Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: www.saspublishers.com

OPEN ACCESS

Pathology

Histopathological Changes of Placenta in Toxemia of Pregnancy

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| **Received:** 11.03.2019 | **Accepted:** 23.04.2019 | **Published:** 30.04.2019
DOI: 10.36347/sjams.2019.v07i04.001

Abstract | **Original Research Article**

Introduction: The growth and development of fetus during pregnancy depends upon placenta as it is responsible for continuation and progression of a pregnancy in addition to fetal nutrition Study was carried out to investigate the morphological changes in pregnancy induced hypertension and to evaluate whether any specific morphological findings have consistent association with respect to its severity. ***Aim:*** To study the morphological features of placenta in toxemia of pregnancy and correlate these findings with respect to severity of pregnancy induced hypertension. ***Material & Methods:*** The present study was conducted in the Department of Pathology in collaboration with Department of Obstetrics and Gynecology, Teerthanker Mahaveer Medical College, Moradabad during February 2017 to September 2018. The cases were graded for degree of pregnancy induced hypertension, placental gross features and microscopic findings on routine hematoxylin and eosin staining. ***Result:*** Majority of cases had eclampsia (n=16; 64%). There were 7 (28%) cases diagnosed as preeclampsia and 2 (8%) as preeclampsia with superimposed eclampsia. Most of them (52%) wereyoung adults (20-25 years), from rural background (84%) and were nullipara (60%). 88% cases were anaemic. On gross examination 60% of placenta were circular in shape and rest were oblong with number of cotyledons ranging from 3 to 12.Histopathological changes in placenta and foetoplacental weight ratios (FPWR) showed a significant association with severity of anemia.FPWR was significantly lower in cases with eclampsia/PE with superimposed eclampsia as compared to those with preeclampsia. Amongdifferent histopathological features, presence of syncytial knots (84%) was most common finding. ***Conclusion:*** The findings of present study showed that morphological and histopathological changes take place in toxemia affected placenta and this change is affected by clinical severity of toxemia.

Keywords: Placenta, Toxemia of pregnancy, Histopathological changes.

INTRODUCTION

Placenta is extracorporeal organ on which the human fetus is totally dependent during the entire nine months of intrauterine life[1], upon which fetal growth and its culmination into a healthy live birth during pregnancy depend. However, some maternal conditions, such as inadequate nutrition, diabetes, obesity and pregnancy induced hypertension, are known to induce toxemia during pregnancy and adversely affect placental function, with negative impact on the fetus and newborn[2]. It is also noted that pregnancy induced hypertension (PIH), one of the hypertensive disorders of pregnancy, affects about 5-8% of all pregnant women worldwide[3]. In pregnancies complicated by hypertension a number of changes in placental villi take place. These villous changes are manifested as cytotrophoblastic proliferation, paucity of vasculosyncytial membrane, trophoblastic basement membrane thickening and fibrinoid necrosis of villi. It has been shown that these changes are directly correlated with the severity of disease and perinatal outcome is worse with advancing grades of hypertension[4]. The complications of hypertensive disorders in pregnancy have been attributed to abnormalities in placental morphology. Placental infarctions are the most common lesions and their presence is indicative of pathological involvement. If they are numerous, thick, centrally located and randomly distributed, placental insufficiency may develop. Avascular villi and villitis are more frequent in preeclampsia and subsequently necrosis of villous tissue develops from ischemia, thus explaining the relationship between hypertension and placental pathologies. Placenta are examined macroscopically

and microscopically for a variety of reasons - diagnostic, either for the mother or for the neonate, prognostic prediction of future pregnancies, investigative and for legal purpose.

MATERIALS AND METHODS

Study Area and Design: The present study was done in the Department of Pathology in collaboration with the Department of Obstetrics and Gynaecology, Teerthanker Mahaveer Medical College and Research Centre (TMMC&RC), Moradabad, during the period from February 2017 to September 2018. Study was of descriptive type after satisfying inclusion and exclusion criteria, having sample size 25, which were collected from Obstetrics and Gynaecology department

Ethical Considerations :Clearance for the project was obtained from the Institutional Ethical Committee. Immediately after delivery, placenta along with membranes and umbilical cord was collected, washed in running tap water, labeled, cut and then fixed in 10% neutral buffered formalin. Gross and microscopic examination of the placenta was carried out in Department of Pathology of TMMC& RC. Parameters like placental weight, diameter and thickness, shape and number of cotyledons were noted. Morphological and histopathological features like infarction, calcification, hematoma, syncytial knot formation, cytotrophoblastic cell proliferation, hyalinization, proliferation of blood vessels, stromal fibrosis and fibrinoid necrosis were noted.

