Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 **VOL13, ISSUE 03, 2022**

ORIGINAL RESEARCH ARTICLE

A STUDY OF VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTORS ON HUMAN PLACENTAE OF PREECLAMPTIC PREGNANCIES

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ABSTRACT

Background: Preeclampsia is a serious complication encountered during pregnancy. Globally, it is reported that, nearly 5-10% of all the mothers and their babies have a risk for preeclampsia. The conventional treatment to manage preeclampsia is with anti-hypertensive drugs, bed rest and early delivery, which may lead to other complications such as elevated liver enzymes, hepatitis, hepatic necrosis, xerostomia, etc. In this aspect, alternative options such as music therapy, *yoga* therapy, etc., which are safer, maybe a promising strategy for the health care community. The purpose of the present study is to assess the effects of two interventions, i.e., soothing instrumental music and *yoga* therapy, in reducing the blood pressure (BP) among preeclamptic women and also to evaluate the expression of membrane bound VEGFR-1 (mVEGFR-1) in the placentae of preeclamptic patients after delivery.

Materials and Methods: A quasi-experimental study was carried out among hospitalised preeclamptic pregnant women (n=75), and normotensive controls (n=25) from the antenatal ward of Yenepoya Medical College Hospital, Mangalore, India, from December 2016 to September 2018. Preeclamptic patients were assigned into experimental/ interventional 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 BP, both systolic (SBP) and diastolic (DBP), was measured before and after the intervention in the study groups 1 to 3, and the results were recorded and interpreted. Placentae were collected after delivery for evaluating the histopathological changes and the expression of mVEGFR-1 in the study groups.

Results: There was a significant difference in the SBP and DBP among the groups 1 and 2 with intervention. In addition, there was no significant difference in the expression of mVEGFR-1 in the placentae of preeclamptic music listening group and *yoga* therapy group as compared with preeclamptic controls ($p>0.05$).

Conclusion: In the present study, soothing instrumental music and *yoga* therapy reduced the BP among the interventional groups. Both the interventions improved the total well-being of the preeclamptic mother and her baby. It can be recommended as a non invasive technique for reducing the severity of illness in preeclamptic pregnant women.

Keywords: Blood pressure; Conventional therapy; Preeclampsia; Soothing instrumental music; Membrane bound Vascular endothelial growth factor receptor-1; *Yoga* therapy.

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INTRODUCTION

In normal pregnancy, the utreo-placental spiral arteries in the myometrium encounter structural changes where the musculoelastic tissue of the tunica media is restored by invading trophoblastic cells encircled by a thick layer of fibrinoid material. The strained vessels undergo continuing vasodilatation. These changes are accountable for the low vascular resistance of the placental bed and allow a large proliferation in blood flow to the intervillous space. A common pathological feature of preeclampsia is the failure of the maternal spiral arteries supplying the placenta to experience the physiological modifications of normal pregnancy to ease proper placental perfusion. Some biochemical variations in the placenta may give rise to the pathophysiology in preeclampsia, such as increased vasoconstrictor and decreased vasodilator production in the placenta. Hence, the placenta must play a central role in this disorder of pregnancy.[1]

VEGF ligands and receptors are highly elevated by the first trimester placenta. In immunohistochemistry, the expression of VEGF, PIGF and VEGFR-1 protein by invasive cytotrophoblasts is altered in preeclampsia.[2] Preeclampsia is linked with an up-regulation of mVEGFR-1 in the placental tissue, which can be seen already at 11 weeks of gestation in chorionic villous biopsies in women with subsequent preeclampsia.[3]

Current treatment guidelines for hypertension include antihypertensive medications and health-promoting lifestyle modifications such as weight reduction, the dietary approaches to stop hypertension, reduced dietary sodium, increased physical activity, and moderation of alcohol consumption. In addition, hypertensive medications can produce troublesome side effects such as insomnia, sedation, dry mouth, drowsiness, impotence, and headaches.[4] Therefore, there is a need for interventions to lower BP through decreases in stress responses in pregnant hypertensive women. Simple relaxation techniques can be used to alleviate the stress and anxiety during pregnancy. Music therapy is one of the effectual relaxation techniques for anxiety and stress relief during pregnancy.[5]

