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Comparative study of histopathology of the placental lesions in pregnancies complicated with foetal growth retardation and stillbirths with non complicated pregnancies

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Abstract

Context: Fetal growth and viability depends on the maternal supply of nutrients and oxygen through the placenta. The foetus, placenta and mother constitute triad of contributors to pregnancy outcome. IUGR and stillbirth are condition associated with placental insufficiency. The placental examination helps in understanding of the specific aetiologies of adverse outcome.

Aims: To study the histopathological changes in placenta of foetal growth retardation (FGR) fetuses and placenta of unexplained intrauterine death foetuses and to compare it with placental findings in uncomplicated pregnancies.

Setting and Design: This study was conducted on specimen of placenta received in Department of Pathology B.R.D. Medical College, Gorakhpur, UP.

Methods and Material: Gross examination of placenta was done to look for abnormalities. Sections were taken one from maternal surface, one from fetal surface, one or two from the cord and membranes and fixed in 10% formalin. Sections were stained with H & E stain and examined microscopically.

Statistical analysis used: Prospective, observational study.

Results: In FGR cases, maximum(44%) were in primipara, maximum (72 %) had birth weight 2000-2500 gram, maximum (64%) had placental weight from 301 to 400 grams, maximum(60 %) showed eccentric cord insertion, maximum (78 %) had placental abnormalities and maximum (76 %) has clinical risk factors.

In Stillbirth cases, maximum(36%) were in nulliparous, maximum (38 %) had birth weight between 500-1000 grams, majority (60 %) had placental weight between 301 to 400 grams, maximum(72 %) showed eccentric cord insertion, maximum (82 %) had placental abnormalities, maxium(80 %) had clinical risk factors.

Conclusion: Histopathological examination of placenta is an important role to determining the cause of intrauterine death at all gestational ages, so pregnancy care and future studies should be focused on clinical conditions associated with placental pathologies.

Keywords: Histopathology, Placental lesion, IUGR, Stillbirth, Complicated pregnancy.

Introduction

Placenta is the vital organ for maintaining pregnancy and promoting development of the fetus [1]. Placental factors and hypoxemia are keys to foetal growth retardation (FGR) and fetal death. Foetal growth retardation (FGR) is a condition associated with placental insufficiency.[2]Known causes of foetal growth retardation (FGR) can be traced in up to 40% of cases studied, including maternal diseases and fetal or placental factors. [4, 5] Maternal factors include cardiac disease, pulmonary or renal disease, anemia, and connective tissue disease. Fetal factors include chromosomal abnormalities, ventral wall defect, or genitourinary defects. Other known placental pathology of foetal growth retardation (FGR) infant includes decrease of placental growth, maternal vasculopathy, chronic villitis and increase of perivillous fibrin, umbilical cord anomaly. [3, 4] The most common causes of stillbirth between 24 and 27 weeks of gestation are infection, abruption and fetal anomalies. [6]

Material And Method

This prospective observational study has been conducted in the Department of Pathology, in collaboration with Department of Obstetrics and Gynecology B.R.D. Medical College, Gorakhpur, U.P, during a period ranging from July 2021 to June 2022, on a total of placenta of 150 women comprising of 3 groups. In Group I placenta of 50 women who had delivered growth restricted foetuses, In Group II placenta of 50 women who had fetal demise (IUD) beyond 24 week of gestation and their gross and histopathological findings were compared with placenta of women with normal deliveries (Group III, n=50). After taking informed and written consent, gross examination was done to look for abnormalities. Sections were taken, one from maternal surface, one from fetal surface, one or two sections from the cord and from the membranes and fixed in 10% formalin. Sections were stained with H & E stain and examined microscopically. Histopathological findings were correlated with risk factors. All relevant data were

collected and appropriate statistical tools were applied to analyses the data. Statistical analysis were done using Chi Square test appropriate for 3 groups. A p value < 0.05 will be taken as significant.

