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Clinicomorphological Evaluation and Review of Placenta – In Intra Uterine Growth Retardation and Intra Uterine Fetal Death – An Indagation

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Abstract: Introduction: *Placenta is one of the most vital organs which give first-hand information related to outcome of pregnancy to the obstetricians. It helps in the exchange of gases, metabolic products between the mother and the fetus, and removal of wastes from fetal blood into the maternal circulation. Placental examination has been proved to be of clinical value in cases of Intrauterine Growth Retardation (IUGR) and Intra Uterine Fetal Death (IUFD).*

Aims and Objectives:*The aim and objective of the present study is to examine the morphological changes in placentae of normal and in the cases of intrauterinefetal death and intrauterine growth retardation, which in turn will improve the quality of placental diagnosis.*

Material and Methods:*Clinicomorphological study of placental lesions in cases of intrauterine growth retardation and intrauterine death with a sample size of 50 placentae. In the present study, 40 placentae were diagnosed cases of intrauterine growth retardation. Ten placentae from cases of full term normal delivery were taken as control. Gross and histomorphological analysis of the placentae was carried out and correlated with the pregnancy outcome in relation to various etiological factors.*

Results: *Amongst 50 placentae; 10 were normal and 40 placentae were collected from IUGR among them 20 placentae were of PIH, 3 were of anaemia, 3 were of polyhydramnios, 3 were of oligohydramnios, 3 were due to heart disease & 8 were due to idiopathic reasons. Among these, one case of severe anaemia leads to Intrauterine Fetal Death. Majority of IUGR cases were of age group 21yrs–25yrs (40%), and the common etiological factor was PIH (Pregnancy Induced Hypertension).Gross placental lesions i.e calcification, infarcts and haematoma were more commonly seen in the IUGR group.Histopathological evaluation shows variable results.*

Conclusion: *Placental evaluation plays a vital role in deriving the pregnancy outcome of etiological factors affecting to a variable extent. The severity of placental abnormalities expressed as cumulative number of placental lesions like infarcts, decreased villous vascularity, and fibrin deposition are significant risk factors for IUGR and have adverse perinatal outcome.*

Key words*: Histopathology; Intra Uterine Growth Retardation (IUGR); perinatal outcome; placenta; pregnancy*

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I. Introduction

Placenta is a complete organ having a maximum reserve capacity. It helps in the exchange of gases, metabolic products between the mother and the fetus, and removal of wastes from fetal blood into the maternal circulation. The placenta is an ephemeral organ interposed between the mother and fetus, often is the target of insults directed at the foetus. Thus it becomes a "diary of gestation"[1]. Thefetus, placenta and the mother form a complete triad of dynamic equilibrium in reproduction. Placenta is the most accessible and readily evaluable component of the triad.The earliest insight into the placenta came from the illustrations of 'Andreas Vesalius', and called after birth, the chorion[2]. The designation, placenta was introduced by Gabriele de Falloppioafter whom the fallopian tubes were named[2].Realdus Columbus represented a term that he borrowed from Latin that means to 'flat cake.Placenta has been a neglected organ until the late 1950's. The placenta did not undergo scrutiny in a critical fashion. Boyd & Hamilton reviewed all essential aspects of placenta, known till 1970; including normal ultrastructure.Placental examination has been proved to be of clinical value in cases of Intrauterine Growth Retardation. Many of disorders of pregnancy which are associated with high perinatal morbidity and mortality are accompanied by gross pathological changes in placenta[3]. Placental changes are directly proportional to the duration of the disease process and its severity. Fetal outcome is adversely

