Comparison of Placental Expression of Basic Fibroblast Growth Factor and Insulin-Like Growth Factor-1 in Placentae of Normal, Pregnancy-Induced Hypertension, and Preeclamptic Pregnancies in Iraqi Mothers

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Abstract

Background: Many pathological insults are associated with elevation of blood pressure levels during pregnancy resulting in a difficult pregnancy and a poor outcome on both mother and baby. **Objective:** In this study, we examine the histological and immunohistochemical markers of the placentae in cases of hypertension in pregnancy and preeclampsia and compared them to a placenta of normal pregnancy among a random sample of Iraqi pregnant women. **Materials and Methods:** Ninety women divided into three groups, 30 in each, selected with straightforward pregnancies (Group A), mothers with pregnancy-induced hypertension (Group B), and preeclamptic mothers (Group C) were chosen from the indoor patients of the gynecology and obstetrics department of Al-Khansaa teaching hospital in Mosul for placental tissues examination. Histological examination was done by using hematoxylin and eosin stain (H & E), and immunohistochemistry was achieved by using immunohistochemical markers named: insulin-like growth factor-1 (IGF-1) and basic fibroblast growth factor (b-FGF) markers, which are expressed in placental tissues. **Results:** Different changes were observed in the placentae affected when compared with normal one, such as syncytial knots formation, thickening of trophoblastic basement membrane, cytotrophoblastic cellular proliferation, fibrinoid necrosis, endothelial proliferation, calcified and hyalinised villous spots, villous edema, and atherosis of the uteroplacental arteries. Significant immunohistochemical changes were obtained when compared with normal placentae where elevation of both b-FGF and IGF-1 in preeclamptic placentae was observed when compared to hypertensive and control cases. **Conclusion:** Significant changes appeared in the placentae of hypertensive and preeclamptic mothers, both in histological and immunohistochemical examinations.

Keywords: b-FGF, IGF-1, placenta, preeclampsia, pregnancy

Introduction

Preeclampsia is pregnancy-related hypertensive disease associated with high rate of maternal and fetal mortality and morbidity.[1] According to the World Health Organization, preeclampsia accounts for about 16% of maternal death.[2] About 10% of perinatal death is due to the complication of preeclampsia, and it is the third cause of maternal death in the USA.[3] In normal pregnancy, the placental bed and uterine circulation undergo massive neovascularization and remodeling to enable the circulation between the embryo and the mother.[4] This process requires an intricate balance between antiangiogenic and proangiogenic factors. Any defect in neovascularization or spiral artery remodeling can result in placental ischemia and injury.[5] The imbalance between angiogenic and antiangiogenic factors can trigger preeclampsia. Normal placentation requires deep invasion

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_40_23

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Submission: 11-Jan-2023 **Accepted:** 08-Feb-2023 **Published:** 02-Feb-2024

How to cite this article: Al-Rubai A-J, Ibraheem MM, Hameed AF, Noel KI, Eleiwi SA. Comparison of placental expression of basic fibroblast growth factor and insulin-like growth factor-1 in placentae of normal, pregnancy-induced hypertension and preeclamptic pregnancies in Iraqi mothers. Med J Babylon 2023;20:681-8.

of trophoblast cells into maternal circulation, whereas in women who destined to have preeclampsia, the invasion is shallow, which leads to reduction in blood flow and subsequent placental ischemia and stress, which, in turn, cause abnormal development of placenta.[6] Therefore, in normal pregnancy, the cytotrophoblast invasion is associated with the formation of new blood vessels, which is facilitated by the release of large amount of angiogenic factors such as basic fibroblast growth factor (b-FGF) and insulin-like growth factor-1 (IGF-1).

The placenta plays an important role in the pathogenesis of preeclampsia.[7]

IGF-1 is one of the important modulators, which stimulate cellular proliferation, and has a crucial role in angiogenesis and trophoblastic growth. Moreover, it has an important role in the physiology of the decidua, trophoblast, and the endometrium. It has been shown that placental insufficiency can be overcome by treatment with IGF-1 either by its delivery into the amniotic fluid or by transgene delivery into the placenta by adenovirus.[8] Additionally, it has been shown that severe fetal growth restriction is associated with low concentration of IGF-1 [9].

b-FGF is a multifunctional regulatory mitogen, which plays an important role in endothelial cell migration and stimulates formation of new blood vessels and early branching process. The b-FGF has been illustrated to be the mitogen of vascular smooth muscles and it is associated with vascular remodeling; therefore, it might play an important role in the development of hypertension during pregnancy.[10]

This study is done to compare the severity of placental changes occurred due to hypertension and preeclampsia from histological and immunohistochemical point of view.

