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Original Research Paper

Clinical Research

HIGH RISK PREGNANCY WITH POOR FETAL OUTCOME- IS PLACENTA THE REAL CULPRIT ?.

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ABSTRACT

Background: In high risk pregnancies with poor fetal outcome careful examination of placenta along with microscopic study may frequently point to the cause of perinatal death. So we have planned a prospective observational study was to illustrate the gross and microscopic changes in placenta in certain normal and abnormal pregnancies and to analyses the relationship of placental pathology with fetal outcome. **Methods:** A prospective study of 100 deliveries at a tertiary teaching hospital in India. Each placenta was studied macroscopically in labour room and sent for microscopic examination. The study included placentas of normal pregnancies and those with high-risk pregnancies. Microscopically placentas were studied for vessel wall thickening, infarction, villitis, chorioangiosis, calcification and intervillous hemorrhage. The outcome variables were studied in each histological group and compared with the normal group using Ψ2 test for homogeneity. For cell frequencies less than 5, Fischer Exact Test was used. **Results:** Vessel wall thickening was demonstrated in 51% patients. Infarcts were demonstrated in 14%. **Conclusions:** Placental abnormalities like vessel wall thickening, and infarction is associated with abnormal fetal and neonatal outcome.

KEYWORDS : Pregnancy at Risk, Abnormal Fetal outcome, Placental Microscopy

INTRODUCTION

Placenta has multifaceted roles in fetal development and survival. Placenta and membranes plays important role in passage of nutrients and gases from mother to fetus. During its intrauterine existence, the fetus is dependent on the placenta as its lungs, liver and kidneys.

Human placenta produces diverse amount of steroid hormones and other proteins to control endocrine orchestra in human pregnancy.. In spite of placenta being important organ in human fetal development there is not much research about it. Recently various clinical studies have appreciated the plethora of knowledge that can be gained from the study of placenta.

Real time assessment in ongoing pregnancy is difficult due to largely inaccessible position of the placenta. It has hampered studies on placenta and it is thus called the 'least understood' human organ. Macro and microscopic examination of placenta may frequently answers various questions on cause of perinatal death.

The American College of Pathologists and ACOG has provided guidelines for the examination of placenta.1 Now a days when medicolegal problems threaten the practicing obstetrician, so study of placenta with histology can delineate exact cause behind perinatal death and can protect doctor from the consumer forum.The objectives of the present study were to observe the gross and histopathological changes in placenta in certain normal and abnormal pregnancies and to analyse the relationship between placental pathology and fetal outcome.

METHODS

100 consecutive deliveries at Smt.Kashibai Navale Medical College and General Hospital, Pune was studied over 6 months. Each placenta was studied macro and microscopically in pathology department.

The study included placentas of normal pregnancies and those with various high risk factors for obstetric or neonatal outcome such as preterm, preeclampsia, GDM, jaundice in the mother, Rh negative mothers, postdated pregnancies, intra uterine fetal death, abruption and anomalous fetus. Detailed obstetric history and medical history was taken for each patient in predefined proforma, clinical examination and routine relevant investigations were done.

All patients were studied with regard to mode of delivery, duration of rupture of membranes, colour of liquor, post-partum complications. Each baby was examined for sex, birth weight, date of birth, apgar at 1 minute and followed up for a period of 1 week. The neonates were followed in the post-partum period for neonatal sepsis, jaundice and death within one week of birth.

Collection of placenta

All placentae were weighed in grams with 5 cm cord attached to it . Placenta was examined macroscopically.

Macroscopic examination

Five instruments were used for this purpose. A measuring tape, sharp knife, sharp scissors, toothed forceps and calibrated metal cord were used to measure thickness. Each placenta was examined, and the diameter, circumference and thickness were measured.

Placentae were examined for the maternal surface, amniotic surface, Cut surface, membranes and the umbilical Cord. Pacental surface attached to the uterine wall was studied for the presence or absence of infarction, calcification, fibrin deposits and retroplacental clots. amniotic surface was examined for the colour, cysts, calcification, bands, and fibrin deposits. Membranes were examined for the opacity, fetal vessels, colour and membrane insertion. The Umbilical Cord was examined for the Length and diameter, Site of insertion, vessels and Abnormalities.