influenced by pathological changes observed in placenta.As placentae are rarely examined,there is a confusion regarding the benefits of routine placental examination based on pregnancy outcome, risk assessment for long term neurodevelopmental sequelae.It has been proposed for almost half a century that the placenta can be regarded as a dairy of the pregnancy, yet it is potential contribution to neonatal medicine remains frequently overlooked[4]. The benefits of the placental examination include clarification of the causes of many adverse pregnancy outcomes, improvement of the risk assessment for future pregnancies, and ascertainment of the new-born risk of long term neurodevelopment sequelae[5].As per the college of American pathologists committee on practice guidelines and Placental Pathology Task Forcerecommended indications of placental examination include maternal indications like systemic disorders with clinical concern for mother or infant (eg. Severe diabetes, hypertensive disorders, severe anemia,collagen disorders), premature delivery (<34 weeks), peripartum fever, unexplained third trimester bleeding (>500ml) severe oligohydramnios, recurrent pregnancy complications, thick and viscid meconium etc.Various studies on placenta have been conducted in the past in India and abroad. This work is essentially undertaken to examine the clinicomorphological changes in placentae and their clinical correlation in intrauterine fetal deaths and intrauterine growth retardation and to compare with the observations made earlier.

II. Material and Methods

The present study was undertaken in the Department of Pathology, S.V.Medical College, Tirupati during the period from 2016 to 2018 June. The work was concerned principally with the clinicomorphological study of placental lesions in cases of intrauterine growth retardation and intrauterine death with a sample size of 50 placentae. In the present study, 40 placentae were diagnosed cases of intrauterine growth retardation. Ten placentae from cases of full term normal delivery were taken as control.

Inclusion Criteria

- Pregnant women of all age groups
- Gestational Age > 28 Weeks based on 1st trimester scan, clinical findings and dates.
- Cases of IUGR diagnosed clinically and radiologically.
- Multiple gestations
- IUD

Exclusion Criteria

- Gestational age < 28 Weeks.
- Any infections like Chorioamnionitis.

Detailed obstetric and medical history was taken for all cases and clinical examination done just after delivery all the placentae were collected in a clean tray with the consent of the patient. The blood was removed gently and then washed thoroughly under tap water, mopped with dry cotton pad.

Gross examination: Placental weight (trimmed placentae without membranes and cord) and dimensions, foetal surface, membranes and cord examined, number of vessels in the cord were noted. Any blood clots were measured and completeness of the maternal surface assessed colour of the villous parenchyma and the villous lesions, particularly infarcts, thrombi, haematoma or undefined nodularity were measured and described.

Sampling: Five blocks were taken routinely in addition to the representative blocks from grossly abnormal areas, one each from the umbilical cord and the membranes. All the blocks taken were of full thickness (amnion through basal plate), fixed in 10% formalin, processed and embedded in paraffin blocks, cut at 5µm and stained with haematoxylin and eosin method. Special stains like PAS (Periodic Acid Schiff), is used wherever situation demanded.The following microscopic parameters were used for comparison among various study groups.

- Intervillous fibrin deposition
- Stromal fibrosis
- Cytotrophoblastic hyperplasia
- Villous vascularity
- Basement membrane thickening
- Fibromuscular sclerosis of fetal stem arteritis
- Fibrinoid necrosis
- Syncitial knots
- Calcification
- Inflammation

III. Results

In the present study, 50 placentae were studied, for comparison 10 placentae were taken as control from full term normal pregnancies, 40 placentae were collected from IUGR among them 20 placentae were of PIH (pregnancy induced hypertension), 3 were of anaemia, 3 were of polyhydramnios, 3 were of oligohydramnios, 3 were due to heart disease & 8 were due to idiopathic reasons. Among these, one case of severe anaemia leads to Intrauterine Fetal Death. According to our study, majority of Intrauterine Growth Retardation cases were due to PIH. The incidence results are tabulated in Table 1. The study results were analysed and tabulated. Categorical data is analysed by Chi-square test.

Table 1. Incidence of different etiological factors leading to IUGR

	No: of Cases n=40	**Percentage (%)**
PIH	20	50.%
Oligohydramnios	3	7.5%
Heart disease	3	7.5%
Polyhydramnios	3	7.5%
Anaemia	3	7.5%
Idiopathic	8	20%

Incidence of IUGR in different age groups as tabulated in Table 2 by dividing the cases into 3 groups i.e,.16-20yrs, 21-25yrs, & 26-30yrs.