All placenta were cut along maximum diameter in two equal halves and then were further cut in small pieces. After overnight fixation slides were prepared and stained with Hematoxylin and Eosin (H&E).

Microscopic study

One hundred villi were counted from each of the four sections obtained and histological changes expressed as percentage. To fulfill this criteria, eight random microscopic fields were chosen and hundred villi were counted in each field and studied for the presence of the following criteria:

1. Syncytial knots > 30 % per field
2. Fibrinoid necrosis > 5 % per field
3. Placental infarction > 5% per field
4. Hematoma – Present/absent
5. Calcification – Present/absent
6. Stromal fibrosis > 5 % per field
7. Hyalinization – Present/absent
8. Proliferation of medium sized blood vessels – Present/absent

Feto-Placental Ratio (FPR): This was calculated by dividing the weight of baby with the weight of placenta. Data so collected was recorded on a semi-structured proforma and fed in MS-Excel 2013 worksheet which was subsequently subjected to statistical analysis.

Data Management and Statistical Analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 22.0 statistical Analysis Software. Qualitative data was expressed in terms of frequency and percentage. Chi square test was used for this data. Quantitative data was expressed in terms of mean ± SD. Independent samples't' test (Student 't'-test) and Analysis of Variance (ANOVA) were used to compare this.

OBSERVATIONS AND RESULTS

In present study age of mothers ranged from 20 to 36 years. Majority (n=13; 52%) were aged 20-25 years. Only 1 (4%) was aged >35 years. Mean age of patients was 26.76$\pm$4.34 years.

Majority of patients (n=21; 84%)belonged to rural area, and were nullipara (60%) with 5 of them were para 1(20%) and remaining 5 (20%) multiparous. None of the patients had parity>4.None of the patients had previous history of hypertension, diabetes, tuberculosis, jaundice, drug intake, alcohol or smoking.

On clinical examination, pallor was seen in 22 (88%) cases while pedal edema was noted in 19 (76%) cases. None of the patients had icterus, clubbing or lymphadenopathy. Presence of pallor and pedal edema are known and recognized signs of toxemic pregnancy, however, there presence alone does not confirm the diagnosis of a toxemic pregnancy. Despite non-specific nature of these factors, these signs are useful clinically for early identification and screening for preeclampsia. On systemic examination, none of the patients had any cardiovascular abnormality.

Fetoplacental ratio ranged from 2.9 to 7.2. Maximum (n=12; 48%) had fetoplacental ratio <5, followed by those having fetoplacental ratio in 5-6 range (44%). There were only 2 (8%) patients with fetoplacental ratio >6. Mean fetoplacental ratio was 4.96$\pm$0.99.

Table-1: Distribution of patients according to morphological and histopathological characteristics of placenta

SN	Finding	No.	%
1.	Shape		
	Circular	15	60.0
	Oblong	10	40.0
2.	Mean placental thickness±SD (Range) in cm	1.54±0.31 (1.2-2.3)	
3.	Mean placental diameter±SD (Range) in cm	13.38±1.02 (12-15)	
4.	Mean placental weight±SD (Range) in gm	367.12±32.03 (320-420)	
5.	Mean No. of cotyledons±SD (Range)	7.56±2.40 (3-12)	
6.	Vascularity		
	Hypovascular	19	76.0
	Normal	6	24.0
7.	Infarction	6	24.0
8.	Calcification	11	44.0
9.	Retroplacental hematoma	4	16.0
10.	Syncytial knot	21	84.0
11	Cytotrophoblastic proliferation	14	56.0
12	Fibrinoid necrosis	12	48.0
13	Hyalinization	13	52.0
14	Proliferation of medium sized blood vessels	1	4.0
15.	Stromal fibrosis	20	80.0

Among different histopathological features, presence of syncytial knots (84%) was most common finding followed by stromal fibrosis (80%), hypovascularity (76%), cytotrophoblastic proliferation (56%), hyalinization (52%), calcification (44%), infarction (24%), retroplacental hematoma (16%) and proliferation of medium sized blood vessels (4%) respectively [Tab: 1, Figure: 1-4].

