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Research Paper

HISTOMORPHOLOGICAL AND MORPHOMETRICAL CHANGES OF PLACENTAL TERMINAL VILLI OF NORMOTENSIVE AND HYPERTENSIVE MOTHERS

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Background & Objectives: Placental examination has clinical value in preeclampsia (PE) and IUGR. The luminal diameter of the uterine spiral arterioles in women with PE is narrowed leading to placental ischemia thus causing fetal hypoxia and pathological changes in placenta. The main objective of the present study is to compare morphological and histomorphometrical changes in placentas of preeclamptic and normotensive mothers. Methods: 50 placentas from both vaginal and LSCS delivery were collected at Dept. of OBG in a tertiary care center, half of them from normotensive pregnancies and the rest from preeclamptic mothers. An inclusion criterion for control was normal blood pressure and no proteinuria. Exclusion criteria for both control and study group was DM, obesity, severe anemia or any systemic disorders. Placental thickness, weight, diameter and surface area were recorded. Histopathological sections stained with H&E were observed for surface area and diameter of TV. Results: The mean placental weight in PE was 430 g. The placental diameter was decreased in PE (16 cm) compared to controls (19 cm). Neonatal weight followed the same trend. Histologically, the changes in the TV and blood vessels was significant; there was decrease in the diameter of villi in PE cases(0.01 μm) when compared to controls (0.05 μm). There was significant decrease in the diameter of blood vessels in PE (0.0049 μm) than in controls (0.01 mm). Conclusion: This study has revealed that there are significant changes in the placenta in cases of PE both morphologically and histologically. There is also a need for further studies to prove the molecular and genetic factors involved in preeclampsia.

Keywords: Histology, Hypertension, Morphometry, Placenta, Preeclampsia, Terminal villi

INTRODUCTION

The placenta is an ephemeral organ interposed between the mother and fetus and is vital for the survival of the fetus (Mardi, 2003). Fetal growth depends on the proper development and function of the placenta, which serves to maintain maternofetal interference for the exchange of blood gases, nutrients and waste (Vogel, 2005).

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The placenta, at term, is almost a circular disc with a diameter of 15-20 cm and thickness of about 3 cm at centre. It thins off towards edges. The architecture of the placenta is altered in many maternal diseases such as diabetes mellitus, hypertension, preeclampsia (PE), and eclampsia. Although the placenta is a vital organ, its systemic study has been neglected; however, in recent times, it has evoked great interest, and much work is being conducted to understand the unique biological status of this complex organ. Placental examination has clinical value in cases of PE and Intrauterine Growth Retardation (IUGR), both of which are associated with high perinatal morbidity and mortality accompanied with gross pathological changes in the placenta.

PE is unique pregnancy-related disease that affects 5-7% pregnancies worldwide (Bdolah, 2005). It is associated with hypertension and proteinuria. The primary cause of PE is the widespread apoptosis of cytotrophoblast cells but the disease has a multifocal nature of pathogenesis. The mean luminal diameter of uterine spiral arterioles in women with PE is less than one-third of the diameter of similar vessels from uncomplicated pregnancies (Catwright, 2010). Consequently, uteroplacental perfusion reduces, and the placenta becomes ischemic as gestation progresses. This causes fetal hypoxia as well as morphological and histological changes in the placenta, leading to PE, which contributes to premature delivery and fetal death. It is important to know the pathologic changes in PE to understand the prognosis of disease. This study aims at finding the histological and morphological changes in the placenta complicated by PE.

LITERATURE REVIEW

Hypertension is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. It is a sign of an underlying pathology which may be preexisting or appears for the first time during pregnancy. The identification of this clinical entity and effective management play a significant role in the outcome of pregnancy both for mother and the baby. Hypertension in pregnancy includes gestational hypertension, preeclampsia and eclampsia. This study emphasizes on pregnancies complicated by preeclampsia.

Preeclampsia is a multisystem disorder of varied etiology characterized by development of hypertension to the extent of 140/90 mm Hg or more with proteinuria after the 20th week in a previously normotensive and non proteinuric woman. The preeclamptic features may appear even before 20th week as in case of hydatidiform mole and acute polyhydramnios.

AMERICAN CONGRESS OF OBSTETRICS AND GYNAECOLOGY (ACOG) CRITERIA FOR DIAGNOSIS OF SEVERE PRECLAMPSIA (ACOG, 2002)

Preeclampsia is considered severe if one or more of the following criteria are present,

- Blood pressure of 160mm of Hg, systolic or higher or 110 mm of Hg diastolic or higher, on two occasions at least six hours apart while the patient is on bed rest
- Oliguria of less than 500 mL in 24 h
- Cerebral or visual disturbance

- Pulmonary edema or cyanosis
- Epigastric or right upper quadrant pain
- Impaired liver function
- Thrombocytopenia
- Fetal growth restriction.