Histological examination of placenta

The placentae were sent to the pathology department after fixing in 10 % formalin. Placentae were sliced into segments of 1-inch thickness. Following sections were taken from each placenta, one from membranes and cord, 1 from lateral placental tissue, 2 from superficial placenta, 2 from basal placenta. Placental sections were fixed in paraffin and stained properly before preparing pathology reports. Important microscopic findings noticed were vessel wall thickening, infarction, villitis, chorioangiosis, calcification and intervillous hemorrhage. Fetal and neonatal morbidity or mortality were primary outcome variables studied in our study. Placenta histopathological findings in abnormal outcome group were compared with the normal group using $\chi 2$ test for homogeneity. For cell frequencies less than 5, fischer exact test was used.

RESULTS

100 consecutive deliveries at SKNMC &GH lying in hospital were studied over 6 months. These included both low risk and high-risk pregnancies. Out of these 55 were primigravida and 45 were multigravida. Some patients had more than 1 risk

factor. The risk factors are described in Table 1. Out of 100 placentae, 70 (70%) placentae were of discoid shape, 15 (15%) were ovoid, 10 (10%) were bilobed.

Table 1: Distribution of cases

Risk factors if any	No. of primigravida	No. of multigravida
Preeclampsia	5	2
Abruptio placenta	3	1
PROM	10	5
IUD	5	
Post term	06	5
Preterm	04	5
Anemia	5	
Rh Negative	5	3
Diabetes	2	2
Congenital Anomalies	4	5
BOH	4	1
Low risk	8	10

There was one patient with a membranous placenta. The outcome was poor in succenturiate placenta, both were preterm. The number of cotyledons varies from 10-38 and are incompletely separated by placental septa. The study group showed an average of 20 cotyledons per placenta. The maximum number being 23 and the minimum being 13. The average number of cotyledons in twins was 30 and did not have any functional significance. In majority of the cases the cord insertion was central in 80 (80%), followed by eccentric insertion in 20 (20%). One case had velamentous insertion. It was an abnormal fetus with anencephaly. The average weight of the placenta in primigravida was 450.25 grams and that in multigravida was 500.72 grams. It is seen that placental weight increases with parity.

Table 2: Fetal growth and placental weight.

Fetal Growth	No	Mean Placental weight (in gms)	Mean fetal weight (in kgs)	Mean F:P ratio
Full term	80	400	2.8	6
Preterm (AGA)	4	320	2.1	6.5
Post term	11	425	2.76	6.49
IUGR	5	318	2	6.28
Preterm(SGA)	5	300	1.75	5.8

The mean Feto-placental ratio was 6 for full term babies. It was reduced in IUGR, SGA and preterm babies as shown in Table 2. The Mean Feto-placental ratio was reduced in conditions causing chronic uteroplacental insufficiency, such as preeclampsia, and liver disease as described in Table 3.

In a case of gestational diabetes, the ratio was higher (6.66). Analysis of 9 congenitally malformed fetus showed that fetoplacental ratio was reduced in them. There were 8 Rh negative pregnancies in the study. Fetoplacental ratio of 2 neonates with hydrops fetalis was less when compared to unimmunised fetus's.

Table 3: Feto-placental ratio in high risk cases.

Risk factors	No	Mean Placental weight (in gms)	Mean fetal weight (in kgs)	F:P RATIO
Preeclampsia	7	400	2.21	5.5
Abruptio placenta	4	320	1.75	5.4
PROM	15	375	2.1	5.6
IUD	5	350	2.5	7
Anemia	5	440	1.8	4.09
Rh Negative	8	412	2.7	6.55
Diabetes	4	420	2.8	6.66
Congenital Anomalies	9	340	1.61.	4.74
BOH	5	220	1.24	5.6

The commonest histological change in preterm delivery was vessel wall thickening (80%) followed by villitis (46.67%) and infarction (40%) as shown in Table 4. In term delivery, vessel wall thickening was found in 48.68% followed by normal histology in 38.15% and villitis in 32.89%. In placenta of patients who delivered 1 week beyond dates, 50 % had infarction and 87.5% showed calcification.

Table 4: Analysis of histological features with gestational age.