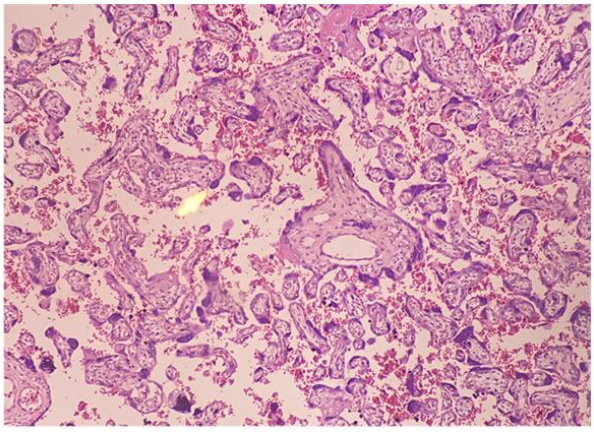

Fig-1: Shows Syncytial knot

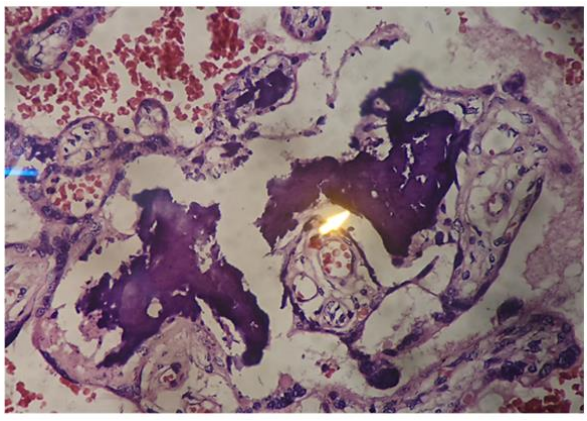

Fig-2: Shows calcification

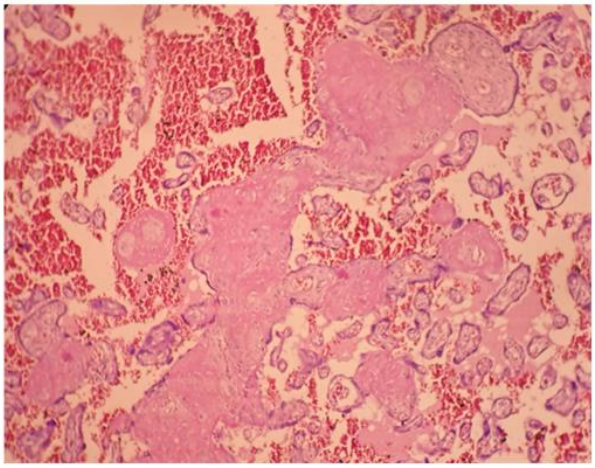

Fig-3: Shows placental infarcts demonstrates pale, necrotic chorionic villi

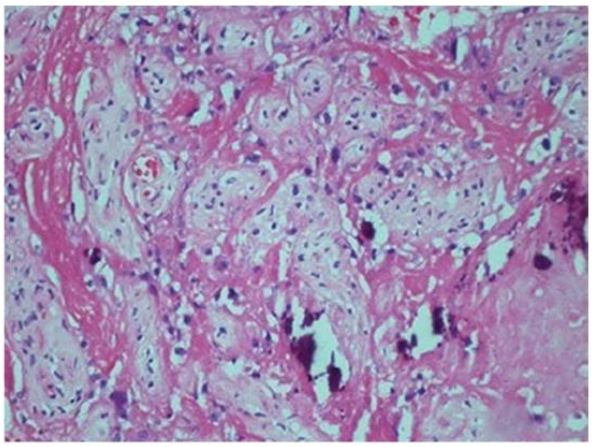

Fig-4: Shows stromal fibrosis

All the cases with preeclampsia had circular placenta, however, majority of cases with eclampsia/PE with superimposed eclampsia (55.6%) had oblong placenta. Statistically, this difference was significant (p=0.020). Mean placental thickness, diameter and weight were 1.46±0.21 cm, 13.11±1.01 cm and 358.78±31.66 gm respectively in cases with eclampsia/PE with superimposed eclampsia as compared to 1.76±0.44 cm, 14.07±0.73 cm and 388.57±22.77 gm respectively among those having preeclampsia. Statistically, the difference between two groups was significant for all the three parameters (p<0.05). Although mean number of cotyledons was also higher in those having eclampsia/PE with superimposed eclampsia (8.06±2.26) as compared to those having preeclampsia only (6.29±2.43) yet this difference was not significant statistically (p=0.098).

