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Original Research Article

CLINICOPATHOLOGICAL STUDY OF PLACENTA IN IUFD IN A TERTIARY CARE CENTER

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Abstract

Background: Stillbirth is a tragic event for both parents and obstetrician. It is one of the most unfortunate complications of pregnancy. Placenta is a vital organ through which transfer of nutrients and oxygen to foetus occurs and also acts as immune barrier. Placental pathology plays an important role in the foetal deaths to the tune of 11% to 65%. Histopathological examination of placenta and its correlation with the clinical conditions can help in understanding the pathogenic events occurring in cases of stillbirth. The aim and objective are histopathological study of placental study in IUFD and its clinical correlation. **Materials and Methods:** This is a prospective observational study conducted over two years at MKCG Medical College, Berhampur; Odisha. During this period 232 placentas of intrauterine fetal death (IUFD) cases were examined and sent to histopathology. At the end of the study collected data were tabulated and analyzed. **Result:** Out of 232 placentae examined, maximum percentages of IUFD (26.7%) were associated with hypertensive disorders in pregnancy (HDP) followed by abruptio placentae in 14.2% cases and unexplained in 35.7% cases. Other conditions associated with intra uterine fetal death(IUFD) like chronic hypertension, IUGR, PPROM, GDM, malaria, congenital anomalies and placenta previa were 2.2%, 5.2%, 6%, 3%, 0.9%, 5.2% and0.9% respectively. On histopathological examination, intervillous fibrin was present in highest number of placental specimen (81.5%). Retroplacental clot, thrombotic vasculopathy, hypertension related changes, infarction, increased syncytial knotting, intervillous fibrin deposit, intervillous hemorrhage, calcification, villitis and chorioamnionitis were present in 25.9%, 20.2%, 10.8%, 25.8%, 11.2%, 28.8%, 32.7%, 39.7%, 22.8% and 34% of cases respectively. **Conclusion:** Thrombotic vasculopathy and hypertension related changes were significantly associated with IUFD complicated by HDP. In unexplained intrauterine fetal deaths, the incidence of infarction, thrombotic vasculopathy, intervillous/perivillous fibrin deposition, chorioamnionitis and villitis were higher in histology of placenta. Placental examination plays vital role in identifying the cause of stillbirth. In certain cases, it also predicts risk of recurrence in subsequent pregnancy and helps in prevention of adverse pregnancy outcome.

INTRODUCTION

Stillbirth is a tragic event for both parents and obstetrician. It is one of the most common and unfortunate complications of pregnancy. Stillbirth is an important global health problem affecting over 7000 families every day and is associated with emotional, social and economic consequences.[1] In 2019, an estimated 2.0 million babies were stillborn at 28 weeks or more gestation globally. The third trimester stillbirth rate in south Asia and sub-Saharan Africa is approximately 10 times that of developed countries (29 vs. 3 per 1000 births).[2]The Every Newborn Action Plan, a global multi-partner movement to end preventable maternal and neonatal deaths and stillbirths has established a goal to

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reduce stillbirth rates globally to 12 or less per 1000 births by 2030. The mean still birth rate for India is 13.9 per 1000 births in 2019.[3,4]

The current definition of fetal death adopted by the Centers for Disease Control and Prevention National Centre for Health Statistics is based on a definition recommended by the World Health Organization (Mac Dorman, 2015). It states that "Fetal death means death prior to complete expulsion or extraction from the mother of a product of human conception irrespective of the duration of pregnancy and which is not an induced termination of pregnancy. There is no universally accepted definition when a fetal death is called a stillbirth vs. spontaneous abortion; the reporting policies in the different countries and within the states of a same country are not uniformly followed and there are also differences in terms of how the gestational age is assessed and interpreted.[5-8] Placenta is a vital organ through which transfer of nutrients and oxygen to fetus occurs and also acts as immune barrier. Placental pathology plays an important role in the etiology of 11% to 65% fetal deaths. Placenta provides record of intrauterine events in the pregnancy.[9] The placental pathology may be the sole cause of stillbirth and other clinical conditions like HDP, abruption, and IUGR. These conditions are recurrent and may also cause intrauterine fetal death (IUFD) in subsequent pregnancy.10 Histopathological examination of placenta and its correlation with the clinical conditions can help in understanding the pathogenic events occurring in cases of stillbirth for which the current study was aimed.

Aims and Objectives: Histopathological study of placental in IUFD and its clinical correlation.