Histological feature	Preterm N=15		Term N=80		Past date N=11		Total N=100	
	No	%	No	%	No	%	No	%
Vessel wall thickening	10	66.6	35	43.75	6	54.5	51	51
Infarction	5	75	5	6.25	4	36.36	14	14
Villitis	8	53.33	20	25			28	28
Chorioangiosis	1	6.67	10	12.5			11	11
Calcification	1	6.67	25	31.25	8	72.72	34	34
Intervillous hemorrhage	1	6.67	22	27.5	5	45.45	28	28
Normal	3	20	28	35			31	31

Analysis of histological features with fetal outcome

Vessel wall thickening was identified in 51 patients (51%), 8had Apgar <5/10 while 2neonates of normal histology had Apgar <5/10. The occurrence of IUD was significantly high when compared to those with normal histology, as shown in Table 5.

The vessel wall thickening was mild in 25 (49.01%), moderate in 20(39.21%) and marked in 6 (11.76). Vessel wall thickening was identified in normal new born also but it was of a milder type. 14 Placentae (14%) had infarction characterized by ischemic villous necrosis with ghost like villi with diffuse fibrinoid material. 08were preterm births of which 3 had preeclampsia; 4 were IUD, 1 neonate had Apgar < 5 at 1 minute. Infarcts were seen in normal new born also but to a lesser extent. The incidence of abnormal neonatal events was significant when compared to the normal group, as shown in Table 6. An increase in sepsis and preterm labour was found in placenta showing villitis, but it was not statistically significant. Villitis was identified in placentas of normal neonates also but it was more of mild variety.

Table 5: Analysis of placenta with vessel wall thickening.

Neonatal Outcome	Vessel wall thickening N=51		Normal histology N=31		P value
	No	%	No	%	
1 min apgar <5/10	6	30.6	2	6.45	SD p <0.05 Ψ2ld.f =5.69
Infections	4	7.84	1	3.22	
Anomalies	2	3.92			
Preterm birth	12	23.52	3	9.67	
IUD	3	5.82	2	6.45	
IUGR	2	3.92	1	3.22	
Normal Newborn	5	9.80	6	19.35	

Table 6: Analysis of placentas with infarction.

Neonatal Outcome	Infarction N=14		Normal histology N=31		P value
	No	%	No	%	
1 min apgar <5/10	1	35.71	3	9.67	SD P<0.01 Ψ2ld.f =8.95
Infections	2	14.28	1	3.22	
Anomalies	1	7.14			
Preterm birth	8	57.14	6	19.35	

IUD	4	28.57	2		
IUGR	6	42.85	3		
Normal Newborn	4	28.57	20		

Villitis was mild in 28 patients (28%), moderate in 10 , diffuse in 8 .11 placentas had chorioangiosis characterized by increase in number of capillaries per villi. On comparing with normal group, 1-minute Apgar <5/10 was seen in 22.2%, but it was not statistically significant. Calcification was identified in placentas of post term and term neonates. It was not correlated with abnormal fetal outcome. 28 placentas with intervillous hemorrhage were studied. The incidence of IUD was 16.3% and IUGR was 18%. However, it was not statistically significant. The placentas had features other than those studied in detail. They include fibrin deposits, villous edema and hyaline changes. The neonatal outcome was not statistically significant for these features when compared to the normal group.

DISCUSSION

Placental size and weight

According to Benirschke et al the normal placenta at term is on average 185 mm in diameter and 23 mm in thickness with average volume 497 ml and weight 508gms.2,3 In our study, the average size was 19 cm and thickness 2.16 cm. In this series, the average weight of placentas in primigravida was 450.25 gms and that in multigravida was 500.72 gms. The placenta of multigravida weighed more than primigravida.

Placental villous architecture

Human placenta is described as hemochorio endothelial.4 Maternal blood bathes the syncitiotrophoblast and villi and is separated from the fetal blood by endothelium lining the fetal blood vessels.

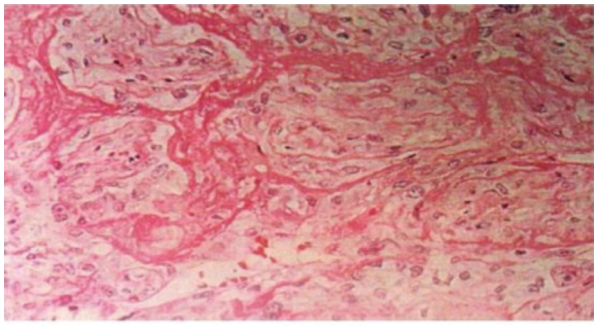

Figure 1: Vessel wall thickening with ischemic changes.