In eclampsia/PE with superimposed eclampsia group, presence of syncytial knots (88.9%) was the most common histopathological finding followed by stromal fibrosis (83.3%), hypovascularity (77.8%), cytotrophoblastic proliferation (66.7%), fibrinoid necrosis (61.1%), calcification (55.6%), hyalinization (50%), infarction (27.8%) and retroplacental hematoma (16.7%) respectively. None of the cases in this group showed proliferation of medium sized blood vessels.

On the other hand, in preeclampsia group, presence of syncytial knots, hypovascularity and stromal fibrosis were most common histopathological findings seen in 5 (71.4%) cases each followed by hyalinization (57.1%) and cytotrophoblastic proliferation (28.6%).

On evaluating the difference between two groups, the difference was not found to be significant statistically (p>0.05) for any of the histopathological features.

Mean FPR was found to be significantly higher among those with preeclampsia (5.67±0.82) as compared to that in eclampsia/Eclampsia with superimposed preeclampsia (4.68±0.93) (p=0.021).

No significant association between severity of anemia and shape of placenta could be seen (p=0.688). However, mean placental thickness, placental diameter and placental weight of mothers having Hb<10 g/dl was significantly lower as compared to that of mothers having Hb in 10-12 g/dl

range. On the other hand, mean number of cotyledons were significantly higher in mothers having Hb<10 g/dl as compared to that of mothers having Hb levels in 10-12 g/dl range (p=0.019).

In women with Hb<10 g/dl, syncytial knots and stromal fibrosis (92.3% each) were the most common histopathological findings followed by hypovascularity (84.6%), fibrinoid necrosis (69.2%), calcification (46.2%), hyalinization (46.2%), infarction (23.1%) and retroplacental hematoma (15.4%) respectively. None of the cases showed proliferation of medium sized blood vessels.

In women with Hb 10-12 g/dl too, syncytial knot was the most common finding (75%) followed by hypovascularity and stromal fibrosis (66.7% each), cytotrophoblastic proliferation and hyalinization (58.3% each), calcification (41.7%), infarction and fibrinoid necrosis (25% each), retroplacental hematoma (16.7%) and proliferation of medium sized blood vessels (8.3%) respectively.

Statistically, a significant difference between two groups was observed for fibrinoid necrosis which was seen in significantly higher proportion of women with Hb<10 g/dl (69.2%) as compared to those with Hb 10-12 g/dl (25%) (p=0.047). For all the other histopathological features, there was no significant difference between two groups. Mean FPR was also found to be significantly higher among those with Hb$\geq$10 g/dl (5.40$\pm$0.50) as compared to that in women with Hb<10 g/dl (4.55$\pm$1.16) (p=0.028).

DISCUSSION

Toxemic conditions like preeclampsia and eclampsia during pregnancy have an impact on the placental function. It has been shown that pregnancies complicated by hypertension impair placental function, in terms of abnormal placental weight or histology and may account for the phenomenon of obstetrical and fetal or neonatal complications that are quite frequent in pregnancy induced hypertension[5].

The present study was planned to study the histomorphological features of placenta in toxemia and determine its clinical significance. Placental morphology and histopathology was evaluated in a total of 25 placenta obtained from women with pregnancies complicated by hypertensive disorders, *viz.*, preeclampsia and eclampsia.

The age of women enrolled in the study ranged from 20 to 36 years. This is generally the most common age group of pregnant women in India where 20 to 30 years of age is generally considered to be the best age for motherhood. Although the present study had 4.8% of cases above age >35 years, which is termed as advancing age pregnancy and is more susceptible to hypertensive disorders thus specifying that the advancing age of women was not a major issue in present study.

The present study had a dominance of women from rural areas (84%). These findings are in agreement with the observation of a recent study that has shown that in India preeclampsia is significantly higher in rural women as compared to that in urban women[6].

Majority of patients in present study were nullipara (60%). Relationship between preeclampsia and parity is well known. A number of studies have shown that women in their first pregnancy have a higher risk of preeclampsia [7, 8]. Dominance of nulliparous women in present study also endorsed this risk.

In present study, clinically women were characterized by presence of pallor (88%) and pedal edema (76%). Presence of pallor and pedal edema are known and recognized signs of toxemic pregnancy [9,10] however, there presence alone does not confirm the diagnosis of a toxemic pregnancy.

All the women enrolled in the present study were anemic (Hb<12 g/dl). Keeping in view the fact that majority of women in present study (84%) were from rural areas and most of the women were from economically deprived classes could be responsible for high prevalence of anemic women in our study and for determining the pattern of placental growth[11-13]. This is an important finding and shows that the clinical impact of anemic levels could be associated with the morphological and histopathological changes in placenta.

