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Placental Abnormalities and Adverse Perinatal Outcomes in High-Risk Pregnancies: A Prospective Analytical Study among Mothers Delivering In a Tertiary Care Hospital Of Maharashtra, India.

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Abstract:
Background*: The placenta is considered the most accurate record of the pre-natal experiences of infants. Examination of the placenta in high-risk pregnancy yields information regarding the nature and duration of processes that have occurred during the gestational period. The present study was conducted to assess the incidence of placental abnormalities in high-risk pregnancies and its association with adverse perinatal outcomes.*
Materials and Methods*: The present study was a prospective observational study carried out in a tertiary care teaching hospital of Maharashtra, India for 18 months. The population for the study was pregnant women of ≥37 weeks of gestation. The women were divided into two groups of 50 mothers each, Group A having uncomplicated pregnancies and Group B having women with high-risk pregnancies. Following the birth of the babies, the placenta was collected from each of the women and examined grossly and histopathologically.*
Results*: The mean age of the study participants of Groups A and B were 24.02±2.42 years and 24.72±2.85 years respectively. The mean gestational age was 38.6±0.9 weeks and 38.4±1.0 weeks respectively. The incidence of stillbirth, low-birth-weight babies, neonatal infections, neonatal intensive care unit (NICU) admission, and neonatal mortality were significantly higher among high-risk mothers as compared to the control group mothers. The group B mothers had significantly lighter and thinner placenta. On gross examination, they had significantly higher incidence of maternal surface abnormalities but not in fetal surface abnormalities. Histopathology showed that group B mothers had significantly higher incidence of basal plate and villous abnormalities as compared to group A mothers. Significant association were observed between different placental abnormalities and adverse perinatal outcomes among the mothers.*
Conclusion: *The findings of the present study indicate that examination of placental morphology and histopathology after delivery can be of value in predicting neonatal health.*
Key Word*: Placental abnormalities, low-birth weight, neonatal mortality, high-risk pregnancies, India.*

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I. Introduction

The placenta is a matter of interest and curiosity for ages because of its unparalleled importance in the intrauterine development of the human being. The placenta acts as a mirror reflecting the intrauterine status of a fetus. It is considered the most accurate record of the pre-natal experiences of infants, so the study of the placenta and umbilical cord gives valuable clues in cases of adverse fetal outcomes.[1] However, despite its importance, placental pathology has historically received very little attention from obstetricians and pathologists.[2]

The placenta connects the fetus to the uterine wall thereby allowing an exchange of gases, nutrient uptake, and waste elimination through the maternal blood supply.[1] A well-nourished and healthy newborn is the best evidence of adequate placental circulation. Furthermore, the placenta, being a fetal organ shares the same stress and strain to which the fetus is getting exposed in-utero. Thus, any disease process affecting the mother and fetus also has a great effect on the placenta. The fetus, placenta, and mother form a composite triad of dynamic

equilibrium, and dysfunction in any one of them can affect the others.[3] So, the study of the placenta and umbilical cord gives beneficial clues in cases of adverse fetal outcomes.[4] Any disturbances in maternal health affect the placenta, leading to reduced placental perfusion and in turn, causing fetal mortality and morbidity. Disturbance in the placental function itself can affect fetal growth. The numerous placental changes bear a direct relation to the severity and duration of the disease process and so help in the assessment of the degree of fetal insult in-utero and form an essential part of pre-natal or fetal autopsy and help in adding important or conclusive information.[5]

Examination of the placenta in a high-risk pregnancy therefore has its value as it yields information regarding the nature and duration of processes that have occurred during the gestational period. Such evaluation requires thorough and thoughtful gross examination, careful sectioning, and a clear understanding of the basic microscopic features and the numerous changes in a list of pathologic processes.[6] However, published research exploring this topic, especially in the Indian subcontinent is scarce. Therefore, to address that gap, the present study was conducted with an aim of finding out the incidence of placental abnormalities in high-risk pregnancies and comparing them to that of uncomplicated pregnancies among women presenting to a tertiary care hospital of Western India. The study further assessed any association between placental abnormalities and adverse perinatal outcomes among the women.