Results

In our study a total case of 150 women were enrolled in the study were divided into 3 groups of 50 each as above and examine microscopically during one year duration. In the Group I, the age of patient ranged from 19 to 29 years with mean of 23.73± 2.36 years. Maximum include of FGR (88%) were seen in maternal agegroup of 20-30 years. In the Group II, the range of age varied from 19 to 32 years with mean of 24.72± 2.92 years. Most of stillbirth(52 %) were in women of 20-24 years age group followed by 40 % of women who were 25 to 29 years of age group. Maximum(44%) FGR cases were in primipara and only 6 % in parity more than 2. Stillbirths were mostly in primigravida (36 %) followed by 28 % in gravida 2. Most stillbirths were inage group of 20-30 years. 28 % of FGR were at gestational age of 28-31 weeks, 50 % in 32-37 weeks and in 22 % less than 28 weeks of gestational age. 52 % stillbirth occurred in women with gestational age of 28- 31 weeks, followed by 26 % at gestational age 32-37 weeks. 11 stillbirths (22 %) were in women with gestational age of less than 28 weeks. Grade III preterm placental calcification was seen in Group II 20 cases (40 %), 12 cases (24 %) in Group I, followed by 3 cases (6 %) in control Group. BMI in FGR mother was 21.51±2.02, in women with stillbirth (IUD) was 22.02±2.08 whereas mean BMI in normal pregnant women was 25.86±1.89. BMI has a critical role in intrauterine growth. In FGR cases (Group I), maximum(72 %) low birth weight babies had birth weight 2000-2500 grams followed by 18 % of babies having birth weight between 1500-2000 grams. In stillbirths 38 % had birth weight between 500-1000 grams followed by 32 % with birth weight between 1000-1500 grams and 16 % babies were of 1500-2000 grams. In Group I, placental weight maximum in 64 % cases from 301 to 400 grams with mean placental weight was 321.86±48.08. In Group II, majority of stillbirths (60 %) had placental weight between 301 to 400 grams and 19 stillbirths (38 %) had placental weight between 200 to 300 grams. In control group, maximum weighted between 451 to 550 grams with mean placental weight of 508.26±40.72 grams. The placentas from pregnancies with FGR Group I and Group II (IUD cases) tend to be smaller than those collected for the control group. The placental thickness was lower in Group I and Group II in comparison to control groups. The difference was found to statistically significant. In the Group I, 30 placentas (60 %) showed eccentric cord insertion and 19 placentas (38%) showed central cord insertion and cord was inserted marginally in only 1 cases (2 %). In IUD cases (Group II), 36 placentas (72 %) showed eccentric cord insertion and 12 (24 %) showed central insertion and in 1 (2 %) case cord was inserted marginally and in another case of IUD group velamentous cord seen while in control group majority of placentas (46 cases, 92 %) showed central cord and eccentric cord was observed in 4 placentas (8 %). Meconium staining of placenta was significant findings in stillbirth group (12 cases, 24 %) while in FGR cases, 6 cases (12 %) showed meconium staining of placenta. In study group and control group, most of placentas had marginal membranous insertion. On microscopy, Abnormal histopathological findings in placenta were in 36 (72 %) women who had IUD and in 33 (66 %) who showed fetal growth retardation. Uteroplacental insufficiency (38.8 %) and acute inflammation (18 %) were the identifiable abnormalities

in IUD group, were also found significantly in FGR group as well (57.6 %). In IUD, 41 cases (82 %) had placental abnormalities (either gross pathology or histopathology or both), 9 cases (18 %) had no abnormalities. In FGR, 39 cases (78 %) had abnormalities (either grossly or microscopically or both), 11 cases (22 %) had no abnormalities. In control group, majority of placenta showed no pathology, only 4 (8 %) placenta showed syncytial knot and 2 (4 %) showed fibrinoid necrosis. In IUD group, 40 cases (80 %) had clinical risk factors, among which histopathology was found to correlate in 25 cases (62.5 %), in 5 cases (12.5 %), other abnormal histopathological findings were found while in rest 10 cases (25 %) no abnormality found. In FGR group, (Group I), 38 cases (76 %) had clinical risk factors among which histopathological findings correlated in 15 cases (39.4 %), other associated abnormal histopathological changes were found in 11 cases (28.9 %) and no abnormality was found in 12 cases (31.5 %). In IUD group, uteroplacental vascular insufficiency was most commonly observed (37.5 %). Leucocytic infiltration was seen in (20 %) of cases. No pathology was seen in 9 cases (22.5 %). In preeclampsia, uteroplacental vascular insufficiency was seen in 14 out of 28 cases (50 %). In FGR cases uteroplacental vascular insufficiency was seen in (36.84%) cases. No abnormality is seen in (31.57 %) of cases. Among women with preeclampsia, uteroplacental vascular insufficiency was seen in 6 out of 19 cases (31.5 %) followed by villous capillary hypervascularity. Uteroplacental vascular insufficiency was also observed in 3 out 7 cases of oligohydramnios, both cases of overt diabetes and 3 out of 8 cases of anaemia.

Discussion

Advanced maternal age is a known risk factor for both increased prenatal morbidity and mortality. The majority of stillbirths (90 %) were seen in age group of 20 to 30 years. Similar finding are observed by Rajgopal et al[7]. In FGR maximum (50 %) were seen in 20-25 years as this is accordance with Sinha S et al[8]. In our study, FGR cases were in primipara (44%).

