International Journal of Gynaecology and Obstetrics Research
www.gynaecologyjournal.in
E-ISSN: 2663-3612, P-ISSN: 2663-3604
Received: 10-08-2020 Accepted: 25-08-2020; Published: 11-09-2020
Volume 2; Issue 2; 2020; Page No. 04-09

A comparative gross and microscopic study of placenta in intrauterine growth restriction and appropriate for gestational age

Abhipsa Mishra[1*], Chingling Yi[2]
[1] Assistant Professor, Department of Obst and Gynecology, Kalinga Institute of Medical Science, Orissa, India
[2] Professor, Department of Obst and Gynecology, TNMC and Nair Hospital, Mumbai, Maharashtra, India

Abstract
Background: Pathological processes interfering with placental function may result in abnormalities of fetal growth. The purpose of this study is compare the gross and microscopic changes of placenta of intrauterine growth restricted fetus and appropriate for gestational age
Methods: It was a cross sectional study conducted in the department of Obstetrics & Gynaecology and pathology in TNMC Nair Medical College, Mumbai. Seventy number of Placenta, from full term intrauterine growth restricted (IUGR) and appropriate for gestational age (AGA), each studied Gross and microscopically.
Results: On gross examination, placenta weight, placenta Diameter, placenta thickness were significantly less in IUGR group. No significant difference in length of the umbilical cord found. On microscopic examination, maternal surface calcifications, intervillous fibrin deposit, infarction, villitis, maternal fibrinoid necrosis, Syncitial knot, Basement membrane thickening were significantly high in IUGR group.
Conclusion: Gross and histological changes can be the cause of IUGR, but single lesion or multiple lesions leading to the causation of IUGR is unclear.

Keywords: placenta, umbilical cord, intrauterine growth restriction, appropiate for gestational age

Introduction
In the realm of its popular description as 'THE ROOT THAT NOURISHES THE BABY', the placenta has long been accredited a major role in the control of fetal growth and the causation of its restriction. It is the most accurate record of the infant's prenatal experience (Benirschke, 1981) [1]. The placenta not only "records" and reflects the intrauterine environment, it also provides valuable information on the cause and timing of many adverse events and conditions. The most common causes (75-80%) of IUGR are placental abnormalities, affecting maternal or fetal circulation or both [2, 3]. Other known causes are maternal disease, fetal factors and rest are idiopathic. Common causes are Placental injuries, Mosaicism [4], Thrombophilia related uteroplacental abnormalities, Chronic inflammation, Chronic placental abruption, Extensive infarction, Velamentous or marginal insertion of umbilical cord, Chorioangioma, Single umbilical artery, Bilobate placenta, Placenta previa, Circumvallate placenta etc.
It is clearly tempting to attribute the birth of an unduly small infant to a functional inadequacy, or insufficiency of the placenta and many have succumbed to this attractive prospect without, however having examined critically the evidence for this association. This exactly is what this study attempts to achieve. Documentation of the delivery room examination of the placentas, plus the pathological examination will preserve valuable information.

Aims and Objectives
1. To study gross morphological changes in placenta, amniotic, chorionic site, umbilical cord of growth restricted fetuses.
2. To study histopathological changes in placenta of growth restricted fetuses.
3. 3. To analyze the different changes, which supplement clinical knowledge of the cause of intrauterine growth restriction.

Materials and Methods
It was a cross sectional Study conducted in the labor room of department of Obstetrics & Gynaecology and Histopathological room of the department of pathology of TNMC and Nair Hospital. The Placentas from 70 singleton third-trimester pregnancies complicated by IUGR taken as cases and from 70 normal uncomplicated term pregnancies appropriate for gestational age (AGA) taken as controls, studied Gross and microscopically. The proportion of various variables among cases and controls were analysed by Chi-square tests. The mean of different continuous variables were analyzed by unpaired t-test. Results were considered significant at $P<0.05$.
An IUGR fetus was defined as one with a birth weight less than those in the 10th percentile. Birth weight percentiles were determined by previously published normal curves. The normal control group was selected at random from the same; the birth weights of all of these infants were ≥10th percentile. Samples

were taken from both vaginal deliveries (assisted and normal) and cesarean sections. Gestational age was calculated according to LMP or, when it was impossible to determine the LMP, by early (up to 12 weeks) ultrasound examination.