In a meta-analysis undertaken to investigate the effect of music in hypertensive patients, it has been summarised that music resulted improvement in SBP. Listening to relaxing music can reduce BP and heart rates in hospitalized pre-hypertensive pregnant women during third trimester. The BP lowering effect of relaxing music listening is more evident for SBP.[6] *Yoga* is explained as a mind-body practice that incorporated traditional physical postures and may include other components, such as breathing exercises and meditation. Relaxation decreases tension in the hypothalamus, through which autonomic functions such as BP are controlled.[7] The effect of yogic relaxation in the treatment of high BP is explained as decreasing excessive stimulation of the hypothalamus from which autonomous functions of the autonomic nervous system and endocrine system are controlled.[8]

MATERIALS AND METHODS

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.[9]

Selection of normotensive control group

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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).[10]

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.[11]

Study setting

Before conducting the study, permission was obtained from the institutional ethics committee. A quasi-experimental study was carried out among hospitalised preeclamptic pregnant women (n=75), and normotensive controls (n=25), in the antenatal ward of Yenepoya Medical College Hospital, Mangalore, India, and the duration of the study was from December 2016 to September 2018.

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

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 in the frequency of 33000 Hz, 32 bit float rhythm and the volume kept between 50 to 60 decibels. The intervention was carried out in a room with quiet environment and soft lighting.

Procedure of intervention: Group 2 - *yoga* therapy

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.

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)

Immunohistochemistry – Paraffin (IHC-P)

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For the detection of mVEGFR-1 in the placental tissue, sections of placental parenchyma of 1 cm × 1cm × 0.5 cm from the central part of the maternal and foetal side of each placenta was stained using standard methodology (Cat No. ab1250; abcam; UK).[12]

Evaluation of mVEGFR-1 in the placental tissue of the study groups

The expression of mVEGR-1 in the placental tissue was evaluated under compound light microscope at a magnification of 40x. Tissue sections were evaluated for protein localization and intensity. Five high power fields of each section, selected at random were examined for the extent of positivity and the intensity of staining in the cells and an average was obtained. The positivity and the intensity of staining of mVEGFR-1 expression were evaluated on syncytiotrophoblasts cells, cytotrophoblast cells, foetal endothelial cells and maternal endothelial cells. Photomicrographs were taken under an Olympus magnus microscope (MLXi Plus, Olympus America, USA). All sections were evaluated by two independent observers, who were blinded to the clinical observation.

Staining score was based on the extent of positivity and the intensity of staining in each slide. The extent of positivity was scored as 1 when the percentage of positive cells was <10%; 2 when 10-50%; 3 when >50%. The intensity of staining was scored as 1, absent / weak; 2, moderate; 3, strong. The final score of immunoreactivity was obtained by multiplying the extent of positivity and intensity scores, giving a range from 1-9. The expression of mVEGFR-1 immunoreactivity was categorised as strong when the final score was >6, intermediate when the score was between 4-6, and reduced when the final score was between 1-3.[13]

RESULTS

Evaluation of immunohistochemical expression of mVEGFR-1 in the placentae of study groups

Table 1: Quantitative analysis of staining intensity of mVEGFR-1 in the placentae of study groups

Groups & Cells (per HPF)	Staining intensity (mVEGFR-1)			
	Negative (-)	Weak (+)	Moderate (++)	Strong (+++)
Group 1 (n=8)				
Syncytiotrophoblast	-	-	2 (25.0)	6 (75.0)
Cytotrophoblast	-	-	6 (75.0)	2 (25.0)
Endothelial cells	-	2 (25.0)	5 (67.5)	1 (12.5)
Group 2 (n=8)				
Syncytiotrophoblast	-	-	1 (12.5)	7 (87.5)
Cytotrophoblast	-	1 (12.5)	4 (50.0)	3 (37.5)
Endothelial cells	-	2 (25.0)	5 (67.5)	1 (12.5)
Group 3 (n=8)				
Syncytiotrophoblast	-	-	-	8 (100)
Cytotrophoblas	-	-	5 (62.5)	3 (37.5)
Endothelial cells	-	1 (12.5)	5 (62.5)	2 (25.0)
Group 4 (n=8)				
Syncytiotrophoblast	-	1 (12.5)	6 (75.0)	1 (12.5)
Cytotrophoblast	-	4 (50.0)	3 (37.5)	1 (12.5)
Endothelial cells	-	3 (37.5)	4 (50.0)	1 (12.5)