There are 5 types of placental villi. Mesenchymal villi apppear at 7-8 weeks of pregnancy and the reticular appearance persists till 14 weeks. Apparent spaces are actually stromal channels. Terminal villi appear at 30 weeks. Also, there are, immature intermediate villi, mature intermediate villi and stem villi as shown in Figure 1.

Rohr Fibrinoid is the condensed extracellular material near the intervillous spaces and Nitabuch layer is the deeper layer of fibrinoid tissue. Blood from the maternal decidual spiral artery enters the intervillous space and fills the intra-cotyledonary cavity. The venous openings in the basal plate are arranged about the periphery.

Indications for placental examination were reported by Altshuler et al.1,5 They include maternal conditions like diabetes mellitus, preeclampsia, premature rupture of membranes, preterm delivery (before 37 weeks), post term delivery >42 weeks, unexplained fever, poor previous obstetrical history and h/o drug abuse including cocaine.

Fetal and neonatal characteristics requiring placental examination include still birth, neonatal death, multiple gestation, prematurity, intra uterine growth retardation, congenital anomalies, erythroblastosis fetalis, transfer to neonatal ICU, ominous fetal heart tracings, presence of meconium and low apgar scores.

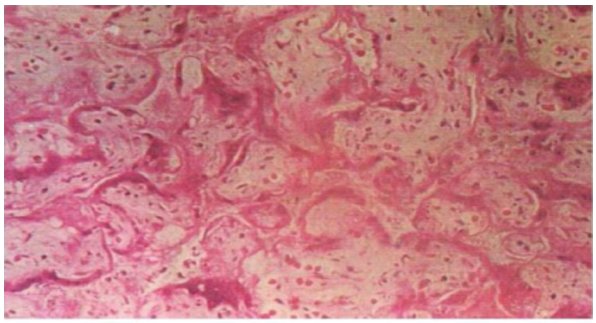

Figure 2: Infarct with ghost like villi.

Kaplan et al has studied the fetoplacental ratio in detail.5 The ratio was found to be 4 at 24 weeks and increases to 7 at term. The ratio is reduced in hydrops fetalis and diabetes and the ratio is increased in uteroplacental insufficiency.

The feto placental ratio is more significant of fetal well being than weight of the placenta alone. In this study, the average feto placental ratio is reduced in preeclampsia, IUD, and BOH (Figure 2).

According to Richard and Naeye et al feto placental ratio is increased in conditions of chronic placental insufficiency and reduced in conditions causing placentomegaly like Rh incompatibility, syphilis and diabetes.6,7

Shape

Irregular non-ovoid shapes are due to abnormalities of implantation, failed involution of chorion levae and intracavitary uterine abnormalities.8 They result in retained placenta, velamentous vessels, placenta previa and premature placental separation. In this series, the shape of the placenta was discoid in 74.16%, ovoid in 17.5% and bilobed in 5.83%. According to Benirschke et al 81.6% were round, 16% ovoid and 2.4% irregular.2,8

In succenturiate placenta accessory lobes are seen in addition to normal placenta. Placenta membranaceae is thin expansive placenta. Circummarginate placenta is a condition where a rim of placental tissue is seen extending beyond the vascular plate with margins having fibrin probably due to abnormal placentation/development. Circumvallate placenta is similar to circummarginate placenta but membrane folds and hemorrhage is seen at the margins causing PROM, prematurity and Antepartum hemorrhage.2,8

In a series of 1,95,000 cases studied by Benirschke and Kaufmann, had marginal insertion (7%) and velamentous insertion in 0.83%. In this series central insertion was found in the majority in 75.2%, eccentric in 23.14%, marginal in 5.3%, velamentous insertion in 0.83%.

The identification of velamentous insertion of cord antenatally is important because it can cause catastrophic fetal blood loss after rupture of membranes producing fetal distress. The incidence of the condition is 1% and is associated with fetal anomalies and vasa previa.2,8

Cord complications

In this study, long cord was found in 0.7% and short cord in 0.5%. Edema of the cord was seen in all cases of IUD. A case of twin pregnancy (twin II) with anencephaly showed a single umbilical artery. The incidence of single umbilical artery according to Benirschke and Dodds was 0.85% in singleton and 5% of all cords in at least one twin.2 The incidence of

congenital anomalies in such fetuses is higher 18-68%. They include renal aplasia, neural tube defects, limb reduction defects and atresia of hollow organs.