A detailed history, age, economic status, diet, smoking, past history of significant medical or surgical disorder, present medical disorder of mother, present associated obstetric disorder, previous pregnancy and pregnancy complications, including hypertension and diabetes mellitus, was recorded by interview with the mother within 1 day of birth. Details of labour and delivery, signs of fetal distress, APGAR and the baby's condition at birth from the hospital record noted. In addition to birth weight, each infant had measurements of length, head circumference, and mid-arm circumference done immediately at birth.

Table 1

Inclusion criteria	Exclusion criteria
Gestation age - 37-42 wk	Gestation age - <37 >42 wk
Single fetus	Multiple pregnancy
Baby wt <2.5 kg	Baby wt >2.5kg, =2.5kg
Insufficient fundal height growth	IUFD
Inadequate ultrasonographic fetometry	

Placental examinations were performed according to a modification of Benirschke's method [1] and all placentas were examined by pathologists. Placentas were collected, inspected for membranes, fetal and maternal surfaces. Any gross abnormalities noted, Dimension of cord taken, Cord insertion to placenta was determined immediately after placental expulsion. Presence of true knot or false knot evaluated. The maternal surface of placentas inspected for grossly visible calcification, retroplacental haematoma. The fetal surface of placenta was examined for large vessels, amnion nodosum, palpated for thrombi, aneurysm or traumatic damage. The Umbilical cord cut transversly to inspect the number of umbilical artery and vein. Placentas were put in 10% formalin, sent immediately or within 24 hr to pathology laboratory for histopathology examination.

Pathological examination of placentas was done as per book by FOX Harold Pathology of placenta [6] by pathologist. Placentas were wiped dry and weighed after the removal of the umbilical cord and membranes. Placental thickness was estimated by performing three cross-sections: one in the middle part and two cuts 2 cm from the margin of the placenta in the opposite sites. The mean value of these 3 measurements was taken to analysis. Cord cut off 2-4 cm from placental insertion. A transverse section for microscopic examination was taken from cut end, middle of the cord and from any macroscopically abnormal area of cord. The placental membranes were examined for glossiness, translucency, amnion nodosum and meconium staining.

Entire placenta cut in to vertical slices each 0.5 cm in thickness and slices laid in orders. All visible lesions readily and specifically identified by naked eye appearance eg. Septal cyst, intervillous thrombi, subchorionic plaque were not examined histologically. In addition to taking sections from those lesions whose nature is not obvious on naked eye examination, blocks of macroscopically normal placental tissue were also sectioned for histological examination. The villous appearance varies from centre to periphery of placenta as recommended by FOX (1964). A H&E stain is sufficient for study of histological abnormalities of placenta, but a PAS stain is useful for study of trophoblastic basement membrane changes. A trichrome stain is necessary for evaluation of stromal fibrosis. Placental histologic data included decidual vasculopathy, infarction, fetal thrombotic arteriopathy, chorangiosis, acute inflammation (acute necrotizing deciduitis, acute chorioamnionitis or subchorionitis, acute funisitis and umbilical vasculitis), chronic deciduitis, intervillous thrombus, intervillous fibrin deposit and microcalcification. The presence, or absence, of these lesions was used in the analysis. Chorangiosis was diagnosed using the criteria by Altshuler [102]. The pathologists were blinded to clinical data except the gestational ages.

Results

Table 1: Comparison of various variables between Case and Control group.