Materials and Methods

From March 2021 to March 2022, 90 women with straightforward pregnancies, mothers with pregnancy-induced hypertension, and preeclamptic mothers were chosen from the indoor patients of the gynecology and obstetrics department of Al-Khansaa teaching hospital in Mosul. Ethical approval was obtained from Mustansiriyah University/College of Medicine. The groups for this study were named "Group A" for normal pregnancy (30 mothers), "Group B" for pregnancy-induced hypertensive 30 women, and "Group C" for preeclamptic mothers (30 mothers). These mothers are primigravidae and paragravidae 2–3, ranging from 20 to 38 years old. Pregnancy-induced hypertension without proteinuria and edema affected 15 of these hypertensive women, whereas edema or proteinuria or both affected the other 15 of them. Before becoming pregnant, these mothers had normal blood pressure.

Mothers were clinically checked (for height, weight, blood pressure, pulse, signs of anemia, and jaundice), and their medical history was recorded (history of past illness and history of previous childbirth). We looked over their investigative reports (blood sugar, urea, creatinine, hemoglobin levels, and urine for albumin and pus cells). Blood pressure in hypertensive mothers ranged from 140/90 to 160/110 mmHg and beyond. Placentas were taken after delivery for histopathological and immunohistochemical research. Placenta weight was also recorded. The newborn infants were examined for the presence of congenital abnormalities, and their birth weights were recorded.

Samples from different placental tissue areas were obtained for histopathological and immunohistochemical research.

Histopathology

The placentae specimens were immediately fixed in 10% of neutral formalin, opened longitudinally, and then cut into pieces. Pieces of tissue measuring about 1 cm by 0.5 cm were then removed from various regions. The specimens were then dehydrated, cleared, and embedded in paraffin, serially sectioned at a thickness of about 4 μm, and finally stained with hematoxylin and eosin for studying the general histology. Staining methods and procedures were carried out using Druray and Willington as a guide.[11]

Immunohistochemistry

Two serial sections, each measuring 4-μm thick, were collected for every sample. A positively charged slides were used to place the first serial section for immunohistochemical staining with an anti-b-FGF antibody (Abnova catalog no. PAB16168 Lot No. SB105PABGGF, Neihu District, Taipei City, Taiwan), the second placed slide for anti-IGF-1 antibody (Abnova catalog no. sc-7269 Code PAB12663). The secondary antibody detection kit was obtained from Abcam (Abcam code ab80436 mouse specific horseradish peroxidase/3,3-diaminobenzidine, Boston, MA, USA). Samples that had been fixed in formalin and tissue sections that had been implanted with paraffin were gradually dewaxed with xylene. Antigen retrieval was carried out using citrate buffer under pressure for 20 min. The background lowering dilution buffer (Abcam, code ab64211) was used to dilute the primary anti-b-FGF and anti-IGF-1 antibodies to a concentration of 1:200 before keeping them heated at room temperature for 30 min. Labeled streptavidin-biotin from the Abcam secondary detection kit was used for detection, which was then followed by DAB and chromogen staining. The immunohistochemical staining was rapidly followed by dibutylphthalate polystyrene xylene mounting, hydration, and counterstaining with hematoxylin. Each tissue sample underwent evaluation without any prior knowledge.[12]

Staining percentage and intensity were calculated as follows: staining intensity was scored: 0 (no staining), 1+ (weak), 2+ (moderate), and 3+ (strong). Extent of staining (percentage) was categorized by percentage: 0 = nil, 1 = <10% of cell stained positively, 2 = 10%–50%, 3 = 51%–80%, and 4 = ≥80%.[13]

Statistical analysis

Statistical analysis was performed by using the SPSS (Statistical Packages for Social Sciences, Armonk, NY, USA) V26. Categorical variables were evaluated by measuring the percentage and mean + standard deviation. The qualitative data were verified using the Pearson Chi-square test and independent sample *t* test.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number ECP: 21/19 on February 15, 2021.

Results

In control placentas, light microscopic villous structures appeared with central connective tissues core covered by trophoblastic cell layers; each villous was rich with fetal capillaries. Also, villi were separated from each other by intervillous spaces filled with maternal blood [Figure 1].

Histological study of placental villi

It had been noticed that on examination under microscope, a significant number of syncytial knots [Figure 2], thickening of trophoblastic basement membrane [Figure 3], cytotrophoblastic cellular proliferation [Figure 4],

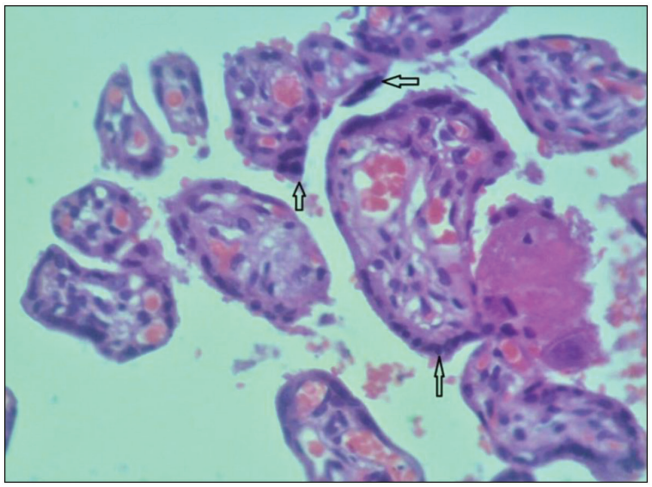

Figure 2: Placenta with significant number of syncytial knots H & E 400X. H & E: hematoxylin and eosin stain