Table2. Incidence of IUGR in different age groups

Age Group	**Normal n (%)**	**PIH n (%)**	**Heart disease n (%)**	**Anaemia n (%)**	**Oligo hydramnios n (%)**	**Poly hydramnios n (%)**	**Idiopathic n (%)**
16 -20Y	4 (40 %)	7 (35.5 %)	-	-	-	1 (33.33 %)	1 (12.5 %)
21 -25Y	4 (40 %)	8(40%)	3 (100%)	3 (100%)	2 (66.66 %)	1 (33.33 %)	5 (62.5 %)
26-30Y	2 (20 %)	5(25%)	-	-	1 (2.5 %)	1 (33.33 %)	1 (12.5 %)
Total	10	20	3	3	3	3	8

In the 16yrs-20yrs age group 7(35%) were of PIH cases, one (33.3%) case ofpolyhydramnios, and one (12.5%) case of idiopathic. In 21yr-25yr of age group 8(40%) cases were of PIH, 3(100%) cases were of heart disease, 3(100%) cases were of anaemia, 2(66.66%) cases were ofoligohydramnios, 5(62.5%) cases were of idiopathic. In 26yrs-30yrs age group there were 5(25%) of PIH, one case (33.33%) each of oligohydramnios, polyhydramnios& idiopathic. IUGR cases were of age group 21yrs–25yrs (40%), and the common etiological factor was PIH.

Maximum number of IUGR cases was seen in primigravida(65%) when compared to Multigravida (35%). In the primigravida, the most common etiological factor was PIH,with 15 cases, 1 case of heart disease and polyhydramnios, 2 cases of anemia and oligohydramnios and 5 cases of idiopathic. In multigravida 5 cases of PIH, 2cases of heart disease and polyhydramnios each, 1 case of anemia and oligohydramnios, & 3 cases of idiopathic were observed.

Table 3. Incidence of IUGR in relation to gravid status

Gravid status	**Normal n (%)**	**PIH n (%)**	**Heart disease n (%)**	**Anaemia n (%)**	**Oligo hydramnios n (%)**	**Poly hydramnios n (%)**	**Idiopathic n (%)**
Primi	7 (70 %)	15 (75 %)	1(33 %)	2 (66.66 %)	2 (66.66 %)	1 (33.33 %)	5 (62.5 %)
Multi	3 (30 %)	5 (25%)	2 (66%)	1 (33.33 %)	1 (33.33 %)	2 (66.66 %)	3 (37.5 %)
Total	10	20	3	3	3	3	8

Data recorded according to the gestational age by dividing them into 3 groups i.e., 28-32wks, 33-36wks, 37-42wks. Maximum number of IUGR cases i.e., 26 was in the age group of 33-36wks and 6 cases were in the 28-32wks. As tabulated in Table 4. In the present study, 80% of IUGR cases were preterm deliveries and only 20% were delivered at term. Placental weights were studied in relation to various etiological factors of IUGR by dividing weight of placenta into 3 groups i.e., 200 – 300gms, 301 - 400gms, & 401 -600gms. Maximum number of IUGR cases had the placental weight within 200 – 300gms.In the cases where the placental weight was in 200 -300gms, the maximum number of cases was due to PIH. All the placentae in control group were ranging from 300-600gms. Out of 40 cases of IUGR, 12 cases of PIH were <300gms, 6 were <4oogms and 2 were <600gms. Details recorded in Table 5.

Table 4. Incidence of IUGR cases based on Gestational age

Gestational age	Cases	Control
28 – 32 Wks	6 (15%)	-
33-36 Wks	26 (65%)	3 (30%)
37-42 Wks	8 (20%)	7 (70%)
Total	40	10

Gross placental lesions i.e calcification, infarcts and haematoma were more commonly seen in the IUGR group. Only the presence of calcifications was statistically significant, while the other two were not significant statistically as depicted in Table 6.

Table 5. Placental Weight(s) and comparison with respect to etiological factors and IUGR.