II. Material And Methods

Study design: The present study was a prospective observational study with an analytical design.

Study area: The study was carried out in the department of Obstetrics and Gynecology of a tertiary care teaching hospital of Maharashtra, a state of Western India.

Study duration: The study was conducted for 18 months, from April 2021 to October 2022

Study population and inclusion criteria: The study was carried out among pregnant women of ≥37 weeks of gestation. The women were divided into two groups, Group A having uncomplicated pregnancies and Group B having women with high-risk pregnancies. For the purpose of the study, a high-risk pregnancy was defined as a pregnancy which was complicated by one of the following risk factors:

1. Pre-eclampsia/eclampsia/Hypertension in pregnancy
2. Gestational diabetes mellitus
3. Anemia in pregnancy
4. Oligohydramnios
5. Placenta previa
6. Abruptio placenta
7. Intrauterine growth restriction
8.

Exclusion criteria: The exclusion criteria for the present study were:

1) Pregnant women other than primigravidae.
2) Pregnant women < 21 years and > 35 years.
3) Gestational age < 37 weeks.
4) All non-consented pregnant women under inclusion criteria.
5) HIV, HBsAg, Tuberculosis, and Syphilis complicating pregnancy.
6) Pregnant with known medical/ surgical/ obstetrical complications
7)

Sample size and sampling technique: The sample size for each group was calculated as per the data reported by Natarajan et al. The calculated sample size was 49 in each group, which was rounded off to 50.[7] A consecutive sampling technique was adopted. Mothers fulfilling the inclusion criteria and not excluded as per the exclusion criteria were recruited in each of the two study groups. The mothers recruited in the two study groups were matched according to their age (±2 years) and gestational age (±1 week).

Study methodology: After the recruitment of the eligible women into the two study groups, written informed consent was obtained from them. Following that, a predesigned pre-tested questionnaire was administered to obtain socio-demographic data from each of the participants. The women were then followed up to their delivery, the characteristics of which were also noted. Following the birth of the neonates, the placenta was collected from each of the women and were washed with tap water after checking for retroplacental clots and drained off its blood. On initial examination of the placenta, any gross abnormality of shape, structure, and umbilical cord insertion, morphometric measurements like weight, thickness, and measurement of cord length were noted. A gross examination of the maternal surface and fetal surface of the placenta were done and abnormalities were noted. After gross examination, each placenta was kept in a container in 10% formalin solution and transported

to the pathology department of the institution for gross and histopathological examination along with case record proforma with mentioned details.

After 'fixation' with 10% formalin for 48 hours, 'sections' were made from the umbilical cord, membranes, and placental tissue of each placenta. The sections made from each placenta were kept in 'tissue cassettes' of particular determined sizes, and kept in an 'automatic tissue processor' for 12 hours. After getting processed with a tissue processor, 'Block embedding' of tissue was done by fixing it with paraffin wax in tissue molds followed by 'Block cooling' of paraffin molded tissue, followed by trimming and cutting, following which they were transferred to slides. These slides were kept in xylene solution for half an hour for 'Dewaxing' and then proceeded with 'Staining' with Hematoxylin and Eosin. After staining, the slide was mounted in DPX mountant (refractive index-1.52) and then proceeded with microscopy of a mounted slide. Each slide was examined under microscope, first under low power and then under high power for pathology. Histopathology of the basal plate, membrane, umbilical cord, and villous pathology of each placenta were examined separately. 8 random microscopic fields were chosen and 100 villi were counted in each field for the study.