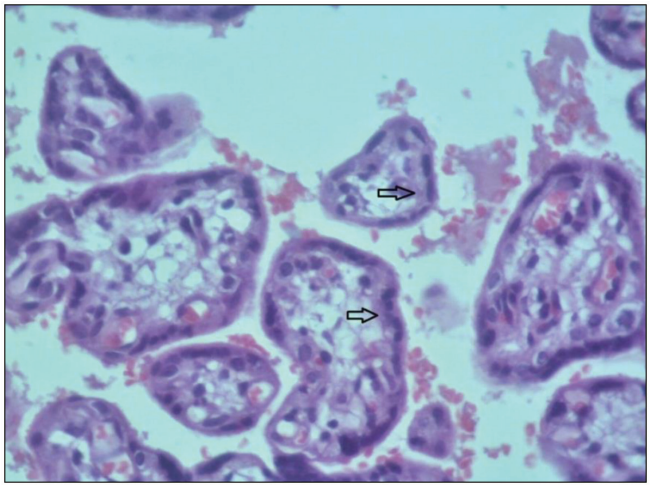

Figure 3: Placenta with thickening of trophoblastic basement membrane H & E 400X. H & E: hematoxylin and eosin stain

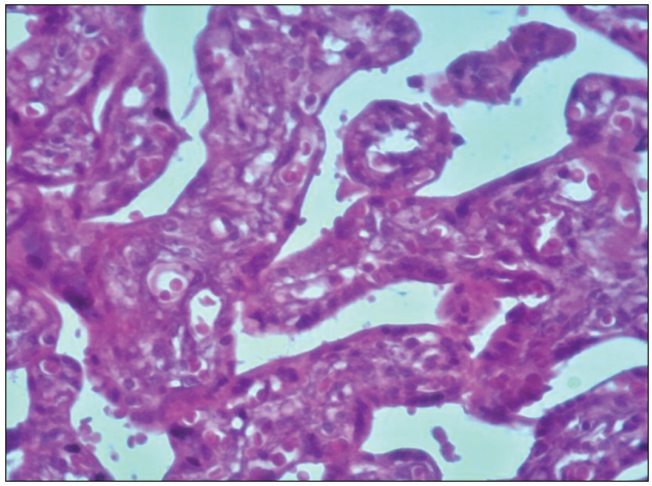

Figure 1: Normal placental tissue H & E 400X. H & E: hematoxylin and eosin stain

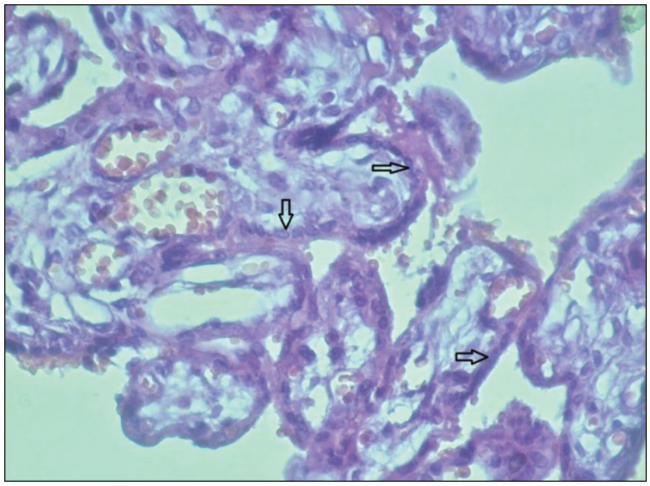

Figure 4: Placenta with cytotrophoblastic cellular proliferation H & E 400X. H & E: hematoxylin and eosin stain

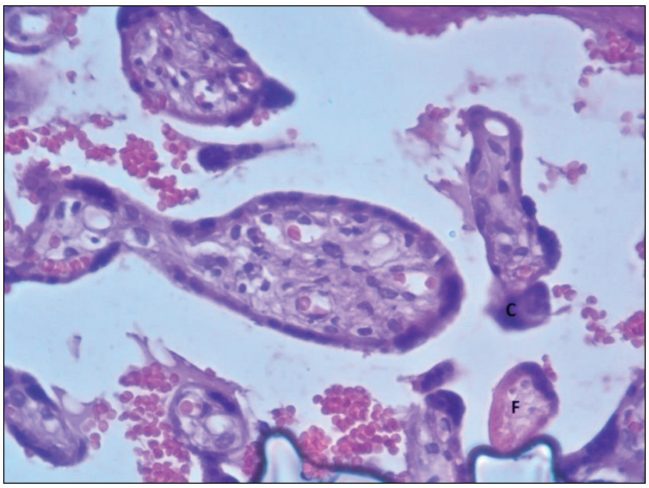

Figure 5: Placenta with fibrinoid necrosis (F), calcified villous spots (C) H & E 400X. H & E: hematoxylin and eosin stain

