis was present, but it was less than 10%. The two main factors responsible for the formation of stromal fibrosis are normal aging and reduced blood flow. Fox, (1968), concluded that reduced foetal blood flow through the villi results in stromal fibrosis in toxaemic cases [15] But Mathew *et al*., (1973), found stromal fibrosis in 3% of villi in term placentae, claiming that this lesion may be a part of aging process [16].Fox, (1968), reported that placentae from mature pregnancy should not contain villi with fibrinoid necrosis of more than 3%. Relatively higher incidence of this lesion is revealed in pregnancies complicated by hypertension [17].

Vasculo-syncytial membrane

Vasculo-syncytial membranes are a result of sinusoidal dilatation of the terminal villous capillaries, which protrude against the trophoblastic surfaces and alter them to thin lamellae; the incidence is closely related to fetal villous vascularisation. Vasculo-syncytial membrane counts measure the estimation of the villi to optimal maturity and hence give a good evidence of the ability of the placenta to supply oxygen to the foetus [18]. In the present study, vasculo-syncytial membrane paucity was present in 75% of placental samples of preeclamptic cases as compared to the placentae of normotensive control group. Becker and Blegyl, (1961), have claimed that placentae from pregnancies complicated by preeclampsia have a low proportion of villi with vasculo-syncytial membrane [19]. Fox, (1967), found that vasculo-syncytial membrane was present, but was found in less than 5% of villi in the placentae of hypertensive pregnancies. This deficiency of membrane can be considered as a failure of trophoblast differentiation [18].

Narrowing of the Intervillous space

Narrowing of the intervillous areas were present in 41% of placental samples of preeclamptic cases and it was absent in the placentae of normal pregnant group.

Calcifications

Calcifications were present in the placentae of both the preeclamptic groups and normotensive control group. But were numerous in the placentae of preeclamptic study groups as compared to normotensive controls. Excessive placental calcification causes uteroplacental insufficiency and compromises foetal circulation and growth [20].

Histopathological changes in the placentae of preeclamptic music intervention and *yoga* therapy groups with preeclamptic controls

In the present study, evaluated the histopathological changes in the placentae of preeclamptic pregnancies after giving interventions of music listening and *yoga* therapy for duration of 14 days in the third trimester of pregnancy. The parameters studied are cytotrophoblastic cell proliferation, syncytial knots, basement membrane thickening, vasculo-syncytial membrane, fibrinoid necrosis, stromal fibrosis, intervillous fibrinoid deposition, narrowing of the intervillous space and calcified areas. There was a reduction in basement membrane thickening in 37% in the the placental samples of preeclamptic music listening group and a reduction in 25% of placentae of preeclamptic *yoga* therapy group as compared with preeclamptic controls.

There was an increase of vasculo-syncytial membrane in 25% of the placentae of preeclamptic music listening group as compared to preeclamptic controls. Paucity of vasculo-syncytial membrane leads to foetal hypoxia with poor foetal outcome. Stromal fibrosis is due to reduced blood flow and seems more conclusive as excess stromal fibrosis was seen in preeclampsia. There was a reduction of stromal fibrosis in 50% of placentae of preeclamptic *yoga* therapy group as compared with preeclamptic controls. There was no significant difference in cytotrophoblastic cell proliferation, syncytial knots, fibrinoid necrosis, intervillous fibrinoid deposition, narrowing of the intervillous space and calcified areas in preeclamptic music listening and *yoga* therapy group as compared with preeclamptic controls.

CONCLUSION

There was no statistically significant difference in histopathology of cytotrophoblastic cell proliferation, syncytial knots, fibrinoid necrosis, intervillous fibrinoid deposition, narrowing of the intervillous space and calcified areas in pre-eclamptic music listening and yoga therapy group with pre-eclamptic controls, but further pathological changes of chorionic villi got reduced in music intervention and *yoga* therapy

group as compared with placentae of preeclamptic controls.

Conflicts of Interests: None

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