Abnormal Histopathological Findings noted on microscopy were recorded under the following heads:

1. Basal plate:
    - Infarct
    - Abscess
    - Inflammation
    - Fibrinoid necrosis
    - Thrombosis
2. Villous pathology:
    - Syncytial knots
    - Fibrinoid necrosis
    - Basement membrane thickening
    - Stromal fibrosis
    - Cytotrophoblast proliferation
    - Infarct
    - Villous hypervascularity
    - Intervillous hemorrhage
3. Membrane & cord pathology:
    - Inflammation
    - Necrosis
    - Vessel count
    -

Statistical analysis: The data thus collected were entered in a Microsoft™ Excel spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 25.0. The data were presented as proportions and percentages for categorical variables and mean and standard deviation for continuous variables. Principles of analytical statistics were followed to compare between the two groups. A P-value of <0.05 was considered to be statistically significant.

Ethical considerations: Clearance and appropriate permissions for the present study were obtained from the administration and the institutional ethics committee of the study institution before conducting it (MUHS/EC/31/2021). Written informed consent was obtained from each of the study participants. Anonymity and confidentiality of the information was ensured.

III. Result

Two groups of 50 patients each were studied. Group A consisted of women with uncomplicated pregnancies and Group B consisted of women with high-risk pregnancies. The mean age of the study participants of Groups A and B were 24.02±2.42 years and 24.72±2.85 years respectively. The mean gestational age was 38.6±0.9 weeks and 38.4±1.0 weeks respectively. There was no statistically significant difference between the two study groups with respect to their maternal and gestational age. The incidence of stillbirth was significantly higher in the Group B (16%) as compared to Group A (4%). The incidence of low-birth-weight babies, neonatal infections, and neonatal intensive care unit (NICU) admission of the babies were also significantly higher among high-risk mothers as compared to the control group mothers. Neonatal mortality was also significantly higher in Group B as compared to Group A. (Table 1)

Table 1. Maternal and perinatal characteristics of the participants (n=100)

Parameter	Group A (n=50)	Group B (n=50)	P-value
Maternal characteristics			
Age (years, mean ± SD)	24.02±2.42	24.72±2.85	0.631
Gestational age (weeks, mean ± SD)	38.6±0.9	38.4±1.0	0.773
Perinatal characteristics			
Stillbirth (%)	2 (4)	8 (16)	0.022*
Female (%)	23 (46)	27 (54)	0.257
Low birth weight (%)	17 (34)	33 (66)	0.001*
APGAR <7 at 1 min (%)	8 (16)	16 (32)	0.011*
NICU admission (%)	11 (22)	30 (60)	<0.001*
Congenital anomaly (%)	2 (4)	3 (6)	0.558
Neonatal sepsis (%)	1 (2)	7 (14)	0.011*
Neonatal death (%)	1 (2)	7 (14)	0.011*

*Statistically significant, unpaired student's t-test for continuous variables, chi-square test for categorical variables done

The mean placental weight in Group A and Group B was 498.01 ±37.74 and 476.21 ±67.18 grams respectively, a difference that was found to be statistically significant (p-value 0.04). High-risk patients were also found to have statistically significantly lower thickness of their placenta as compared to the mothers with uncomplicated pregnancies (2.75 ±0.27 and 2.57 ±0.44 cm; P-value 0.02). On gross examination of the maternal surface of the placentas, it was observed that the high-risk group mothers had significantly higher incidence of infarct, placental bleeding, calcification, and hematoma as compared to the control mothers. On the other hand, no significant differences were observed between the two groups with respect to the fetal surface characteristics of the placentas. (Table 2)

Table 2. Placental examination findings of the participants (n=100)