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All values are expressed as frequency with percentage in parenthesis. Abbreviations used: mVEGFR-1: Membrane bound vascular endothelial growth factor receptor-1, Group 1: Preeclamptic music intervention, Group 2: Preeclamptic yoga thrapy, Group 3: Preeclamptic controls, Group 4: Normotensive controls, HPF: High-power field.

Table 2: Assessment of the extent of positivity of mVEGFR-1 in in the placentae of study groups

Groups & Cells (per HPF)	Extent of positivity (mVEGFR-1)		
	< 10%	10-50%	>50%
Group 1 (n=8)			
Syncytiotrophoblast	-	-	8 (100)
Cytotrophoblast	-	1 (12.5)	7 (87.5)
Endothelial cells	-	1 (12.5)	7 (87.5)
Group 2 (n=8)			
Syncytiotrophoblast	-	-	8 (100)
Cytotrophoblast	-	-	8 (100)
Endothelial cells	-	1 (12.5)	7 (87.5)
Group 3 (n=8)			
Syncytiotrophoblast	-	-	8 (100)
Cytotrophoblast	-	-	8 (100)
Endothelial cells	-	-	8 (100)
Group 4 (n=8)			
Syncytiotrophoblast	-	4 (50.0)	4 (50.0)
Cytotrophoblast	-	5 (67.5)	3 (37.5)
Endothelial cells	-	6 (75.0)	2 (25.0)

All values are expressed as frequency with percentage in parenthesis. Abbreviations used: mVEGFR-1: Membrane bound vascular endothelial growth factor receptor-1, Study groups- Group 1: Preeclamptic music intervention, Group 2: Preeclamptic yoga thrapy, Group 3: Preeclamptic controls, Group 4: Normotensive controls, HPF: High-power field.

Estimation of immunohistochemical expression of mVEGFR-1 in the placentae of preeclamptic study groups with normotensive control group

Table 3: Comparison of immunoreactivity of mVEGFR-1 in the placentae of group 1 with group 4

Expression of mVEGFR-1	Group 1 (n=8)			Group 4 (n=8)			p-value
	Reduced (%)	Intermediate (%)	Strong (%)	Reduced (%)	Intermediate (%)	Strong (%)	
Syncytiotrophoblast	-	2 (50.0)	6 (75.0)	1 (12.5)	6 (75.0)	1 (12,5)	0.04
Cytotrophoblast	-	6 (75.0)	2 (25.0)	5 (62.5)	2 (25.0)	1 (12.5)	0.25
Endothelial cells	2 (25.0)	5 (62.5)	1 (12.5)	3 (37.5)	4 (50.0)	1 (12.5)	0.80

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All values are expressed as as frequency with percentage in parenthesis. Abbreviations used: mVEGFR-1: Membrane bound vascular endothelial growth factor receptor-1, Group 1: Preeclamptic music intervention, Group 4: Normotensive controls. Statistical test used: Fisher's exact probability test. Level of significance: *Significant ($p<0.05$), Non significant ($p>0.05$).

Table 4 Comparison of immunoreactivity of mVEGFR-1 in the placentae of group 2 with group 4

Expression of mVEGFR-1	Group 2(n=8)			Group 4 (n=8)			p-value
	Reduced (%)	Intermediate (%)	Strong (%)	Reduced (%)	Intermediate (%)	Strong (%)	
Syncytiotrophoblast	-	1 (12.5)	7 (87.5)	1 (12.5)	6 (75.0)	1 (12.5)	0.01*
Cytotrophoblast	1 (12.5)	4 (50.0)	3 (37.5)	5 (62.5)	2 (25.0)	1 (12.5)	0.17
Endothelial cells	2 (25.0)	5 (25.0)	1 (12.5)	3 (37.5)	4 (50.0)	1 (12.5)	0.80

All values are expressed as as frequency with percentage in parenthesis. Abbreviations used: mVEGFR-1: Membrane bound vascular endothelial growth factor receptor-1, Group 2: Preeclamptic yoga thrapy, Group 4: Normotensive controls. Statistical test used: Fisher's exact probability test. Level of significance: *Significant ($p<0.05$), Non significant ($p>0.05$).