MATERIALSANDMETHODS

This is a prospective observational study conducted over two years at MKCG Medical College, Berhampur; Odisha. Cases are selected basing on the following inclusion and exclusion criteria. Inclusion criteria: (a) singleton IUFD diagnosed ante partum ≥28 weeks of gestation (b) maternal conditions like Diabetes, Hypertensive disorders, APH, Rh-ve pregnancy, Thyroid disease, Renal disease, Antiphospholipid antibodies, Thrmbophilias, Uterine rupture (c) foetal conditions like congenital anomaly, hydrops fetalis (d) The management of specific medical conditions associated with increased risk of late IUFD. Exclusion Criteria: (a) multiple pregnancies with surviving fetus (b) still birth following late feticide (c) uterine rupture (d) Trauma and accidents

Methodology: After satisfying the eligibility criteria, patients presenting with stillbirth at 28 weeks or more period of gestation were recruited. Detail history regarding age, parity, SES, qualification, past history of IUFD and relevant medical history was collected. Thorough clinical examination and basic investigation-complete haemogram, renal function test, liver function test, thyroid function test, glucose tolerance test(GTT), coagulation profile, bacteriology workup in case of fever were noted down. At the time of delivery, detailed examination of the baby was done to examine for any congenital malformation and overall appearance of the fetus. Detailed examination of placenta, umbilical cord and membrane was done. The placenta was weighed and diameter was measured. Gross examination was done to look for the areas of infarct, retroplacental clot, accessory lobe, twin placenta, site of cord insertion –central eccentric, marginal, velamentous, circumvallate placenta. The umbilical cord was grossly examined for single umbilical artery and presence of knot. Then, placenta with umbilical cord was immediately fixed in 20% formalin and was submitted for histopathology examination to the Department of Pathology of above medical college. Multiple random samples were taken from each placenta from maternal and fetal side (2 sections), two sections from umbilical cord, one section from extra placental membranes. For all cases, 4 sections of 4 micrometer thickness were cut on rotary microtome and mounted on clean gelatinized slides, and stained with haematoxylin and eosin stain. Sections were analyzed by light microscopy. Microscopic evaluation included features of retroplacental clot, infarction, villitis, leucocytic infiltration, thrombotic vasculopathy, perivillous fibrin deposit, intervillous haemorhage, calcification and increased syncytial knot. The data were tabulated in the MS Excel spreadsheet. Statistical analysis was performed by the SPSS program for Windows, version 25.0. . Levene's test of equality of variance was applied to compare the mean values between groups. A "p" value <0.05 was considered significant.

RESULTS

During the study period 232 placentae of IUFD cases were examined, out of which maximum percentage of IUFD (26.7%) were associated with hypertensive disorders in pregnancy (HDP). Abruptio placentae were associated in 14.2% cases and unexplained in 35.7% cases. Other conditions associated with IUFD like chronic hypertension, IUGR, PPROM, GDM, malaria, Congenital anomalies and placenta previa were 2.2%, 5.2%, 6%, 3%, 0.9%, 5.2% and0.9% respectively.

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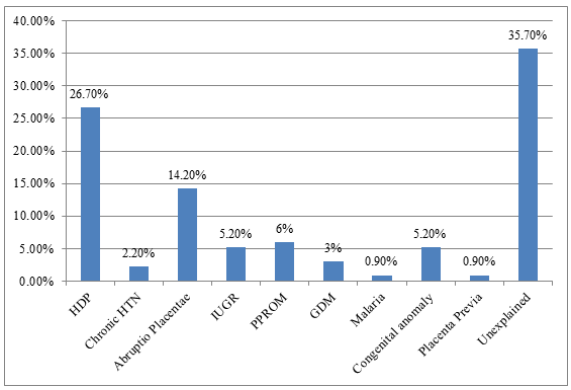

Figure 1: Associated clinical risk factors with IUFD

Among the placentas of IUFD, 216(93.1%) had central cord insertion and 11(6.9%) had marginal cord insertion, only 11(4.7%) had single umbilical artery and the mean placental weight was 343(±112) grams and mean placental diameter was14 (±1.5) cm. [Table 1]

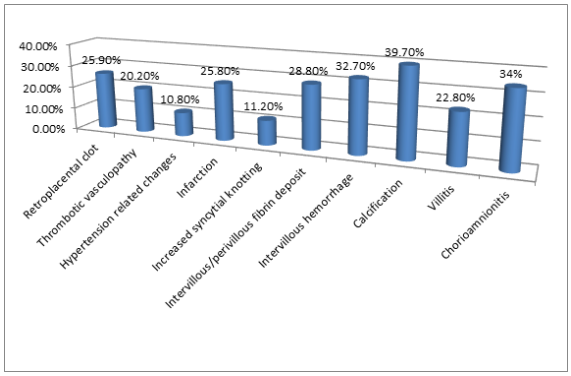

Figure 2: Graphical presentation of histopathological changes in placenta

On histopathological examination, out of 232 IUFD cases, intervillous fibrin was present in highest number of placental specimen (81.5%). Retroplacental clot, thrombotic vasculopathy, hypertension related changes, infarction, increased syncytial knotting, intervillous fibrin deposit, intervillous hemorrhage, calcification, villitis and chorioamnionitis were present in 25.9%, 20.2%, 10.8%, 25.8%, 11.2%, 28.8%, 32.7%, 39.7%, 22.8% and 34% of cases respectively. [Figure 2]