Parameter	Group A (n=50)	Group B (n=50)	P-value
Placental characteristics			
Placental weight (g, mean ± SD)	498.01±37.74	476.21±67.18	0.044*
Placental thickness (cm, mean ± SD)	2.75±0.27	2.57±0.44	0.027*
Gross maternal surface findings			
Infarct (%)	2 (4)	9 (18)	0.016*
Fibrosis (%)	0 (0)	2 (4)	0.143
Placental bleed (%)	0 (0)	4 (8)	0.035*
Calcification (%)	18 (36)	26 (52)	0.022*
Hematoma (%)	0 (0)	4 (8)	0.035*
Gross fetal surface findings			
Meconium stained (%)	17 (34)	12 (24)	0.108
Fetal surface anemia (%)	0 (0)	2 (4)	0.143
Circummarginate (%)	0 (0)	2 (4)	0.143
Basal plate characteristics			
Inflammation (%)	0 (0)	3 (6)	0.077
Abscess (%)	0 (0)	0 (0)	-
Infarct (%)	5 (10)	29 (58)	<0.001*
Fibrinoid necrosis (%)	2 (4)	22 (44)	<0.001*
Thrombosis (%)	0 (0)	3 (6)	0.077
Villous pathology			
Syncytial knots (%)	18 (36)	44 (88)	<0.001*
Fibrinoid membrane (%)	3 (6)	36 (72)	<0.001*
Basement membrane thickening (%)	2 (4)	33 (66)	<0.001*
Stromal fibrosis (%)	3 (6)	34 (68)	<0.001*
Cytotrophoblast proliferation (%)	2 (4)	29 (58)	<0.001*
Infarct (%)	9 (18)	36 (72)	<0.001*
Calcification (%)	29 (58)	42 (84)	<0.001*
Villous hypervascularity (%)	3 (6)	28 (56)	<0.001*
Intervillous hemorrhage (%)	5 (10)	22 (44)	<0.001*
Membranes			
Inflammation (%)	0 (0)	2 (4)	0.143
Necrosis (%)	0 (0)	0 (0)	-

*Statistically significant, chi-square test for categorical variables done

On histopathology, it was seen that as per the basal plate characteristics, high-risk group mothers had significantly higher incidence of infarction and fibrinoid necrosis as compared to control mothers, while the incidence of inflammation, abscesses, and thrombosis were not significantly different between the groups. When the villous pathology was considered, it was seen that group B patients had significantly higher incidence of syncytial knots, fibrinoid necrosis, basement membrane thickening, stromal fibrosis, cytotrophoblast proliferation,

infarct, villous hypervascularity, and intervillous hemorrhage as compared to Group A women. The two groups did not differ significantly from each other with respect to their membrane pathology. (Table 2)

When association between placental pathology and adverse perinatal outcomes were analyzed, it was observed that that was a statistically significant correlation between maternal surface abnormality, basal plate abnormality and villous pathology and low-birth weight babies. Significant associations were observed between basal plate pathology and villous pathology with stillbirths. Fetal surface abnormalities were significantly associated with APGAR score <7 at 1 min and requirement of NICU admission among the neonates. It was also found to be associated with neonatal death. For neonatal sepsis, a significant association was observed only with basal plate pathology. Maternal surface abnormalities, fetal surface abnormalities, and basal plate pathology were significantly associated with neonatal mortality among the participants. (Table 3)

Table 3. Association between placental abnormalities and perinatal outcomes (n=100)