Numerous invitro and animal models have been used to study aspects of preeclampsia, the most common being models of placental oxygen dysregulation, abnormal trophoblast invasion, inappropriate maternal vascular damage, and anomalous maternal-fetal immune interactions. Investigations into pathophysiology and treatment of preeclampsia continue to move the field forward, albeit at a frustratingly slow pace. There remains a pressing need for novel approaches, new disease models and innovative investigators to effectively tackle this complex and devastating disorder.

The multiple criteria for the diagnosis of severe preeclampsia illustrate the multifocal nature of the disease. There are multiple theories and little argument about the cause of preeclampsia. The disease is characterized by disruption of vascular remodeling, a systemic antiangiogenic response, oxygen dysregulation, immune changes.

In normal pregnancy cytotrophoblast cells originating in anchoring villi of fetal portion of placenta attach to and invade the maternal endometrium. A subset of these extravillous trophoblast cells acquire endothelial characteristics and invade maternal spiral arteries and plug the arteries maintaining a hypoxic uterine environment in turn replacing some of the endothelial cells of vessel wall and leads to alteration of vessel compliance causing filling up intervillous space of placenta (Kaufmann, 2003).

Hunkapiller and Fisher study also supports this theory of trophoblast invasion where invitro models of trophoblast invasion, including cultured placental explants, primary trophoblast cells, human embryonic stem cells and human choriocarcinoma cells.

These cells are cultured in typical conditions using invasion chambers and thus supporting the theory of invasion. These trophoblast invasion leads to histological changes in terminal villi and blood vessels (Hunka, 2008).

The placental samples examined at term as well as from Doppler ultrasound study of placental perfusion show that the remodeling of spiral arteries is incomplete in patients with preeclampsia (Khong, 1986). Thus poor trophoblast invasion is a vital event in disease progression although it has not been determined whether it is the cause of preeclampsia or a result of another underlying problem. It is hypothesized that without proper remodeling the placenta is deprived of oxygen and that the resulting hypoxia triggers the symptom of preeclampsia and the histomorphological and morphometrical changes in the placenta (Roberts, 2009).

A study was conducted by Wu *et al.* (2010) showing strong evidence that changes in circulating levels of regulators of angiogenesis cause many of the clinically significant symptoms of preeclampsia. Members of the vascular endothelial growth factor family, VEGF-A, VEGF-B and Placental Growth Factor (PLGF) act through membrane receptors to regulate angiogenesis. Binding of VEGF-A to VEGFR-2 or PLGF to VEGFR-1 promotes angiogenesis where as soluble form of FLT-1 (sFLT-1: Fms-like tyrosine kinase-1) inhibits angiogenesis.

Clinical studies conducted by Levine *et al* (2004) demonstrated an increase in circulating levels of sFLT-1 and a significant increase in the ratio of sFLT-1 to PLGF in both early and late onset preeclampsia.

Similarly studies done by Venkatesha *et al*. (2006) demonstrated increased placental expression and circulating concentration of soluble endoglin, an inhibitor of capillary formation are associated with preeclampsia and are positively correlated with disease severity.

There are other studies showing models of oxygen dysregulation in the pathophysiology of preeclampsia. Studies conducted by Abitbol (1982) and Makris *et al.* (2007) used Reduced Uterine Perfusion Pressure (RUPP) model to demonstrate hypoxic stimulus for the changes in preeclampsia. These models used rat for exhibiting RUPP model. A related hypothesis states that hypoxia is not only a result of insufficient trophoblast invasion but a cause for it. These models have been used to examine the effect of hypoxia and hypoxia reperfusion injury on extravillous trophoblast differentiation and invasion (Hunka, 2008).

The studies done on a transcription factor i.e. hypoxia- inducible factor 1α (HIF-1α) assess the role of hypoxia in preeclampsia. These include HIF-1α over expressing transgenic mice (Tal, 2010), knockdown of HIF-1α inhibitor CITED 2 (Withington, 2006) knockout of the COMT enzyme which produces HIF-1α inhibitor 2-methoxyestradiol (Kanasaki, 2008). These models show incomplete remodeling of maternal spiral arteries, fetal and placental growth restriction, hypertension and proteinuria. These hypoxic events lead to changes in the numerical density of blood vessels due to chronic stimulation for angiogenesis.

There are several lines of evidence supporting a role for maternal immune response in the development of preeclampsia. First, several immune associated risk factors increase the probability that a woman will develop preeclampsia including pre existing auto immune disease (Duckitt, 2005; Trogstad, 2011). Second, primiparity, a change of partner and a short initial coitus-to-conception interval are all risk factors for preeclampsia suggesting that the response to paternal antigens play a role (Trogstad, 2011, Basso, 2001). Finally, concentrations of inflammatory cytokines are significantly increased and placental production of anti-inflammatory cytokines IL-10 is decreased in woman with preeclampsia (Kumferminc, 1994; Vince, 1995; Makris, 2006).