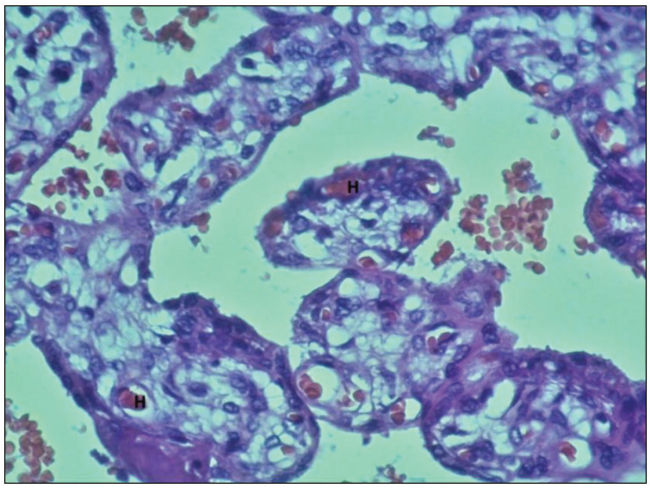

Figure 6: Placenta with hyalinised villous spots (H) H & E 400X. H & E: hematoxylin and eosin stain

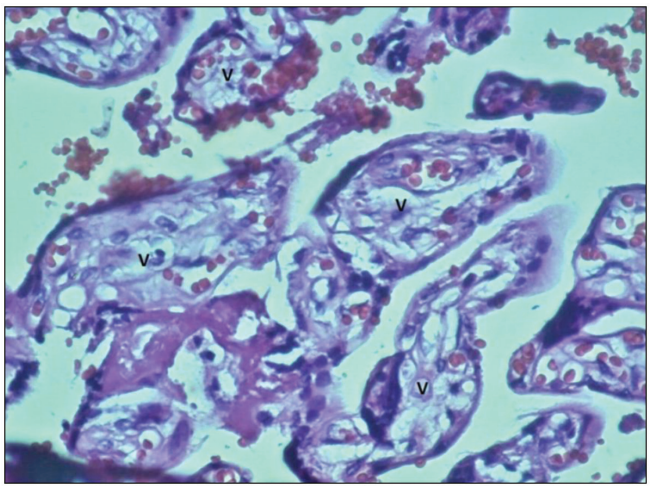

Figure 7: Placenta with villous edema (V) H & E 400X. H & E: hematoxylin and eosin stain

fibrinoid necrosis, endothelial proliferation, calcified and hyalinised villous spots [Figures 5 and 6], villous edema [Figure 7], and atherosis of the uteroplacental arteries were observed in the hypertensive and preeclampsia groups in comparison with the control group.

Immunohistochemical study of placental villi

Examined placental tissue shows great difference in staining percentages among normal tissue from Group A, pregnancy-induced hypertension placenta (Group B), and preeclamptic placental tissue (Group C), where there was an increasing percentage of staining of b-FGF marker among Group C placental tissues (more than 95%) when compared with staining percentage of Group A and Group B placental tissues (maximum 45% and 75%, respectively) stained with b-FGF [Table 1].

IGF-1 stained only in syncytiotrophoblast cell of the placenta where it also shows many discrepancies among the three groups with high statistical significant difference (0.001), where Group C (preeclamptic placental tissue) shows a high percentage of staining when compared with Group A and Group B [Table 2 and Figures 8–13].

Total Immunohistochemical scoring of basic fibroblast growth factor

The preeclamptic placental tissues show high statistical staining difference with high immune score when compared in the three groups [Table 3 and Figures 14–19].

Total immunohistochemical scoring of insulin-like growth factor-1

The preeclamptic tissue shows a great score when compared with normal placental tissue and the placental tissue from pregnancy-induced hypertension with a highly statistical difference *P* (0.001) [Table 4].

Discussion

The histology of placenta of hypertensive mothers also shows a significant increase in syncytial knot formation, cytotrophoblastic cellular proliferation, proliferation of endothelial lining of capillaries, stromal fibrosis, calcification, and hyalinization of villi in comparison with the control group. On postmortem examination, Genset[14] reported that stromal fibrosis and excessive syncytial knot formation are seen in generalized form as invariable results of the overall reduction of fetal perfusion of the placenta.