Table 5 Comparison of immunoreactivity of mVEGFR-1 in the placentae of group 3 with group 4

Expression of mVEGFR-1	Group 3 (n=8)			Group 4 (n=8)			p-value
	Reduced (%)	Intermediate (%)	Strong (%)	Reduced (%)	Intermediate (%)	Strong (%)	
Syncytiotrophoblast	-	-	8 (100)	1 (12.5)	6 (87.5)	1 (12.5)	0.0006*
Cytotrophoblast	-	5 (62.5)	3 (37.5)	5 (62.5)	2 (25.0)	1 (12.5)	0.03*
Endothelial cells	1 (12.5)	5 (25.0)	2 (25.0)	3 (37.5)	4 (50.0)	1 (12.5)	0.53

All values are expressed as as frequency with percentage in parenthesis. Abbreviations used: mVEGFR-1: Membrane bound vascular endothelial growth factor receptor-1, Group 3: Preeclamptic controls, Group 4: Normotensive controls. Statistical test used: Fisher's exact probability test. Level of significance: *Significant ($p<0.05$), Non significant ($p>0.05$).

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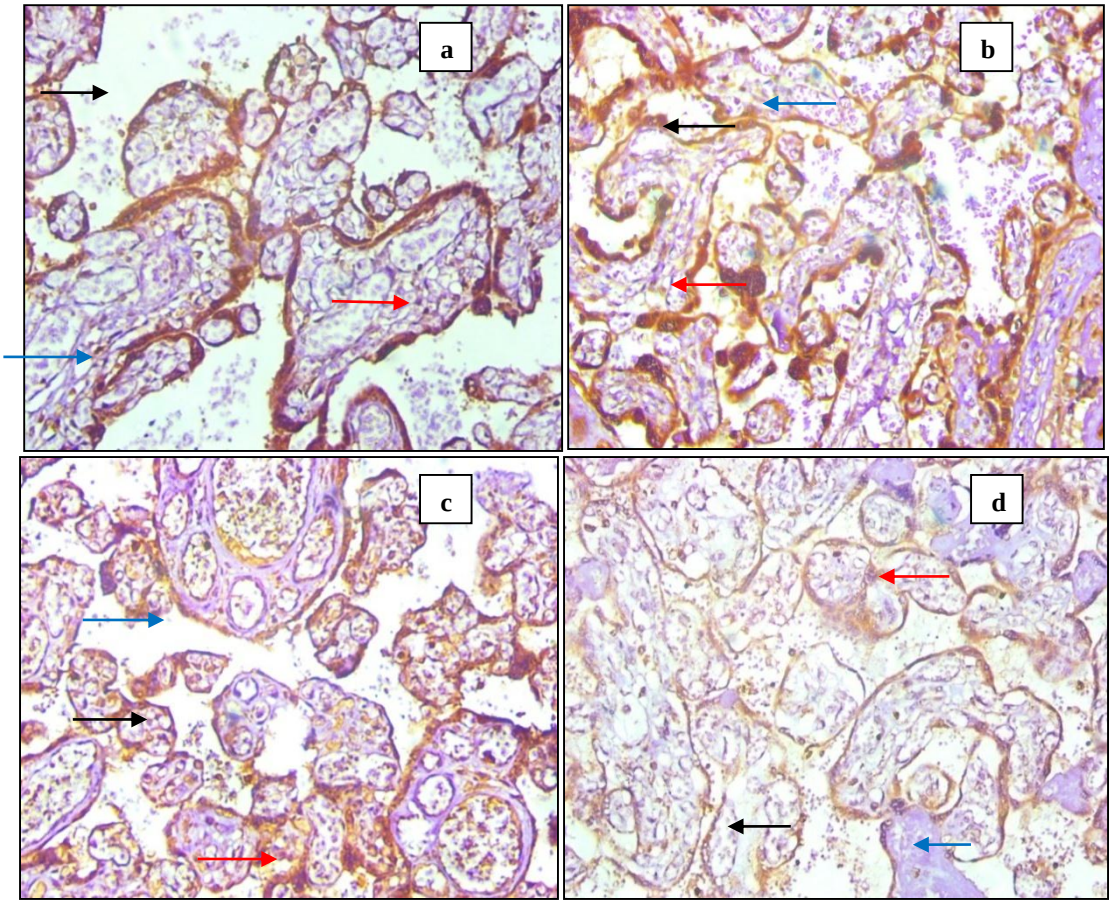