Placental Weight	Normal n (%)	PIH n (%)	Heart disease n (%)	Anaemia n (%)	Oligo hydramnios n (%)	Poly hydramnios n (%)	Idiopathic n (%)
200 – 300 gms	0	12(60%)	2(66.66%)	1(33.33%	-	-	2(24%)
301 – 400 gms	4(40%)	6(30%)	1(33.33%)	-	2(66.66%)	1(33.33%)	3(37.5%)
401 – 600 gms	6(60%)	2(20%)	-	2(66.66%	1(33.33%)	2(66.66%)	3(37.5%)
Total	10	20	3	3	3	3	8
	P value = < 0.001						

Intervillous fibrin deposition is seen in 10% of normal pregnancies, 85% of PIH cases, 66.66% of anaemia, 50% of idiopathic and 33.33% of heart diseases, which is statistically significant. Cytotrophoblastic proliferation was found in 20% of normal pregnancies.70% of PIH cases, 33.33% of anaemia cases and 25 % of idiopathic cases, which is statistically significant. Abnormal villous vascularity is seen in 80% of PIH cases, 66.66% of anaemia, heart diseases &polyhydramnios cases, 50% of idiopathic cases, which is statistically significant. Basement membrane thickening is seen in 55.57% of PIH cases, 50% of idiopathic cases, and 33.33% in case of anaemia, oligohydramnios, polyhydramnios& heart diseases.

Table 6. Gross lesions of Placenta

	Cases	Control	P. value
Calcifications	13/40	2/10	0.002
Infarcts	8/40	-	
Hematoma	2/40	-	

Fibromuscular sclerosis of fetal stem arteritis was seen in 70% cases of PIH, 33.33% of anaemia and 50% of idiopathic cases.This is statistically very highly significant. Fibrinoidnecrosis is seen in 10% of normal pregnancies, 80% of PIH, 33.33% of anaemia & 50% of idiopathic, which is statistically significant.Syncytial knots were seen in 30% of normal placentae & were significantly increased in 75% of PIH cases, 100% of anaemia, 66.66% of polyhydramnios, and 75% in idiopathic cases.Calcifications were common in both groups of placentae & it accounted for 30% of normal placentae, 60% of PIH, 66.66% of anaemia, 33.33% in oligohydramnios and polyhydramnios cases,50% in idiopathic.This is statistically very highly significant. Infarction was observed in 20% of normal pregnancies, 30% of PIH, 33.33% of anaemia, 66.66% of oligohydramnios, 25% idiopathic cases, 33.33% of heart diseases.The incidence of histological lesions like cytotrophoblastic hyperplasia, abnormal villous vascularity, basement membrane thickening, fetal stem artherosis, finbrinoid necrosis,syncitial knots,calcifications are seen more in PIH cases leading to IUGR, which was closely followed by idiopathic cases. Calcifications were common in controls and IUGR placentae.In one case of idiopathic IUGR, the umbilical cord showed one artery and one vein, but there were no gross abnormalities seen in the newborn. All the parameters are in detail tabulated in Table 7. The pictographic review of various lesions we have come across during this study - gross and histomorphological features is depicted in Figure 1 & 2.

IV. Discussion

The study of placenta though retrospective provides a reflection of hazards the fetus has been subjected to during its growth and development. Fox suggested the placental pathology is quantitative rather than qualitative[6]. Benrischke and Fox stressed the significance of placental findings only when these had a bearing on the fetal outcome[2,6].We observed that IUGR was mostly associated with PIH accounting for 75% of cases and idiopathic 62.5%.

Table 7. Comparision of Histological lesions of placenta according to etiological factor

Features	Normal n (%)	PIH n (%)	Anaemia n (%)	Heart diseases n (%)	Oligo hydramnios n (%)	Poly hydramnios n (%)	Idiopathic n (%)	P Value
Intervillous Fibrin Deposition	1(10%)	17(85%)	2(66.66%)	1(33.33%)	-	-	4(50%)	
Cytotrophoblatic Hyperplasia	2(20%)	14(70%)	1(33.33%)	-	-	-	2(25%)	< 0.001
Abnormal Villous Vascularity	-	16(80%)	2(66.66%)	2(66.66%)	-	2(66.66%)	4(50%)	
Basement membrane thickening	-	11(55%)	1(33.33%)	1(33.33%)	1(33.33%)	1(33.33%)	4(50%)	-
Fetal stem arteritis	2(10%)	14(70%)	1(33.33%)	-	-		4(50%)	
FibrinoidNecrosis	1(10%)	16(80%)	1(33.33%)	-			4(50%)	< 0.001
Calcification	3(30%)	12(60%)	2(66.66%)	-	1(33.33%)	1(33.33%)	4(50%)	
Infarction	(0%)	6(30%)	1(33.33%)	1(33.33%)	2(66.66%)		2(25%)	-
Syncytial Knots	4(30%)	15(75%)	3(100%)		1(33.33%)	2(66.66%)	6(75%)	-