On histological observation of placentae, evidence of cytotrophoblastic cellular hyperplasia and patchy necrosis of the villous syncytiotrophoblastic cells are obvious in the study group in comparison to the control group. This is also very much in accordance with the previous studies conducted by Jones and Fox.[15]

Table 1: Staining percentages of basic fibroblast growth factor in placental tissues of normal placental tissue, pregnancy-induced hypertension, and preeclamptic placental tissues

Staining percentage of b-FGF	*N*	Minimum %	Maximum %	Mean ± SD	*P* value
Syncytiotrophoblast					
Group A	30	25	45	32.03 ± 5.9	0.001
Group B	30	55	75	64.7 ± 5.33	
Group C	30	80	95	87.4 ± 5.7	
Smooth muscle cell (SMC)					
Group A	30	20	35	24.5 ± 3.8	0.001
Group B	30	40	55	46.5 ± 5.4	
Group C	30	65	85	74 ± 7	
Chorionic villous stromal cell (CVSC)					
Group A	30	15	30	20.3 ± 4.66	0.001
Group B	30	35	55	43.17 ± 6.5	
Group C	30	40	65	54.33 ± 7.5	

b-FGF: basic fibroblast growth factor, SD: standard deviation

Table 2: Staining percentages of insulin-like growth factor-1 in syncytiotrophoblast of normal placental tissue, pregnancy-induced hypertension, and preeclamptic placental tissues

IGF-1	*N*	Minimum	Maximum	Mean	*P* value
Group A%	30	30	45	37.1 ± 5.4	0.001
Group B%	30	45	65	56 ± 5.9	
Group C%	30	70	95	82.67 ± 6.5	

IGF-1: insulin-like growth factor-1

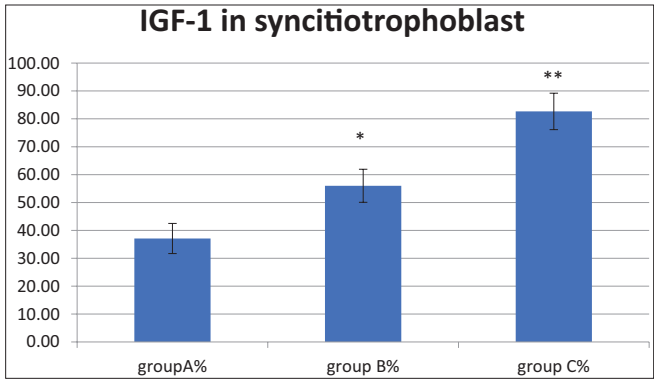

Figure 8: Staining percentages of IGF-1 in placental tissues among groups. IGF-1: insulin-like growth factor-1

Among other microscopical tissue findings on placental examination of the present study was undue thickening of the trophoblastic basement membrane. The most possible clarification is a response to uteroplacental ischemia. This is supported by the finding of Reshetnikova *et al*.[16] who observed an increased basement membrane thickness in placental villi sustained under conditions of low oxygen tension. Other investigators tried to explain this lesion on an immunological basis and they suggested that it is probably due to the deposition of immune complexes or immunoglobulin[17] and their idea has been reinforced by Faulk *et al*.[18] who displayed that IgG can be repeatedly eluted from villous basement membrane.

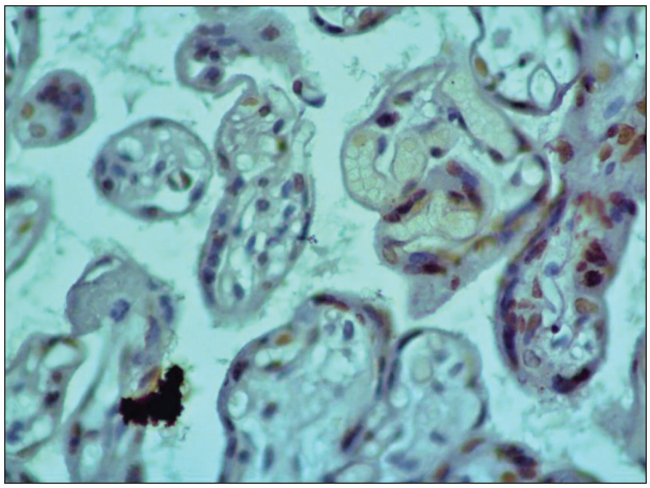

Figure 9: Immunohistochemical reaction of IGF-1 in placental tissues of control subjects 400X. IGF-1: insulin-like growth factor-1

Another moderately significant change observed in this study is the terminal villous edema. Roberts *et al*.[19] stated that with vascular endothelial injury there will be disturbances in the vascular endothelial tight junctional complexes with a concomitant loss of regulated protein and fluid transport which leads to extravasation of fluid and protein from the intravascular compartment. MacPherson[20] indicated that compression of the villous capillaries by the edema was proposed to cause fetal hypoxia and poor Apgar scores by reducing fetoplacental blood flow. Wang *et al*.[21] in their study noted that the