Variables	Group				Unpaired t-test applied		
	Case		Control				
	Mean	SD	Mean	SD	t-value	p-value	Difference is-
Age (years)	26.09	3.07	29.99	3.09	-7.493	7.32E-12	Significant
Weight (Kg)	56.20	5.11	64.71	3.58	-11.427	1.07E-21	Significant
Gravida	1.84	0.86	1.83	0.72	0.106	0.915	Not significant
Gestation age by date (wk)	38.59	1.08	38.71	0.98	-0.705	0.482	Not significant
Gestation age by USG (wk)	38.17	4.23	42.99	35.72	-1.121	0.264	Not significant
Amniotic Fluid Index (cm)	7.26	2.75	10.52	2.41	-7.455	8.97E-12	Significant
Baby wt (kg)	1.99	0.26	2.89	0.20	-23.172	2.05E-49	Significant

In our study, age of the mother of IUGR baby, mean 26.09 yr is significanly less than mother of AGA group, mean 29.9 yr. Weight of the mother of IUGR baby, mean 56.2kg is significantly less than weight of the mother of AGA group, mean 64.71 kg. No significant difference in gravidity between two groups. In our study amniotic fluid index in Ultrasonography in IUGR group is less, mean 7.2 cm than AGA group, mean 10.52 cm. Mean baby weight in IUGR group is 1.9 kg. Mean baby weight in AGA group is 2.8 kg. No statistical difference in association of PIH seen in IUGR and AGA group. In our study out of 70 IUGR babies 77.1% delivered normally and 22.9% through LSCS whereas AGA babies delivered normally 72.9% and 27.15%through LSCS. No statistical significant difference was found in the mode of delivery. In our study, Out of 70 IUGR babies 55.7% were male and 44.3% were female. Out of 70 AGA 48.6% were male and 51.4% were female. No statistical

difference in incidence of sex of the baby found. In our study group Apgar score at 5 minute less than 7 is significantly less in IUGR group (24.3%) than AGA group (0.0%). Table 1 shows comparison of various variables between Case (IUGR) and Control (AGA) group.

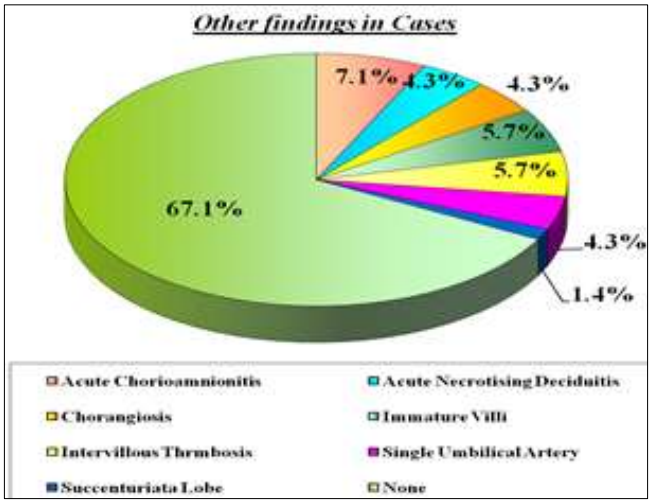
Table 2: Comparison of Gross placental changes between Case and Control group

Variables	Group				Unpaired t-test applied		
	Case		Control				
	Mean	SD	Mean	SD	t-value	p-value	Difference is-
Placenta wt (gm)	315.00	58.48	482.71	26.37	-21.874	1.08E-46	Significant
Fetal-placental ratio	6.28	1.23	5.94	0.46	2.158	0.033	Significant
Placenta Diameter (cm)	15.75	3.12	17.09	1.10	-3.375	0.00096	Significant
Placenta thickness (cm)	2.09	1.10	2.63	0.25	-3.997	0.0001	Significant
Cord length (cm)	42.50	4.41	43.71	5.35	-1.466	0.145	Not significant
Cord (no. of artery)	1.96	0.20	2.00	0.00	-1.758	0.081	Significant
Cord (no. of vein)	1.00	0.00	1.00	0.00			

In our study weight of placenta in IUGR group was significantly less than in the AGA group. Fetal/placental ratio was more in IUGR group than in AGA group. Diameter and thickness was significantly less in IUGR placenta. No significant difference in length of the umbilical cord found. In our study marginal, eccentric and velamentous cord insertion are more significantly associated with IUGR group (p value = 0.041).In our study no significant difference of membrane type found in IUGR group. In our study no significant difference in type of knot found. Table 2 shows comparison of Gross placental changes between Cases and Controls. Table 3 shows comparison of microscopic placental changes.