Table 8. Gestational age of delivery

Study	Gestational age of delivery
Ilker Gunyeli[7](n=26)	31- 35 weeks
Barut et al[8](n=55)	25- 31.5 weeks
Theodora B et al[9](n=40)	36 – 38 weeks
Present study (n=40)	33-36 weeks

Gestational age of delivery among IUGR babies was between 33 -36 weeks,which is in correlation with the study done by Ilker gunyeli[7].Vedmedovska N et al[10],Malliket al[11]and Mehendale[12]have also observed a reduced placental weight among IUGR fetuses. The findings in the present study are in close relation with the study done by Khadija Qamaret al[13].

The incidence of fetal morbidity and mortality were directly related to reduce placental weight. Similar results were noted by Mohan Harshaetal[14]in their study.

On gross examination placental diameter and thickness were noted and in the present study these parameters are reduced with a significant reduction seen with placental diameter than placental thickness. The findings are coinciding with that of Barutet al[8].In the present study, findings on gross examination like infarction, calcifications and hematoma were also noted and the presence of infarcts were seen in close association with IUGR placentas. Similar findings were seen in study done by Kavitha M[1]. Salafiaet al[5] in their study have also observed the presence of infarcts more in IUGR. Naeye[15]found that 1-4 grossly visible infarcts >3cm occupying >20% of the placenta was associated with IUGR at every gestational age. Suskaet al[16]have pointed out that infarcts covering more than 6% of the placental areas play important role in the pathogenesis of IUGR. Bjoro[17]observed that maternal floor infarcts occur more frequently in IUGR placentas.

The incidence of adverse neonatal outcome was observed to be high in presence of gross pathological lesions but the incidence of still birth in presence of a retroplacental hematoma was significant statistically. Similar finding was seen in a study done by Seishi Furukawa et al[18], Chan KH[19]in their study have correlated the presence of calcification with perinatal outcome and have concluded that no relation exists when the calcifications appear in later part of pregnancy.

On microscopic examination, high incidence of intervillous fibrin deposition 60% was found in the present study which was closely related to study done byIlker Gunyeli[7]and it accounted for 65% but the study done by Vedmedovska N[10]showed no significant increase in these parameters among the FGR group compared with normal fetuses.Syncitial knot formation(67.5%)and fibrinoidnecrosis(52.5%).They are also the common findings observed in IUGR. According to Mehendale[12]syncitial knot formation accounted for 48.6%

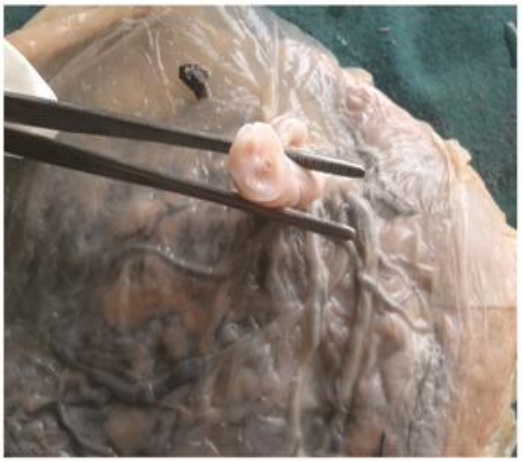
The present study showed basement membrane thickening in 47.5% of cases, it was observed in 56.7% and 40% of cases respectively by Mehendale[12]and Kavitha[1]. Calcifications were variable in various studies and accounted for 38% in Mehendale[12]and 36% in Kavitha[1]. In our study it accounted for 50%.Cytotrophoblastic proliferation was variable in various studies and accounted to 30% in Altshuler[20, 21]; 62% in Mehendale[12]and44% in Kavitha[1].Infarction was observed in30% of cases in present study which is closely related to study done by Kavitha[1]which accounted for 28% of cases. The outcome in the IUGR placenta is low birth weight baby.Neonatal morbidity and mortality may also be high and are mainly due to inflammatory and morphological changes in placenta. The present study showed basement membrane thickening in 55.5% of pregnancy-induced hypertension. Fox[6]studied basement membrane thickening in 159 cases of PIH and observed