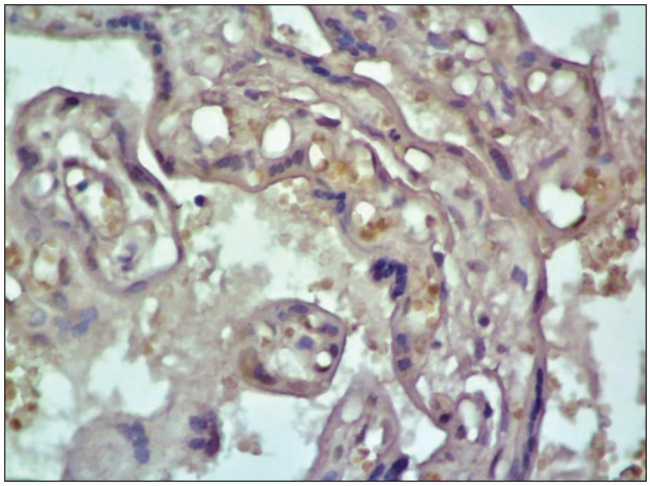

Figure 10: Immunohistochemical reaction of IGF-1 in placental tissues of hypertensive and preeclamptic subjects showing weak +ve reaction (+1) 400X. IGF-1: insulin-like growth factor-1

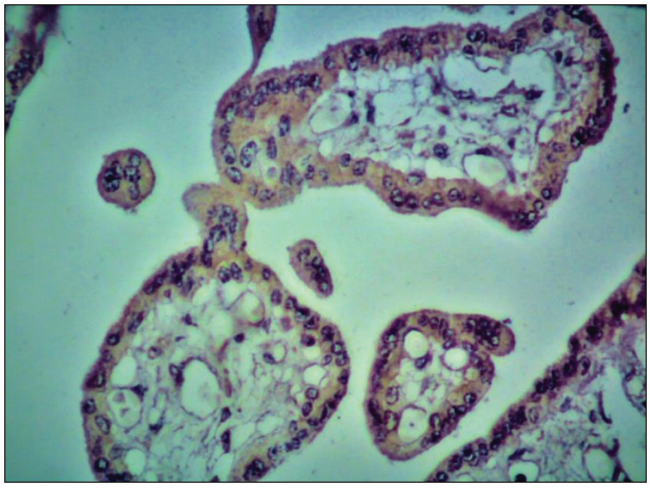

Figure 11: Immunohistochemical reaction of IGF-1 in placental tissues of hypertensive and preeclamptic subjects showing moderate +ve reaction (+2) 400X. IGF-1: insulin-like growth factor-1

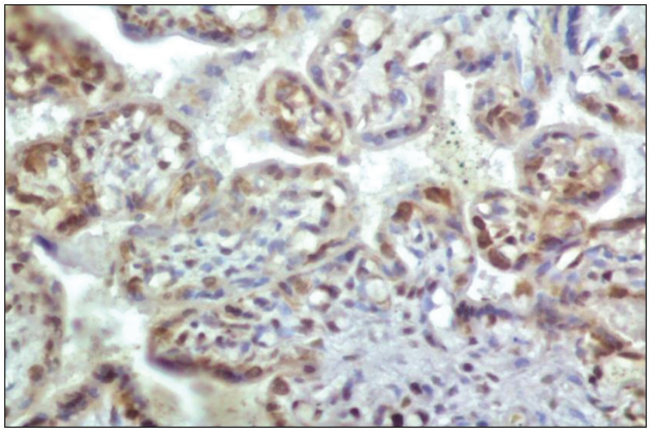

Figure 12: Immunohistochemical reaction of IGF-1 in placental tissues of hypertensive and preeclamptic subjects showing strong +ve reaction (+3) 400X. IGF-1: insulin-like growth factor-1

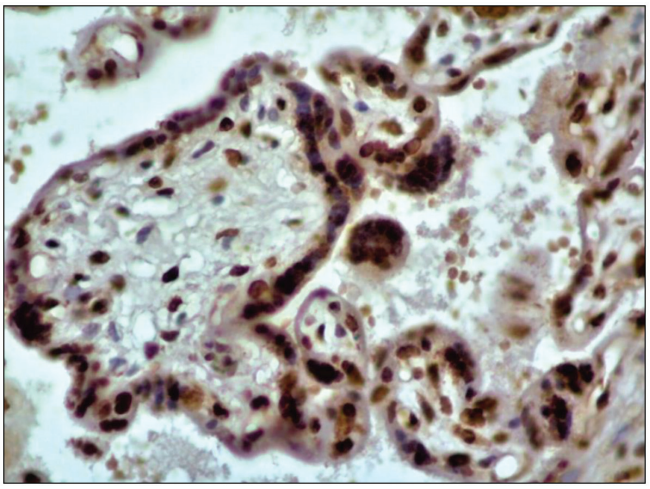

Figure 13: Immunohistochemical reaction of IGF-1 in placental tissues of hypertensive and preeclamptic subjects showing very strong +ve reaction (+4) 400X. IGF-1: insulin-like growth factor-1