Fig. 4.6 Expression of mVEGFR-1 in the study groups

Placental villi of study groups, (a) preeclamptic control group; (b) preeclamptic music listening group; (c) preeclamptic yoga therapy group; (d) normotensive control group. Expression of membrane bound vascular endothelial growth factor receptor -1 (mVEGFR-1) in the syncytiotrophoblasts (red arrow), cytotrophoblast (black arrow) and endothelial cells (blue arrow). Olympus magnus microscope, 20x, Scale bar=100µm.

Estimation of immunohistochemical expression of mVEGFR-1 in the placental tissue of preeclamptic music listening and yoga therapy groups with preeclamptic control group

Table 6 Comparison of immunoreactivity of mVEGFR-1 in the placentae of group 1 with group 3

Expression of mVEGFR-1	Group 1 (n=8)			Group 3 (n=8)			p-value
	Reduced (%)	Intermediate (%)	Strong (%)	Reduced (%)	Intermediate (%)	Strong (%)	
Syncytiotrophoblast	-	2 (50.0)	6 (75.0)	-	-	8 (100)	0.23
Cytotrophoblast	-	6 (75.0)	2 (25.0)	-	5 (62.5)	3 (37.5)	0.64
Endothelial cells	2 (25.0)	5 (25.0)	1 (12.5)	1 (12.5)	5 (62.5)	2 (25.0)	0.82

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All values are expressed as frequency with percentage in parenthesis. Abbreviations used: mVEGFR-1: Membrane bound vascular endothelial growth factor receptor-1Group 1: Preeclamptic music intervention, Group 3: Preeclamptic controls. Statistical test used: Fisher's exact probability test. Level of significance: *Significant ($p<0.05$), Non significant ($p>0.05$).

Table 7 Comparison of immunoreactivity of mVEGFR-1 in the placentae of group 2 with group 3

Expression of mVEGFR-1	Group 2 (n=8)			Group 3 (n=8)			p-value
	Reduced (%)	Intermediate (%)	Strong (%)	Reduced (%)	Intermediate (%)	Strong (%)	
Syncytiotrophoblast	-	1 (12.5)	7 (87.5)	-	-	8 (100)	1.0
Cytotrophoblast	1 (12.5)	4 (50.0)	3 (87.5)	-	5 (62.5)	3 (37.5)	0.99
Endothelial cells	2 (25.0)	5 (25.0)	1 (12.5)	1 (12.5)	5 (62.5)	2 (25.0)	0.82

All values are expressed as frequency with percentage in parenthesis. Abbreviations used: mVEGFR-1: Membrane bound vascular endothelial growth factor receptor-1Group 2: Preeclamptic yoga therapy, Group 3: Preeclamptic controls. Statistical test used: Fisher's exact probability test. Level of significance: *Significant ($p<0.05$), Non significant ($p>0.05$).

DISCUSSION

In the present study, immunoreactivity due to placental expression of mVEGFR-1 was detected in the syncytiotrophoblast, cytotrophoblast, and endothelial cells of the vessels. The immunohistochemical expression of mVEGFR-1 was higher in the trophoblasts and endothelial cells of preeclamptic controls. The expression of mVEGFR-1 staining intensity in the trophoblasts of the chorionic villi of group 1 with music intervention showed a moderate staining in 25% of placental samples and strong staining in 75% of placentae. In group 2 with *yoga* intervention, the staining intensity for mVEGFR-1 in the trophoblasts was moderate, i.e., in 12.5% of placental samples and exhibited a strong staining intensity in the trophoblasts in 87.5% of placentae. In preeclamptic controls, the expression of mVEGFR-1 staining intensity was strong in all the trophoblastic cells of placental villi. In case of normotensive controls the staining intensity was weak in 12.5% of placental villi, moderate in 75% of chorionic villi and showed 12.5% of strong staining cells in the placental samples. The expression of mVEGFR-1 staining was seen mostly in the syncytiotrophoblasts and was strong in syncytial knots of preeclamptic study groups. Moreover, the intensity of staining increased with the severity of disease and decrease of gestational age.