Gestational age at birth is the strongest predictor of neonatal complication and outcome. In our study, most of the IUD were delivered between 28 to 37 weeks (78%). This is in accordance with study of Sailaja Devi K et al[9] who reported that women who had preterm delivery were at increased risk of stillbirth by 14-32 weeks. In FGR group most of the deliveries were in less than 37 weeks (78%). Mahapatra et al[10] observed about 54.15% deliveries in the 34-36 weeks group and rest were in less than 34 weeks group. Socio-economic low level was another important risk factor in our population. Lowest levels were associated with greater rates of FGR, as reported by Colomer et al[11].

Based on the BMI, in Group I, 12 (24%) belonged to underweight category, 24 (48%) belonged to normal weight category, 8 (16%) belonged to overweight category, 6 (12%) belonged to obese category. The mean BMI of Group I is 21.51±2.02 Kg/m2. In Group II, 10 (20%) belonged to underweight category, 20(40%) belonged to normal weight category, 14 (28%) belonged to overweight category, 6 (12%) belonged to obese category. In control Group, 14 (28%) belonged to underweight category, 20 (40%) belonged to normal weight category, 9 (18%) belonged to overweight category, 7 (14%) belonged to obese category. The mean BMI of control group is 22.56±1.89 Kg/m2. The result outcome is statistically significant ($p<0.05$). Myatt L et

al[12] studied that a putative etiology for this association is obesity associated placental dysfunction, as the intrauterine environment of obese mothers has been found to be in a state of higher inflammation and oxidative stress.

Analyzing on placental weight in Group I, 13 (26%) had placental weight between 200-300 grams, 32 (64%) had between 301-400 grams, 2 (4%) had between 401-500 grams and 3 (6%) had >500 grams. In Group II, placenta weight had 19 (38%) between 200-300 grams, 30 (60%) had between 301-400 grams, 1 (2%) had between 401-500 grams and none had >500 grams. In control group, placenta weight had 0 (0 %) between 200-300 grams, 1 (2 %) had between 301- 400 grams, 11 (22%) had between 401-500 grams and 38 (76%) had >500 grams. The result outcome is statistically significant ($p<0.05$).Vedmedovska N et al[13] studied that the placental weight presented with the best correlation with FGR.

On gross examination, attachment of cord was mainly central in the control group (92 %) whereas eccentric attachment was prominent in both study group I and II . 2 cases of stillbirths (Group II) had two vessel cord and 3 cases (6 %) showed true knot ,while among Group I (FGR Group), 1 case (2 %) had two vessel cord and only 1 case had true knot. Similar findings were observed in Nigam J S et al[14] who noted eccentric attachment of cord (66.67 %) of low birth weight baby placentae .Biswas et al[15] observed that in cases of FGR placentas ,there were some abnormal position of insertion of umbilical cord in 11 % placentas (marginal in 7.14 % and velamentous in 3.57%).

Meconium staining of placenta was significant finding in stillbirth group and was observed in 12 cases (24 %) while 5 cases FGR showed meconium staining. In stillbirth Group, two had circummarginate insertion of cord. Calcification, infarction and retroplacental clot were seen in significantly higher number of placentae from study groups than control. Suzuki S et al[16] found that incidence of intrauterine foetal death and other complications (premature delivery and oligohydramnios) was significantly higher in patients with circumvallate placentas than that in controls. In our study, Grade III preterm placental calcification (noted at 28weeks gestation) was associated with higher incidence of stillbirth and FGR, Grade III preterm placental calcification is a significant and independent risk factor for stillbirth. Similar findings were noted by Chen K H et al[17], Sinha et al[8]

Abnormal histopathological findings in placentae were noted in 36 cases (72 %) women who showed foetal demise and in 33 cases (66 %) who showed foetal growth restriction. Uteroplacental insufficiency (38 %) and acute inflammation (18 %) were the leading identifiable abnormalities in Group II (IUD Group), the former was found significantly in FGR group as well. Similar results were observed by Ujwala CH et al[18] who observed that uteroplacental insufficiency and acute inflammation were the leading histopathological findings in both IUD as well as FGR group. Among the clinical unexplained IUD and FGR cases (12 cases in Group I (FGR) and 10 cases in IUD Group II), placental pathology was present in 8 cases (80 %) and 7 cases (58.39 %) respectively. These findings are very well correlated with Ujwala CH et al[18].