Table 3: Total immunohistochemical score of basic fibroblast growth factor marker among three groups

Total score	Group A	Group B	Group C	*P* value
	Mean ± SD	Mean ± SD	Mean ± SD	
Syncytiotrophoblast	0.52±0.09	1.7±0.2	2.8±1.8	0.001
SMC	0.33±0.064	0.455±0.04	1.8±0.46	0.001
CVSC	0.2±0.04	0.31±0.07	0.86±0.1	0.001

CVSC: chorionic villous stromal cell, SD: standard deviation, SMC: smooth muscle cell

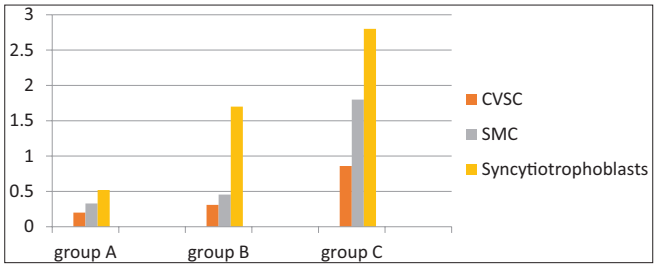

Figure 14: Total score of b-FGF marker among syncytiotrophoblast, smooth muscle cells (SMC), and (CVSC) Chorionic villous stromal cells. b-FGF: basic fibroblast growth factor

relative endothelial cell permeability was significantly increased in cases of preeclampsia, and they explained this lesion as a result of the disorganized and diminished expression of endothelial junctional proteins.

Another study by Wang *et al.*[22] determined a close association between increased endothelial cell permeability and decreased endothelial nitric oxide synthase expression and activity in preeclampsia.

Another highly significant lesion seen in placentae of the preeclamptic group is the acute atherotic changes of the walls of the uteroplacental arteries where the accumulation

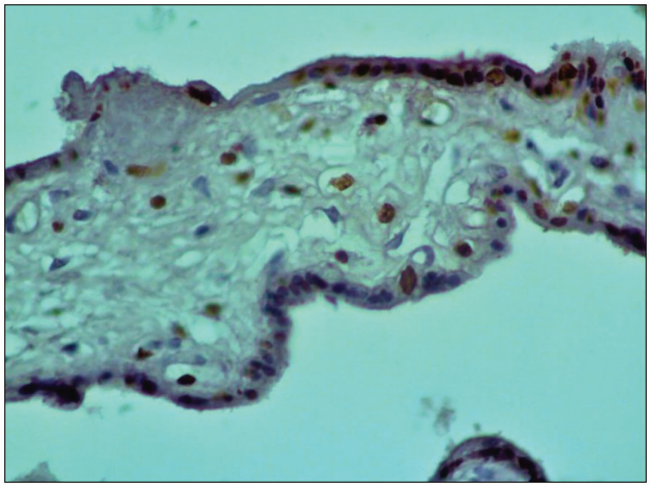

Figure 15: Immunohistochemical reaction of b-FGF in placental tissues of control subjects 400X. b-FGF: basic fibroblast growth factor

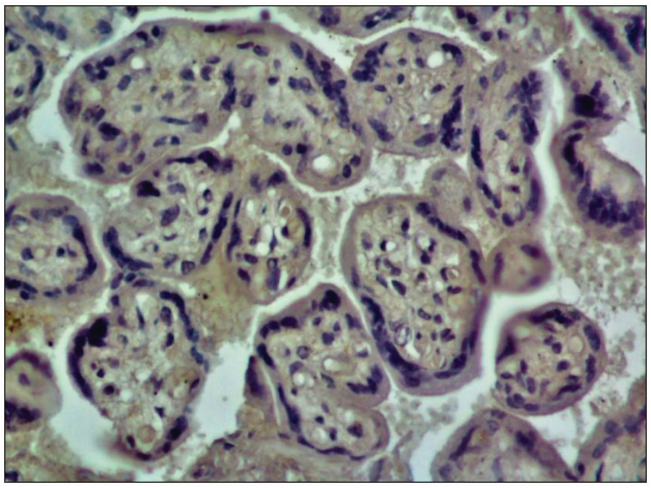

Figure 16: Immunohistochemical reaction of b-FGF in placental tissues of hypertensive and preeclamptic subjects showing weak +ve reaction (+1) 400X. b-FGF: basic fibroblast growth factor