The incidence of single umbilical artery is 0.5 – 1%, according to Geipel et al single umbilical artery arises due to primary agenesis or atrophy and are associated with congenital anomalies in 20 %.9 It is associated with an increase in perinatal morbidity and mortality.

On analyzing placenta of fetuses with congenital anomalies, it was found that the fetoplacental ratio was redu One fetus had cystic hygroma with multiple other defects like short cord, absent nares, fusion of thorax to the head.

The placenta was enlarged and edematous. Later the condition was diagnosed to be a case of non- immune hydrops. Benirschke et al associates abnormal fetal development to placental development. Malformations and disruption of placenta and body wall are seen inbody stalk anomaly, limb body wall complexes, acardia, TRAP, sirenomelia and other anomalies.2

Analysis of placenta of 8 Rh negative mothers in this series showed that fetal outcome was poor in three of them. Two babies had hydropsfetalis showing placentomegaly, edema and pale placenta. The feto-placental ratio was reduced in both.

Histological analysis of placenta

Placental Samples from 100 consecutive deliveries were sent for histopathological analysis. They included both low risk and high-risk pregnancies. In this series 31 % had normal histology, 51% had vessel wall thickening, 14% had infarction, villitis in 28% chorioangiosis in 11%, calcification in 34% and intervillous hemorrhage in 28%. The frequency of placental features was analysed in relation to selected newborn characteristics like Apgar at 1 minute, infections, anomalies, death in 1 week, preterm birth, IUD, IUGR. For comparison, normal featured placenta and their outcome was compared. Abnormal fetal /neonatal events in each histological group were compared with the normal group using 2 test for homogeneity. For cell frequencies less than 5, Fischer exact test was used.

The association of abnormal neonatal events with vessel wall thickening was significant – $p<0.05$. The incidence of neonates with 1 minute Apgar <5 /10 preterm birth and IUD was also significantly high in this group. This supports the hypothesis that adverse neonatal outcome was probably due to ischemia resulting from decreased uteroplacental blood flow.10

An unexpected finding was the occurrence of vascular changes in the placenta of healthy newborns. However, these lesions were of mild variety. Figure 1 shows changes seen with vessel wall thickening. Analysis of infarction in placenta revealed that preterm labour, IUD, and death within 1 week was higher in this group. Statistical analysis showed that the incidence of abnormal neonatal events in placentas with infarction was significant $p<0.01$. Areas of infarct appear as ghost like villi as shown in Figure 2. Sato et al studied the placental findings and maternal and fetal factors in the cases of IUGR (n=257, mean maternal age, 30 years; gestational weeks, 34 weeks) and normal growth pregnancies (n=258, mean maternal age, 30 years; gestational weeks, 33 weeks), and determined risk factors for IUGR. Pathologically, the prevalence of infarction (33% vs. 14%, $P<0.05$), fetal vessel thrombosis (22% vs. 6%, $P<0.001$) and chronic villitis (11% vs. 3%, $P<0.001$) were higher in IUGR cases than those in normal growth pregnancies.11 These findings are similar to this study where vessel wall thickening, infarction and villitis were significantly associated with abnormal neonatal events. On analyzing the group with villitis, the number of newborns with 1 min Apgar <5/10 was higher. Most important was the incidence of sepsis in the neonates of this group but it was not statistically significant probably due to the small sample size. Villitis was seen in placenta of normal newborn also, but it was of mild type. Chorioamnionitis with a bacterial cloud is shown in Figure 3.

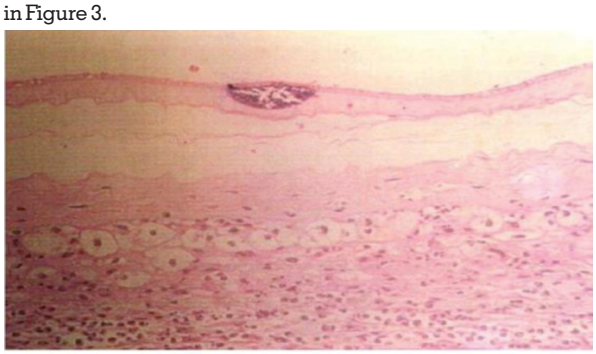

Figure 3: Chorioamnionitis with bacterial cloud.