Incidence of Placental abnormality (n)	**Perinatal adverse outcome (% incidence)**		**Chi-square value**	**P-value**
	Low-birth-weight			
	Present (50)	Absent (50)		
Maternal surface abnormality (%)	32 (64)	22 (44)	4.026	0.045*
Fetal surface abnormality (%)	17 (34)	14 (28)	0.421	0.517
Basal plate pathology (%)	27 (54)	14 (28)	6.986	0.008*
Villous pathology (%)	43 (86)	33 (66)	5.482	0.019*
Membrane pathology (%)	1 (2)	1 (2)	0.000	1.000
	Stillbirth			
	Present (10)	Absent (90)		
Maternal surface abnormality (%)	8 (80)	46 (51.1)	3.024	0.082
Fetal surface abnormality (%)	1 (10)	30 (33.3)	2.291	0.130
Basal plate pathology (%)	9 (90)	32 (35.6)	11.028	0.001*
Villous pathology (%)	10 (100)	66 (73.3)	3.509	0.016*
Membrane pathology (%)	0 (0)	2 (2.2)	0.227	0.634
	Low APGAR			
	Present (24)	Absent (76)		
Maternal surface abnormality (%)	17 (70.8)	37 (48.7)	2.602	0.058
Fetal surface abnormality (%)	12 (50)	19 (25)	5.330	0.021*
Basal plate pathology (%)	12 (50)	29 (38.2)	1.057	0.304
Villous pathology (%)	21 (87.5)	55 (72.4)	2.290	0.130
Membrane pathology (%)	2 (8.3)	0 (0)	2.910	0.088
	NICU admission			
	Present (41)	Absent (59)		
Maternal surface abnormality (%)	25 (61)	29 (49.2)	1.361	0.243
Fetal surface abnormality (%)	21 (51.2)	10 (16.9)	13.282	<0.001*
Basal plate pathology (%)	24 (58.5)	17 (28.8)	8.835	0.003*
Villous pathology (%)	35 (85.4)	41 (69.5)	3.342	0.062
Membrane pathology (%)	2 (4.9)	0 (0)	2.937	0.087
	Neonatal sepsis			
	Present (8)	Absent (92)		
Maternal surface abnormality (%)	4 (50)	50 (54.3)	0.056	0.813
Fetal surface abnormality (%)	3 (37.5)	28 (30.4)	0.172	0.679
Basal plate pathology (%)	6 (75)	35 (38)	4.156	0.041*
Villous pathology (%)	7 (87.5)	69 (75)	0.630	0.427
Membrane pathology (%)	0 (0)	2 (2.2)	0.177	0.674
	Congenital anomaly			
	Present (5)	Absent (95)		
Maternal surface abnormality (%)	3 (60)	51 (53.7)	0.076	0.782
Fetal surface abnormality (%)	2 (40)	29 (30.5)	0.199	0.655
Basal plate pathology (%)	3 (60)	38 (40)	0.785	0.375
Villous pathology (%)	4 (80)	72 (75.8)	0.046	0.830
Membrane pathology (%)	0 (0)	2 (2.1)	0.107	0.743
	Neonatal death			
	Present (8)	Absent (92)		
Maternal surface abnormality (%)	7 (87.5)	47 (51.1)	3.929	0.047*
Fetal surface abnormality (%)	6 (75)	25 (27.2)	7.870	0.005*
Basal plate pathology (%)	6 (75)	35 (38)	4.156	0.041*
Villous pathology (%)	8 (100)	68 (73.9)	2.746	0.097
Membrane pathology (%)	0 (0)	2 (2.2)	0.177	0.674

*Statistically significant

IV. Discussion

In the present study, 2 groups of 50 patients each were studied with respect to their placental abnormalities and perinatal outcomes. One of the groups was composed of high-risk mothers, while the other consisted of mothers with uncomplicated pregnancies. In the study, it was seen that the mean age of the mothers of both the groups were around 24 years. This finding was similar to that reported by Kartheek et al. and Samaddar et al. in their studies on high-risk pregnancies in Indian women.[8, 9] Furthermore, there was found no significant differences between the maternal and gestational age of the mothers. This was expected, as the two groups were matched with respect to their maternal and gestational age.

It was observed that the placenta of women in the high-risk pregnancy group were significantly lighter as well as thinner as compared to the control group mothers. These findings are similar to that reported in their studies by Bourgioti et al. and Stanek et al.[10, 11] This observation is likely due to a combination of factors. In high-risk pregnancies, such as those involving preeclampsia or intrauterine growth restriction (IUGR), there may be decreased blood flow to the placenta. This can lead to decreased oxygen and nutrient delivery to the developing fetus, which can impact fetal growth and development.[12] As a result, the placenta may be smaller and lighter than in uncomplicated pregnancies. Another possible explanation of the observation is that in high-risk pregnancies, there may be abnormalities in the way the placenta itself develops, like in pregnancies involving chromosomal abnormalities or certain genetic disorders, where there might be a deficiency in the development of the placenta itself, which can in turn impact its size and weight.[13]