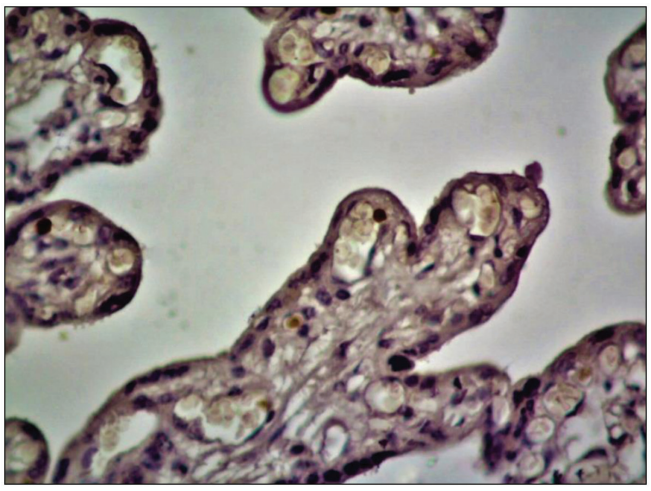

Figure 17: Immunohistochemical reaction of b-FGF in placental tissues of hypertensive and preeclamptic subjects showing moderate +ve reaction (+2) 400X. b-FGF: basic fibroblast growth factor

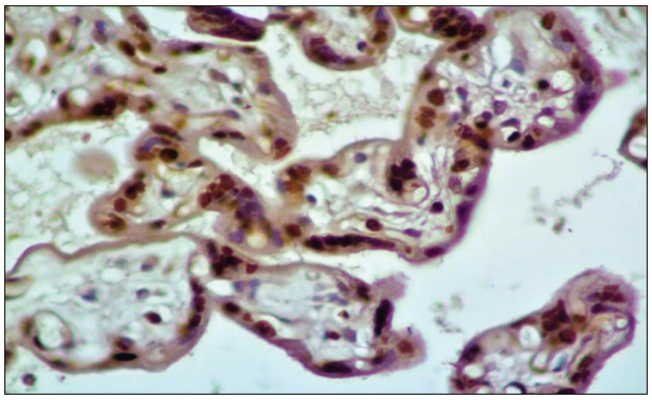

Figure 18: Immunohistochemical reaction of b-FGF in placental tissues of hypertensive and preeclamptic subjects showing strong +ve reaction (+3) 400X. b-FGF: basic fibroblast growth factor

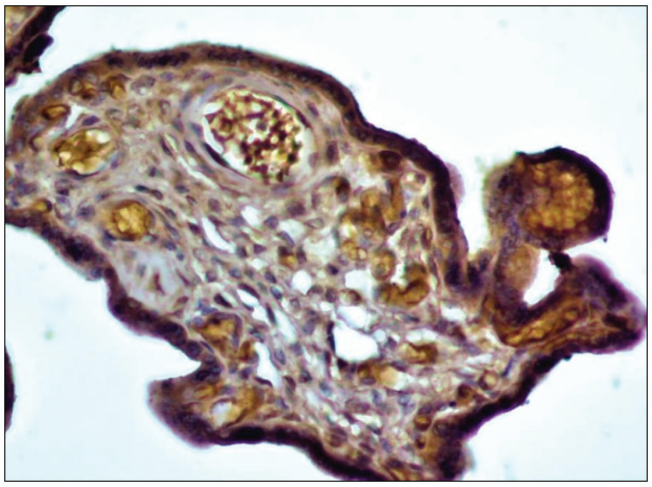

Figure 19: Immunohistochemical reaction of b-FGF in placental tissues of hypertensive and preeclamptic subjects showing very strong +ve reaction (+4) 400X. b-FGF: basic fibroblast growth factor

Table 4: Total score of insulin-like growth factor-1 in syncytiotrophoblast of placental tissues among three groups

Total score of IGF-1	Group A	Group B	Group C	*P* value
	Mean ± SD	Mean ± SD	Mean ± SD	
	0.91 ± 0.07	1.4 ± 0.2	2.2 ± 0.3	0.001

IGF-1: insulin-like growth factor-1, SD: standard deviation

of lipid-laden cells in the arterial wall was clearly evident. This deposition may reflect a response to the increased oxidative stress that is common in preeclampsia and is known to cause vascular wall damage.[23] Salafia *et al*.[24] revealed that lipoprotein-a deposition in the placental spiral arteries is significantly increased in preeclamptic cases compared with the control group. This atheromatous-like lesion seen in preeclampsia could lead to partial or even complete occlusion of the vessel wall and may suggesting an underlying immune mechanism in the development of preeclampsia.[25,26]

The angiogenic growth factor (b-FGF) had a great role in villous proliferation and proper function of trophoblast in addition to its role in angiogenesis,[10] by the formation of new vascular tissue, which altered during preeclampsia.[23] Increased expression of b-FGF in preeclamptic tissue more than placenta of pregnancy-induced hypertension may induce pathological angiogenesis and proliferation of endothelium of blood vessels and this is agreed with the work of many authors in other research.[27,28]

The IGF-1 immunoreaction increased in preeclamptic placental tissue more than other placentas that supported by other researches, which indicate its increase in placental syncytiotrophoblast than other cells and it decreased in bloodstream at this stage.[29-33]

Conclusion

Significant changes appeared in the placentae of hypertensive and preeclamptic mothers, both in histological and immunohistochemical examinations.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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