Perivillous fibrin deposition with villous capillary hypervascularity were found to be significantly associated with stillbirth and FGR cases as compared to control group. Higher amount of intervillous fibrinoid deposition is a pathological finding in FGR related

placenta. The findings of study conducted by Nigam JS et al[15] and Mardi et al[19] also correlated with our study. Mardi K et al[19] also observed syncytial knots in 72.2 % and 64 % respectively in case of hypertensive pregnancies associated with birth of unduly small babies at term . Fibrinoid necrosis was found in 48 % cases of FGR in present study which was similar to that repeated by Mardi K et al[19] and Jain K et al[20] who observed 20 % to 34.4 % of placenta having significant fibrinoid necrosis.

Acute inflammation was seen in 18 % in IUD cases and FGR 4 % cases. Jain et al[20] noted maximum number of leucocytic infiltration in 27.7 % and 30.52 % in FGR placenta respectively . In the present study, preeclampsia and related complication (40 %) and foetal growth restriction (60 %) were found to be the most common risk factors for IUD. The features suggestive of uteroplacental insufficiency observed in preeclampsia and FGR were present in 38 % of IUD cases. Hargital B. et al[21] observed 25.8 % incidence of features of uteroplacental insufficiency in stillbirths . Several authors who studied placenta for placental infection found that chorioamnionitis was more common and also more severe among unexplained stillbirths. However, Hargital B. et al[21] despite finding marked placental inflammation, could not demonstrate bacteria in the intraplacental exudate .

The histopathological evaluation of the placenta also revealed other morpho-pathological changes in the study group, most of them in a certainly higher proportion than in the control group: intervillous thrombi, diffuse calcifications, avascular terminal villi, chronic villitis, villous hypoplasia, syncytiotrophoblastic knots, thickening of the basement membrane, multifocal chorangiomatosis. Although not specific to FGR pregnancies, research revealed that these lesions were linked with FGR, systemic autoimmune disorders, intrauterine infection and sepsis, genetic disorders, toxic substances, abnormal interaction between host and the placenta, and confined placental mosaicism according to Katzman P J et al[22]. The various features suggestive of uteroplacental insufficiency such as increased syncytial knots, infarcts, villous fibrosis, hypovascularity may be found in preeclampsia, chronic hypertension, diabetes mellitus and SLE. Stallmach et al[23], showed that findings of placental maturation defects which can cause foetal hypoxia and stillbirths may be associated with hypertension, diabetes mellitus, foetal anomalies and maternal fetal rhesus incompatibility .

Placental pathology examination gives more accurately the cause of FGR and stillbirths. Stillbirths remain a still ever rising cause of perinatal and postnatal morbidity, histopathological examination of placenta is an important part of the investigative work up. A proper gross and microscopic examination of placenta with documentation of relevant finding still remains of rising relevance in addition to preventive measures to reduce stillbirths in high risk mothers and the scope for study for elucidation of rarer causes of stillbirths.

Conclusion

The findings of this study demonstrate that placental pathology represents a major category of cause of intrauterine death. Therefore, placental examination is an important contributor to determining the cause of intrauterine death at all gestational ages. Since placental pathologies are predominant, pregnancy care and future studies should be focused on clinical conditions associated with placental pathologies.

Legend Tables and Figures

Table 1: Case distribution on the basis of socioeconomic status, Region & Religion and placental weight

		GROUP 1		GROUPII		Control		Chi-Square value	P-Value
		N	%	N	%	N	%		
Socioeconomic status	Lower	4	8	2	4	1	2	5.480	0.241
	Upper Lower	8	16	9	18	9	18		
	Middle	38	76	39	78	40	80		
Region	Rural	26	52	28	56	16	32	2.000	2.368
	Urban	24	48	22	44	34	68		
Religion	Hindu	36	72	39	78	38	76	2.412	0.660
	Muslim	9	18	5	10	8	16		
	Other	5	10	6	12	4	8		
Placenta weight (grams	200-300	13	26	19	38	0	0	134.216	0.000*
	301-400	32	64	30	60	1	2		
	401-500	2	4	1	2	11	22		
	>500	3	6	0	0	38	76		
	MEAN±SD	321.86±48.08		307.00±39.49		508.26±40.72		122.91	

Table 2: Gross placental findings

		GROUPI (FGR,n=50)		GROUPII (IUD,n=50)		Control (n=50)	
		N	%	N	%	N	%
Type of umbilical cord	Central	19	38	12	24	46	92
	Eccentric	30	60	36	72	4	8
	Velamentous cord	1	2	1	2	0	0
	Marginal cord	0	0	1	2	0	0
	Twovessel cord	1	2	2	4	0	0
	Single umbilicalartery	0	0	1	2	0	0
	Rupture umbilical cord	1	2	2	4	0	0
	Umbilical cord torsion	1	2	1	2	0	0
	True knot	1	2	3	6	0	0
Membranous insertion	Marginal	49	98	48	96	50	100
	Circummarginate	1	2	2	4	0	0