According to Altshuler and Hyde, chorioamnionitis is involved in the pathogenesis of preterm labour, fetal hypoperfusion and brain damage.1,2,6 Katz et al in a study of 128 newborns with prolonged rupture of membranes showed that 64 had evidence of histological chorioamnionitis. Gestational age, birth weight, and Apgar scores were significantly lower in this group.10 These findings are similar to our study.

The incidence of neonates with apgar at 1 minute <5/10 was higher when the histological feature of chorioangiosis was analysed but it was not statistically significant. Chorioangiosis was characterized by excess of fetal vessels in the terminal villi as the try to overcome the diminished maternal blood flow.2 The association of calcification with fetal outcome was not significant as a majority of normal healthy newborns also showed this feature. Intervillous hemorrhage is characterized by breaks in the villous epithelium secondary to ischemia and showed a higher incidence of IUD, IUGR and newborn with 1 min Apgar <5, but it was not statistically significant. Figure 4 shows macrophages in the intervillous spaces and Figure 5 shows perivillous fibrin deposits.

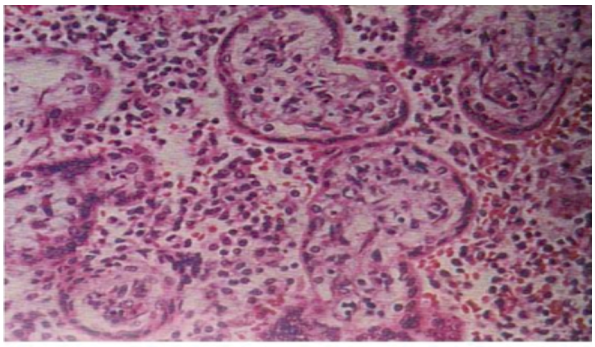

Figure 4: Macrophages in the intervillous spaces.

Marcorelles in a bibliographic review using the Medline and PubMed databases suggests that umbilical cord anomalies, fetal thrombotic vasculopathy, chronic villitis of unknown etiology and chronic histiocytic intervillositis are related to fetal growth restriction. However, there is no direct link between a type of placental pathology and the infant's adverse outcome or his neurological risk. The maternal risk of recurrence is not easily predictable except for the chronic histiocytic intervillositis in which the estimated recurrence rate is very high. In the present study, chronic histiocytic intervillositis was not studied.12

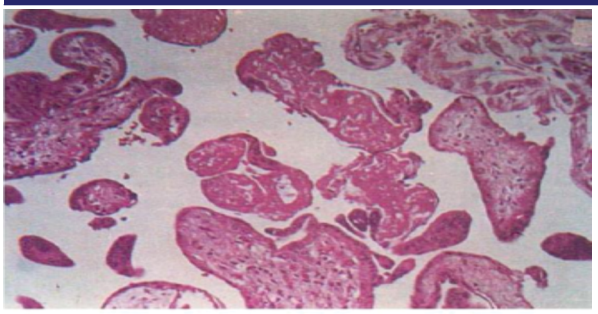

Figure 5: Perivillous fibrin deposits.

One major implication of this study is that gross and histopathological examination of placenta provides insight into neurological illnesses that may occur later in life. It could help protection from medico legal issues to the practicing obstetrician. Existing data and samples can be utilized to identify newer markers and molecular signatures for understanding the biology of normal and adverse pregnancy outcomes.

The strength of the study is that it is a prospective, single institution analysis with a short inclusion period. All pathological examinations were done by a single dedicated pathologist. Therefore, it reduces bias due to changes in the patterns of specimen collection as well as interpretation of pathological slides. A limitation is the nonrandomized design, small sample size and the short follow Also, proteomic or genomic study on the placental tissue would have identified key gestational stage signatures.16

CONCLUSION

Certain placental histological features like vessel wall thickening and infarction are associated with abnormal fetal and neonatal events. The feto- placental ratio is altered in IUGR and prematurity. It is also reduced in conditions producing placental insufficiency such as preeclampsia and chronic medical conditions. Placenta is a readily accessible specimen that assists in clinical diagnosis and to identify the a etiopathology of diseases of pregnancy and newborn

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