Out of 62 cases of IUFD associated with HDP, central cord insertion was present in 57 cases (92%). The average placental weight was 345±112 grams and the average placental diameter was 14.4±2.4cm. Pathological findings like retro placental clot, thrombotic vasculopathy, hypertension related changes, infarction, increased syncytial knotting, intervillous fibrin deposit, intervillous haemorrhage, calcification, villitis and chorioamnionitis were present in 33.9%, 29%, 22.6%, 30.6%, 11.3%, 32.3%, 40.3%, 24.2%, 8.1% and 30.6% respectively. Certain pathological conditions like thrombotic vasculopathy and hypertension related changes (intimal thickening, acute atherosis) were more frequently found in HDP group ($p \leq 0.05$). The frequency of thrombotic vasculopathy, infarction, intervillous/perivillous fibrin deposit and intervillous hemorrhage were higher in HDP group but not statistically significant [Table 2].

Table 1: Gross examination findings of placenta

Gross Examination of Placenta		No. of Cases	Percentage
Cord Insertion	Centre	216	93.1%
	Marginal	16	6.9%
Single Umbilical artery		11	4.7%
Placental weight in grams(SD)		343(±112)	-
Diameter of placenta in cm		14(±1.5)	-

Table 2: Gross and histopathological examination finding in the placenta of IUFD cases complicated by HDP.

Gross and Histopathological finding in the Placenta		HDP(n=62)	Non- HDP(n=170)	P Value
Cord insertion	Central	57(92%)	159	
	Marginal	5(8%)	11(6.5%)	0.672
Single umbilical Artery		3(4.8%)	8(4.7%)	0.966
Placental Weight in grams (±SD)		345±112	343±112	0.732
Placental diameter in cm (±SD)		14.4±2.4	14.4±2.4	0.612
Retroplacental clot		21(33.9%)	39(22.9%)	0.092
Thrombotic vasculopathy		18(29%)	29(17%)	0.045
Hypertension related changes		14(22.6%)	11(6.5%)	0.000
Infarction		19(30.6%)	41(24.1%)	0.315
Increased syncytial knotting		7(11.3%)	19(11.2%)	0.980
Intervillous/perivillous fibrin deposit		20(32.3%)	47(27.6%)	0.493
Intervillous hemorrhage		25(40.3%)	51(30%)	0.138
Calcification		15(24.2%)	77(45.3%)	0.004
Villitis		5(8.1%)	48(28.2%)	0.001
Chorioamnionitis		19(30.6%)	60(35.3%)	0.508A
At 95% CI, p-value significant at ≤0.05				

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Table 3: Gross and histopathological examination finding in the placenta of unexplained IUFD cases

Gross and Histopathological finding in the Placenta		Unexplained(n=83)	Associated complications(n=149)	p-value
Cord insertion	Central	79(95.2%0	145(97.3%)	
	Marginal	4(4.8%)	4(2.7%)	0.351
Single umbilical artery		2(2.4%)	2(1.3%)	0.213
Placental Weight in grams(±SD)		339(±116.5)	346(±110)	0.659
Placental diameter in cm(±SD)		13.7(±1.5)	14(±2.6)	0.336
Retroplacental clot		16(19.3%)	44(29.5%)	0.087
Thrombotic vasculopathy		20(24.1%)	27(18%)	0.278
Infarction		16(19.3%)	44(29.5%)	0.873
Syncitial knot		12(14.5%)	14(9.4%)	0.241
Intervillous/perivillous fibrin deposit		24(28.9%)	43(28.8%)	0.993
Intervillous hemorrhage		8(9.6%)	68(45.6%)	0.000*
Calcification		42(50.6%)	50(33.6%)	0.011*
Villitis		42(50.6%)	11(7.4%)	0.000*
Chorioamnionitis		36(43.4%)	43(28.8%)	0.025*
At 95% CI, p-value significant at ≤0.05*				

In 83 cases of unexplained IUFD the average placental weight was 339(±116.5) grams and the average diameter was 13.7(±1.5) cm. On histopathological examination retroplacental clot, thrombotic vasculopathy, infarction, syncitial knot, intervillous/perivillous fibrin deposit, intervillous haemorrhage, calcification, villitis and chorioamnionitis were present in 19.3%, 24.1%, 19.3%, 14.5%, 28.9%, 9.6%, 50.6%, 50.6% and 43.4% of cases respectively. Certain pathological conditions like calcification, villitis and chorioamnionitis were more frequently found in unexplained group (p≤0.05). The frequency of thrombotic vasculopathy and syncytial knot were higher in unexplained group but not statistically significant. [Table 3]