As was expected, adverse perinatal outcomes were much more common in the high-risk group as compared to the control group. The incidence of stillbirths, low-birth-weight babies, and APGAR of <7 at 1 min were more than double of that of the normal mothers. The incidence of neonatal sepsis and neonatal mortality were seven times that of the uncomplicated pregnancies. The high incidence of adverse perinatal outcomes in high-risk pregnancies is consistent with findings reported by Mukhopadhyay et al. and Ghosh et al. in their studies conducted among high-risk mothers in India.[14, 15] These findings reiterate the need for prompt management of high-risk pregnancies, owing to the significant risk of perinatal morbidity and mortality that these conditions pose.

In the present study, it was observed that maternal surface pathology was significantly more common in the high-risk group as compared to the control group mothers. This was consistent with the findings reported by Salge et al., Li et al., and Gudmundsson et al. in their studies.[5, 16, 17] While the exact mechanism of the development of maternal surface anomalies are not yet well-understood, it has been suggested that in high-risk pregnancies, such as those complicated by hypertensive disorders or diabetes of pregnancy, the blood flow through the placenta and the umbilical cord is compromised, which predisposes the maternal surface to developing infarcts and fibrin deposition.[9, 16] However, pertinently, in this study, there was seen no statistically significant difference between the high-risk and the control group mothers with respect to fetal surface pathological changes in the placenta. This is contrary to that reported by Salge et al. and Costa et al.[16, 18] Histopathological examinations found that basal plate pathologies and villous abnormalities were significantly higher among those with high-risk pregnancies as compared to their normal counterparts. These findings are similar to that reported by Kartheek et al., Guzman et al., Ghidini et al. and others, and are consistent with the postulation that high-risk pregnancies predispose mothers to suffer from abnormalities in the development of the placental tissue.[8, 19, 20] Furthermore, those affected with high-risk pregnancies also have abnormalities in the proper blood supply in the placental tissues, which might lead to the development of adverse histopathological changes in the placenta.

Another key objective of the present study was to find out any existing associations between placental abnormalities and the development of adverse perinatal outcomes in the pregnancies. It was found that placental abnormalities, both gross as well as histopathological, were significantly associated with a number of different adverse perinatal outcomes, especially low-birth-weight babies and neonatal deaths. As discussed earlier, it has been postulated that high-risk pregnancies alter the flow of blood through the placental tissue and thus hamper the feto-maternal circulation. As this pathway is critical for the proper growth and development of the fetus *in utero*, it stands to reason that those fetuses with placental abnormalities will be of lower birth weight than their healthy counterparts, a fact that was substantiated by the findings of the present study, and supported by the reports of Kartheek et al., Salge et al., Roescher et al., and Khong.[8, 16, 21, 22] The associations between fetal surface pathology and neonatal sepsis, NICU admission and subsequent mortality suggests that placental abnormalities such as meconium staining of the fetal surface or fetal surface anemia might predispose the neonates to contracting life-threatening infections in the neonatal period.

The major limitation of the present study was that it was conducted in a single institution on a relatively small sample size of participants. Furthermore, high-risk mothers were managed as per protocol to control their high-risk status during the process of their maternal care in the institution, which might have led to different perinatal outcomes as compared to if those conditions have been left unmanaged. Therefore, larger, multicentric prospective or registry-based studies would generate more generalizable and robust data on the topic.

V. Conclusion

The findings of the present study therefore indicate that not only is the incidence of placental abnormalities significantly higher in high-risk pregnancies as compared to uncomplicated ones, the presence of placental abnormalities are significantly associated with adverse perinatal outcomes among the mothers. Therefore, placental morphology and histopathology after delivery can be of value in the prediction of prognosis of fetuses in the neonatal period.

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