	Meconium-stained membranes	5	10	12	24	0	0
	Retroplacental clot	4	8	6	12	0	0
	Infarction	2	4	5	10	0	0
	calcification	6	12	9	18	0	0
	Depression	1	2	3	6	0	0
	Accessory lobes	2	4	0	0	0	0
	Noab normality	20	40	26	52	0	0

Table 3: Histopathological findings

Histopathological findings	Group I (FGR)(n=50)		Group II (IUD)(n=50)	
	N	%	N	%
Uteroplacental vascular in sufficiency	14	28	19	38
Acute inflammation	2	4	9	18
Peri villous fibrin deposition	2	4	5	10
Intervillous hemorrhage	2	4	2	4
Inter villous thrombi	0	0	2	4
Villous capillary hyper vascularity	8	16	3	6
Calcification	4	8	0	0
Villous dysmaturity	0	0	1	2
Syncytial knot	1	2	0	0
No abnormality	17	34	14	28

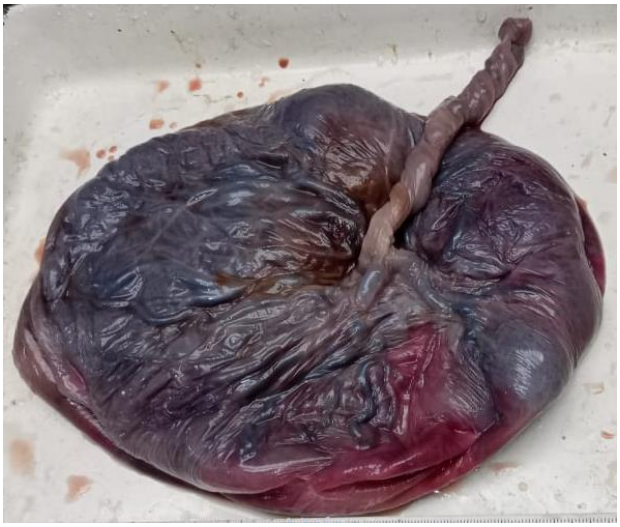

Fig. 1: Gross specimen of placenta showing central attachment of umbilical cord and haematoma

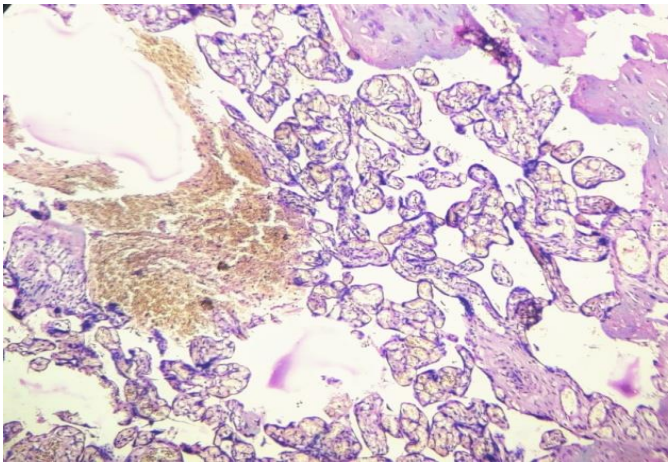

Fig. 2: Histopathology of placental tissue showing haemorrhage (10X, H&E)

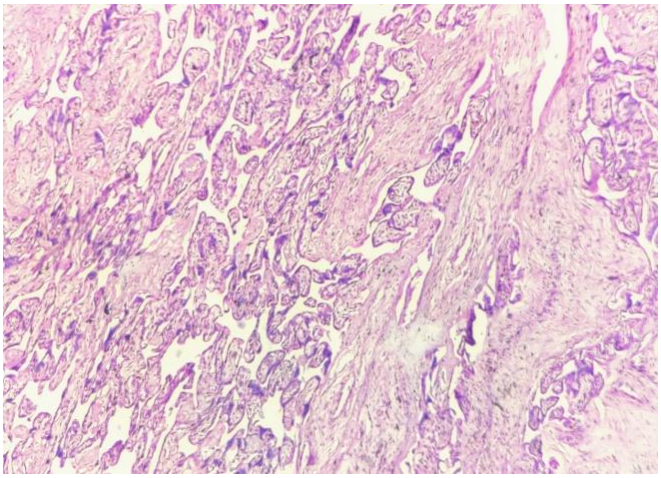

Fig. 3: Placental tissue showing syncytial knots (10X, H&E)

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