DISCUSSION

In our study of 232 cases of IUFD conducted in Department of Obstetrics and Gynecology of MKCG Medical College, Berhampur; Odisha, it was found that 35.7% of cases are without any probable cause [Figure1]. Studies by Singh N et al,[11] and Swapnil Patel et al,[12] found 33% and 38.7% unexplained IUFD respectively which is consistent with our study. The number of unexplained stillbirth has reduced by the increasing resort of necropsy in western countries. Due to social stigma we could not do autopsy of stillborn babies which might have attributed to high incidence of unexplained IUFD in our study. Most common associated cause of IUFD in our study was hypertensive disorders in pregnancy accounting 26.7% which is consistent with studies by Anjali C et al (28.7%),[13] Garg S et al (28.75%),[14] Korde NV et al (26.8%),[15] and Dave A et al (25%).[16] Noon Altijani et al found eclampsia and other hypertensive disorders associated with stillbirth were 11.2% and 5.3% respectively which was much less than our study.[17] Placenta previa was associated in 0.9% cases which was similar to studies by Hazell et al.[18] In this study, eleven histopathological parameters were examined in the placenta of IUFD. Among them, retroplacental clot, villous hypoplasia, thrombotic vasculopathy, hypertension related changes, infarction, increased syncytial knotting, intervillous fibrin deposit, intervillous haemorrhage, calcification, villitis and chorioamnionitis were present in 25.9%, 1.7%, 20.2%, 10.8%, 25.8%, 11.2%, 28.8%, 32.7%, 39.7%, 22.8% and 34% of cases respectively. These findings were comparable to the study done by Bukowski R. et al,[19] with a sample size of 319 singleton stillbirth. They observed retroplacental clot (17%), infarction (33.3%), perivillous/intervillous fibrin deposition (9.2%), vilitis (2.1%) and chorioamnionitis (24.5%) cases of stillbirth. They have concluded that these placental abnormalities might have caused placental dysfunction leading to stillbirth. In our study retroplacental clot, intervillous/perivillous fibrin deposition, villitis and chorioamnionitis were found to be higher than their study. The infarction, Perivillous/ intervillous fibrin deposit, intervillous haemorrhage and villitis were found in higher percentage of cases than Pinar H et al.[20]

In the current study, stillbirth complicated with HDP group, average weight of placenta was 345±112 grams. On histopathological examination, retro placental clot, thrombotic vasculopathy, hypertension related changes, infarction, increased syncytial knotting, intervillous fibrin deposit, intervillous haemorrhage, calcification, villitis and chorioamnionitis were present in 33.9%, 29%, 22.6%, 30.6%, 11.3%, 32.3%, 40.3%, 24.2%, 8.1% and 30.6% respectively. Thrombotic vasculopathy and hypertension related changes are more frequently found in HDP group. Similar observation was found in a study by K. J. Gibbins et al who found that degree of maternal under perfusion on histopathology correlate with clinical severity which is consistent with our study.[21] In their study placental weight was significantly lower than the results of our study as they had included pregnancies above 18 weeks of gestation.

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CONCLUSION

Out of all associated risk factors, HDP was found in maximum percentage of stillbirths (26.7%) followed by abruption placentae (14.2%) and 35.7% were unexplained stillbirths. On histological examination, infarction, intervillous haemorrhage, increased syncytial knots, villitis and intervillous/perivillous fibrin deposition were found in most of the placentas of intrauterine fetal death. In HDP, the incidence of retroplacental clot, thrombotic vasculopathy, infarct, hypertension related changes such as acute atherosis, intimal thickening of arterioles and intervillous haemorrhage were higher in placentas of stillbirth. Thrombotic vasculopathy and hypertension related changes were significantly associated with IUFD complicated by HDP. In unexplained intrauterine fetal deaths, the incidence of infarction, thrombotic vasculopathy, intervillous/perivillous fibrin deposition, chorioamnionitis and villitis were higher in histology of placenta.

Majority of the associated risk factors in our study seem to be preventable. Health education should be given utmost priority. Patients should be motivated for regular antenatal checkups, adequate nutrition and iron folic acid supplementation. Strengthening of information, education and communication (IEC) programmes to specific target population at risk can alleviate the false beliefs and stigma in the society. Early identification of danger signs and timely referral can prevent some adverse pregnancy outcome. In certain cases, it also predicts risk of recurrence in subsequent pregnancy and helps in prevention of adverse pregnancy outcome.

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