In present study, the underlying etiology for toxemia was recognized as eclampsia, preeclampsia and preeclampsia with superimposed preeclampsia in 64%, 28% and 8% cases respectively. Tangirala and Kumar similar to our study followed a non-purposive sampling design and included 54 cases of mild, 36 cases of severe preeclampsia and 10 cases of eclampsia in their study

In present study, oblong placenta was seen in 40% cases. Placental thickness ranged from 1.2 to 2.3 cm, diameter ranged from 12 to 15 cm and Placental weight ranged from 320 to 420 gm. No. of cotyledons ranged from 3 to 12. Mean placental weight in toxemic pregnancies in present study was less than 400 gm which is similar to the observation made by a number of previous studies[14-19].

The present study found mean placental diameter as 13.38 cm which was close to that observed by Kulandaivelu *et al.*[20] who reported it as 13.59 cm. Kulandaivelu *et al*.[20] reported the placental thickness of hypertensive women to be 1.23 cm while Qureshi *et al.* [21] reported it as 2.2 cm, Singh and Gugapriya[16] reported it as 2.39 cm. The reason for variance in placental thickness measurements and difference between the two groups in different studies could be owing to difference in method of measurement in different studies. Incidentally, placental thickness is not even throughout the placenta. It is maximum at the centre and minimum in the area between periphery and centre. In present study, in order to avoid a discrepancy we took average thickness taken at three different points in the three arbitrary chosen locations in placenta.

In present study, among different histopathological features, presence of syncytial knots (84%) was most common followed by stromal fibrosis (80%), hypovascularity (76%), cytotrophoblastic proliferation (56%), hyalinization (52%), calcification (44%), infarction (24%), retroplacental hematoma (16%) and proliferation of medium sized blood vessels (4%) respectively. Many authors have found increased syncytial knots to be a characteristic finding in toxemic pregnancies *that is similar to our studies.*

In present study, fibrinoid necrosis was seen in 77.5% of cases in hypertensive group. It is a quite common finding in toxemic pregnancies and has been reported to be seen in as high as 100% of cases [20, 21]. Akhlaq *et al.* and [22] Nahar *et al.*[23] in their study reported it in 88% and 80% of their cases.

The present study also found hypovascularity as one of the most common findings (76%). Findings like stromal fibrosis and hypovascularity are dependent on the severity of hypertension and have been more commonly encountered in cases with severe hypertension[24].

In present study cytotrophoblastic cellular proliferation was seen in 56% of cases, hyalinization and calcification in 52% and 44% cases. We found supportive evidence from Nag *et al.*[25], Motwani*et al.*[14] Kambale *et al.*[26] and Porwal *et al.*[27]. Motwani *et al.*[14] in their study reported hyalinized areas in 46.66% of hypertensive cases, which is close to that reported in present study.

In present study, stromal fibrosis were seen in 80% of cases. Compared to this, Rana *et al.*[28] reported stromal fibrosis in 40% of hypertensive cases but Porwal *et al.*[27] reported it in 63.3% cases. Our findings are in close proximity with the observations of Das *et al.* [29] who reported it in 72.5% of cases. In present study, proliferation of medium sized vessels was seen in only 4% of cases. Motwani *et al.*[14] also reported it in terms of mean % as 4.19% of hypertensive cases.

The present study observed fetoplacental ratio ranging from 2.9 to 7.2. Mean fetoplacental ratio was 4.96±0.99. Normally, fetoplacental weight ratio varies between 6 to 8, thus the FPWR was much lower than the normal range. The reason for this could be malnutrition in the pregnant women in our settings, as most of the pregnant women belonged to lower socio-economic class where malnutrition is quite rampant. Similar to present study, Kambale *et al.*[26] in their study reported FPR in cases as 5.38 which is much below the ideal range of 6 to 8.

One of the interesting findings of the study was an overlapping anemia in all the cases and severity of anemia seemed to affect the placental morphology and histopathology similar to severity of toxemia observed in terms of hypertensive disorder. Relationship between placental morphological and histopathological features and severity of toxemia has also been reported in earlier studies too[14,26,24].

CONCLUSION

The findings of present study showed that morphological and histopathological changes take place in toxemia affected placenta, which is affected by clinical severity of toxemia as well as presence of anemia. These changes can be detected early by thorough sonological examination of placenta resulting in early diagnosis and timely intervention. The present study was, however, limited by absence of a control group and a small sample size, owing to which it is suggested that morphological and histopathological changes in placenta should be studied in context with severity of toxemia only.

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