A study conducted by Shankar *et al.* revealed that there in increased presence of vasculosyncytial knots in cases of preeclampsia (Sankar, 2012). There are other studies which show there is presence of histological changes in the placenta of mothers whose pregnancies are complicated by preeclampsia. The study done by Devi Shankar *et al*. (2013) concludes there are numerous pathological findings and terminal villi changes in the placentas of PE.

Thus the above studies show conclusively that preeclampsia has a multi factorial nature of pathophysiology leading to both histological and morphological changes in placenta mainly due to ineffective trophoblast invasion, hypoxia and immunological changes.

AIMS AND OBJECTIVES

The main objective of the present study is to compare morphological and histomorphometrical changes in placentas from mothers with hypertension (mainly preeclamptic) with those in

placentas from normotensive mothers, in relation to the surface area and diameter of the terminal villi (TV) and blood vessels.

The study also throws a light upon other pathological changes in the placenta of preeclamptic mothers.

MATERIALS AND METHODS

The study was conducted in a tertiary care center in the months of June and August 2014. 50 placentas were collected at the Department of Obstetrics and Gynecology. Informed consent was obtained from each mother (consent form enclosed) and a clearance from the Institutional ethical Committee was obtained in an appropriate manner.

Half the number of placentas was collected from normotensive pregnant patients (Controls) and the remaining was obtained from patients whose pregnancy was complicated by preeclampsia. Preeclampsia was defined as a blood pressure more than 140/90 mm of hg with protein values more than 300 mg in the 24 h urine or a protein concentration of 1 g/L on two occasions at least 6 h apart.

Placentas were collected from both vaginal delivery as well as LSCS (Lower Segment Caesarian Section) irrespective of the gestational age.

Inclusion criteria for controls were normal blood pressure and no proteinuria. Exclusion criteria for both the control and PE groups was diabetes mellitus, obesity, severe anemia (Hemoglobin <6 g %) and any other systemic or endocrine disorders.

Immediately after the delivery, the umbilical cord was clamped close to the placental insertion point; membranes were trimmed. The placental weight, thickness (thickness at center) diameter and surface area were recorded. For histological studies, full-depth tissue samples were placed in 10% formol-saline solution for 24-48 h and were subsequently embedded in paraffin. The 5 μm thick sections were stained with hematoxylin and eosin. Terminal villi were observed microscopically with a 40x objective. TV was those which had the smallest villi containing capillary loops without any histological artifacts. In addition to TV other pathological findings of placenta were noted.

The following parameters in histomorphometrical analysis were estimated in TV of the control and PE groups.

- Diameter of TV and blood vessels were measured using ocular reticule micrometers.
- The surface area of TV in the control and the PE groups were measured.

Table 1: Macroscopic Findings of Maternal, Neonatal and Placental Parameters in Control and Preeclampsia [Values are presented as mean]

Parameter	Control(n=25)	PE(n=25)
Maternal age (y)	25	28
Gestational age (w)	37	33
Neonatal weight (g)	2,650	2,100
Placental weight (g)	510	430
Placental thickness (cm)	4.15	2.64
Placental diameter (cm)	19	16
Placental surface area (cm^2)	283.38	200.96

The observations were analyzed using SPSS software and the results are tabulated.

OBSERVATIONS AND RESULTS

The placentas collected from both the control and PE groups showed the following results.

The mean maternal age was 25 years in control group and 28 years in the PE group. The mean gestational age in control group was 37 weeks and in PE it was 33 weeks. Infants born to the PE group had statistically and significantly lower gestational age and birth weight than those in the control group. The gross morphological findings of placenta are shown in Table 1.

On gross placental morphometrical study, it revealed that the placental parameters like placental weight, thickness, diameter and surface area were significantly reduced in PE group compared to the control group.

HISTOLOGICAL FINDINGS

The stem villi of the PE placentas showed numerous arteriosclerotic blood vessels with endothelial degeneration presenting progressive fibrosis and subsequent lumen obliteration. These villi had smooth muscle hypertrophy with greatly multiplied numbers of muscle layers in the tunica intima. Stem villi thrombosis seen as atheromatous plaques was observed in the PE placentas.

Perivillous fibrin and intervillous fibrin deposition, which also extended to the intervillous bridges, were observed in the PE cases. The number and structure of TV specifically varied in PE. The total numbers of TV were significantly lesser, indicating distal villous hypoplasia. The paucity of TV was probably because the capillary, which initiates villous sprouting in the placental core, had not been established.