thickening in (52.6%) of cases. The study principally states that the pathogenesis of placenta in relation to IUGR and IUFD is the result of placental ischemia. This was suggested by the finding of a high incidence of basement membrane thickening in pre-eclamptic toxaemia of pregnancy. The high incidence of hypoxic complications in babies of PIH implied that ischemia was due to the basement membrane thickening seen in these cases. The association between basement membrane thickening and Langhan's cell hyperplasia is a response to placental ischemia. There was a high variability of infarction in two different studies conducted by Mehendale[12]and Moldenhauer[22] separately and represented 87% and 19.2% respectively. The present study showed infarction in 30% cases of PIH.Calcifications can be prominent but it is not the characteristic feature in PIH. It is of dystrophic type, where the placenta is damaged due to the discordant blood pressure. It was observed in 60% placentas in our study,whereas Mehendale[12]noted in 75% of cases of PIH.Intervillous fibrin deposition was seen in 19.2% of cases of PIH in Moldenhauer[22]and it was recorded as 85% in our study. It is mainly dueto the access of fetal erythrocytes into the maternal space and initiation of intervillous thrombosis at sites of chorionic villous damage and haemorrhage. Fibrinoid necrosis of villi or intravillousfibrinoid deposition was seen in 80% cases of PIH. It was observed in 10% of normal pregnancies. It is due to degeneration from the placental ageing or hypoxic damage to the trophoblasts.The study of Moldenhaueralso hypothesised that, the placental lesions were more common of women with pre-eclampsias and particularly at early gestational age[22].

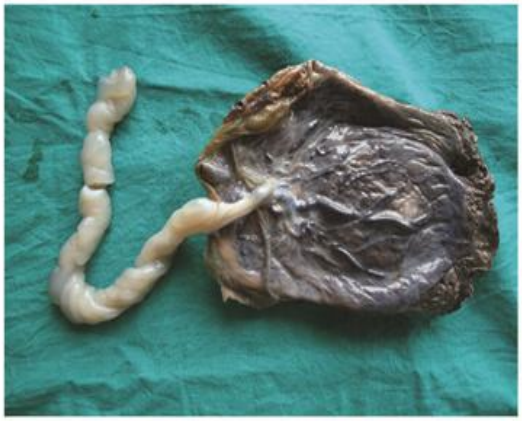
V. Conclusion

Placentae from fetal growth restricted neonates showed numerous gross and microscopic changes which pointed towards reduced blood flow to the placenta resulting in chronic placental insufficiency. The severity of placental abnormalities expressed as cumulative number of placental lesions like infarcts, decreased villous vascularity, and fibrin deposition are significant risk factors for IUGR and have adverse perinatal outcome.

NORMAL PLACENTA WITH CENTRALLY PLACED UMBILICAL CORD



NORMAL UMBILICAL CORD WITH TWO ARTERIES & ONE VEIN



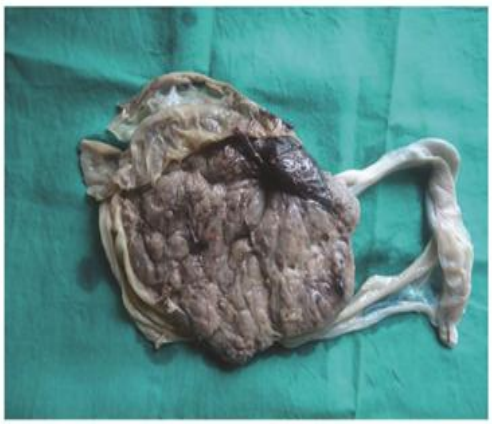
LOW WEIGHT PLACENTA WITH ECCENTRICALLY PLACED UMBILICAL CORD