In the present study, mVEGFR-1 expression was detected in placental syncytiotrophoblasts, cytotrophoblasts and endothelial cells of the placental villi.This finding had resemblance to the study done by Tache *et al*., (2011), who claimed that most Flt-1 staining was seen in syncytiotrophoblasts and in particular, syncytial knots.[14] The extent of positivity of mVEGFR-1 in the placental villi of preeclamptic music listening group was between 10 to 50% in 12.5% of placentae and >50% in 87.5% of placental samples. The trophoblasts in the placental villi of preeclamptic *yoga* therapy group showed a positivity for mVEGFR-1 >50% in all the samples and displayed positivity between 10-50% in 12.5% of endothelial cells. The extent of positivity for the expression of mVEGFR-1 in the trophoblasts and endothelial cells of preeclamptic control group was >50% in all the placental samples and also exhibited a stronger staining intensity (+++) in all the cells. In normotensive control group the extent of positivity of

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mVEGFR-1 in cytotrophoblasts was between 10 to 50% in 62.5% of placental samples and >50% of positivity in 37.5% of samples. A study done by Marini *et al*., (2007), reported that the trophoblast, endothelial cells of the vessels, stromal cells and hofbauer cells in normal placenta showed immunoreactivity for mVEGFR-1. That reactivity of mVEGFR-1 in some trophoblasts, vessels and stromal cells were lower in preeclamptic placenta has been reported earlier.[15]

In the present study, the final score of immunoreactivity of mVEGFR-1 was reduced in 25% of endothelial cells of the placental samples of preeclamptic music listening group and showed an intermediate reactivity in 75% of cytotrophoblasts and strong immunoreactivity in 75% of syncytiotrophoblasts of the placental samples. The final score of immunoreactivity of mVEGFR-1 in preeclamptic *yoga* therapy group was reduced in 25% of endothelial cells, exhibited intermediate reactivity in 62.5% of cytotrophoblasts and strong immonoreactivity in 87.5% of syncytiotrophoblasts of the placental samples. The final score of immunoreactivity of mVEGFR-1 in preeclamptic control group was reduced in 12.5% of endothelial cells of the study samples and 62.5% of cytotrophoblasts of the placental samples showed intermediate reactivity and strong reactivity in all the placental syncytiotrophoblasts. The final score of immunoreactivity of mVEGFR-1 in the placental villi of normotensive control group showed reduced immunoreactivity in 62.5% of cytotrophoblasts, showed intermediate immunoreactivity in 87.5% of syncytiotrophoblasts and strong reactivity only in 12.5% of cells of the study samples.

The present study unveiled a reduction of immunoreactivity of mVEGFR-1 in 25% of the syncytiotrophoblasts and a reduction in 12.5% of the endothelial cells of the placental samples of music intervention group. In *yoga* therapy group there was a reduction of immunoreactivity of of mVEGFR-1 in 12.5% of the syncytiotrophoblasts and in 12.5% of the endothelial cells of the placental samples as compared to preeclamptic controls. This signifies the effect of music and *yoga* in improving the placental insufficiency by reducing further damage due to hypoxia.

CONCLUSION

There was a significant difference in the expression of membrane bound VEGFR-1 in the placentae between preeclamptic study groups and normotensive control group, but there was no significant difference in the expression of mVEGFR-1 in the placentae of preeclamptic music listening group and *yoga* therapy group as compared with preeclamptic controls. Listening to soothing instrumental music and yoga therapy alleviated the blood pressure in hospitalised preeclamptic women.

Conflicts of interests: None

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