Numerous avascular TV surrounded the arteriosclerotic stem villi, possibly reflecting failure of vascular organization (villitis). TV syncytiotrophoblasts invariably developed clusters and sprouts to form syncytial knots; the PE group had significantly more knots than the control group.

Histomorphometrical findings indicated that the terminal villi diameter as well as the blood vessel diameter was significantly decreased in PE group compared to the control group. The villi diameter was extremely significant with p value of 0.032 and the surface area of the villi was also decreased in PE group but statistically not significant. The findings are tabulated below in Table 2.

DISCUSSION

Pregnancies complicated by PE are reflected in the placenta both macroscopically and microscopically. Although the placenta adapts well to the hypoxic condition in PE, the compensatory

Table 2: Histometrical Parameters of Placental Terminal Villi and Blood Vessels in Control and PE Groups [Values are Presented as Mean]

Parameter	Control(n=25)	PE(n=25)
Villi diameter (μm)	0.05	0.01
Villi surface area (μm^2)	0.00196	0.000078
Blood vessel diameter (μm)	0.01	0.0049

changes that occur are insufficient. These compensatory changes cause maldevelopment and inadequate placental mass, causing placental dysfunction that leads to oxidative stress and chronic fetal hypoxemia (Myatt, 2002).

In the present study comparing preeclamptic placentas to control placentas, the mean placental weight, thickness, diameter, and surface area were decreased and were found to be more significant. The macroscopic changes found in the study are analogous to the findings of other PE cases in the literature. The gross reduction of the PE placenta impedes normal placentation and pathologically results in massive microscopic changes in the placenta.

In contrast to the histomorphometrical findings in the normal placentas, changes in the PE placentas cause functional disturbance, which is the result of the oxidative stress/hypoxic conditions due to PE. The surface areas, villi diameters, and blood vessel diameters of the placentas in PE cases were lesser than those of controls in the present study.

In normal placentation, during the first and early second trimesters, the villous growth and arborization are regulated, which are necessary for fetal well being.

The cytotrophoblast cells invade into the uterine spiral arteries and transform them from small-caliber resistance vessels into high-caliber capacitance vessels capable of providing enhanced placental perfusion adequate for the growing fetus. For this transformation, a certain amount of hypoxia is needed to stimulate placental blood vessel formation. Until approximately 10 weeks of gestation, the embryo exists in a hypoxic environment with nutrients provided by the endometrial glands. However, prolonged durations of hypoxia or oxidative stress leads to poor placental perfusion, which is the underlying pathogenesis of PE.

In PE, invasion of the uterine spiral arteries is limited to the proximal decidua, and 30-50% of the spiral arteries of the placental bed escape endovascular trophoblast remodeling. Persistence of muscular and elastic tissues of the media of spiral arteries, fail to dilate and remain responsive to vasomotor influences that lead to high resistance low flow choriodecidual circulation.

The reduction in the vascular dimensions is constantly accompanied by a significant impact on the lumen of the arteriole with changes in its muscular wall. Thus, the average diameter of the blood vessels, which normally expands to 4 times their original size, is greatly decreased in PE.

In the present study there is significant decrease in the diameter of blood vessels. This decrease in lumen ultimately fails to replicate and establish a network into TV. This results in the complete absence of capillaries in the TV in most vicinities of the placenta, leading to the formation of avascular villitis. Consequently, the resultant decreased perfusion causes oxidative stress.

There are studies which show that due to chronicity of hypoxic stimulation, the density of blood vessels and villi are increased and it is believed that the increased villi density and decreased villi diameter in PE cases may have occurred because of the continuous sprouting of the intermediate villi into TV in order to compensate for the placental maldevelopment and dysfunction.

Placental architecture is altered in many maternal diseases such as PE and eclampsia.

Placental weight in women with PE is directly proportional to neonatal birth weight. The present study showed that both morphological and histological changes in the PE placenta such as decreased weight, thickness, and diameter of villi and vessels which are said to be the pathogenesis involved in maternal and fetal morbidity and mortality in women with PE.

CONCLUSION

This study has revealed that there are both histological and morphometrical changes in the placenta of mothers whose pregnancy is complicated by preeclampsia. There is significant decrease in the placental morphological features like weight, thickness, surface area etc. compared to the placenta of normal pregnancies. The histological findings are also significant in cases of preeclampsia. There is decrease in the diameter of villi and blood vessels. Placental changes have a direct effect on outcome of pregnancy like intrauterine growth retardation. Therefore the changes in PE have direct adverse affect on neonatal weight.

It can be concluded that preeclampsia has a multifocal nature of origin and has significant changes in placenta. This study brings out both the morphological and histological changes present in cases of PE by comparing with the normal placentas.

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