UMBBILICAL CORD WITH ONE VEIN & ONE ARTERY

PLACENTA SHOWING INFRACTION

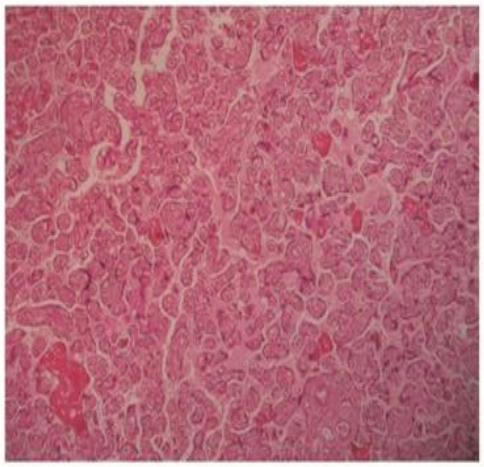
PLACENTA WITH FIBRIN DEPOSTION

Figure 1

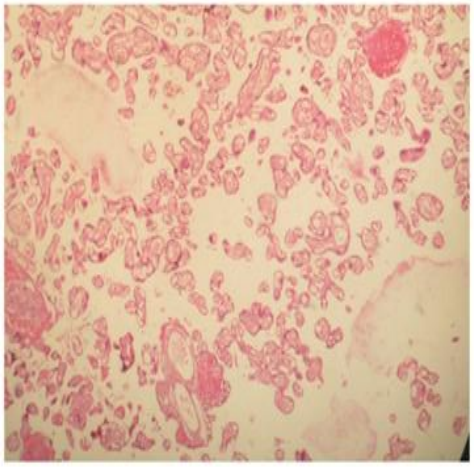


PLACENTA WITH RETROPLACENTAL HAEMATOMA

PLACENTA WITH CALCIFIED AREAS



NORMAL TERMINAL VILLI (H&E X100)



HYPOPLASIA OF TERMINAL VILLI (H&E X100)

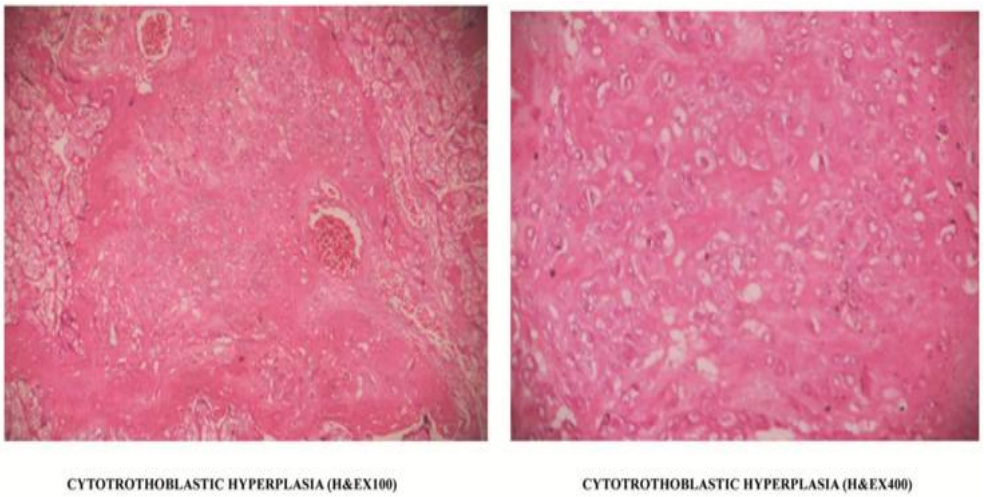


Figure 2

The presence of infarction was associated with poor fetal outcome and retroplacental haematoma was associated with an increased risk of still births. Thus, Placental examination in FGR (fetal growth restriction) related pregnancies can provide a specific pathophysiological explanation that may recur in subsequent pregnancies and lead to changes in follow up and management. The specific findings can also be helpful for a neonatologist in early identification of infants at increased risk of neonatal death or abnormal neurodevelopment.

Conflict of Interest
None

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