Table 3: Comparison of Microscopic study of Placentas in Case and Control group

	Case (IUGR)	Control (AGA)	P value	Difference
Maternal surface calcifications	38.6%	7.1%	<0.05	Significant
Intervillous fibrin deposit	40% has >20% area	1.4%	<0.05	Significant
Infarction	34.3% has > 10% area	2.9%	<0.05	Significant
Villitis	14.3%	1.4%	<0.004	Significant
Maternal fibrinoid necrosis	15.7%	0.0%	<0.001	
Syncitial knot	11.4%	1.4%	0.03	Significant
Basement membrane thickening	14.3	0%	0.003	Significant
Retroplacental haematoma	10%	2.9%		No significant
Thrombosis in fetal vessels	5.7%	0.0%		No significant
Avascular terminal villi	4.3% in >40%area	0.0%		No sigificant



Pie chart 1: Other less but significant findings in Cases

Discussion

Fox in the year 2000 found IUGR is related to a variety of clinicopathologic factors including maternal, uterine, and fetal factors. A definite relationship between histopathology and gross abnormalities of placenta as well as foetal welfare exists [7]. The question whether a small placenta results in a small baby or whether a small baby produces a small placenta has occupied obstetricians for many years.

Preeminent among the maternal factors is severe preeclampsia in which the restriction of growth is probably due to the inadequacy of uteroplacental circulation. Yücesoy *et al*, 2005 found 29.5% of IUGR associated with preeclampsia [5]. However in our study 15.7% of IUGR associated with preeclampsia and 11.4% of AGA is associated with preeclampsia. S.Yagel found 50% of IUGR associated with oligohydramnios [8]. In our study IUGR group is associated with less amniotic fluid index, mean 7.2cm (SD 2.7) than AGA 10.5cm (SD 2.4). Ertan *et al*., 2003 concluded that in pregnancies at risk the placental weights were significantly lower (216 g *vs*. 385 g) [9]. Placental ratio had a strongly negative relationship with birthweight, and it was a strong indicator of impaired prenatal linear growth. Thomas *et al*, 1969 showed that the fetal/placental weight ratio increases from approximately 4.5 in the higher placental weight groups to approximately 7.3 in the lowest [10]. In our study, the placental weights are significantly lower in the IUGR group than in AGA group (315 g vs.482.7 g) and fetal/placental weight ratio is 6.2 in IUGR group and 5.9 in AGA group.

Elchalal *et al*, 2000 determined that placental thickness less than 10th percentile was associated with a twofold risk of birthweight

less than 2500 g as compared to the control group (p = 0.03, 95% CI 1.00–8.14) [11]. Biswas *et al* 2008 found that the placentas associated with IUGR were smaller in diameters than those of control group of placentas [12]. In our study diameter (mean 15.7cm) and thickness (mean 2.09 cm) of placenta is also less in IUGR placentas in comparision to AGA placentas, diameter (mean 17.09cm) and thickness (mean 2.63cm).

There is no significant difference in cord length and type of knot between two groups, in our study. Sepulveda *et al*, 2003 found in approximately 1% of singleton pregnancies cord insertion is located away from placental mass, and only this condition, known as velamentous insertion, has been associated with IUGR. **[13]** Gediminas, 2005 found no influence of cord insertion on IUGR **[14].** Bjøro *et al*, 1981 found velamentous insertion of cord and single umbilical artery associated with IUGR group [15]. In our study velamentous insertion (4.3%), marginal insertion (7.1%) and single umbilical artery (4.3%) are more commonly associated with IUGR. Fox and Sen, 1972 found association of circumvallate placenta with IUGR [16]. In our study there is not a single case associated with circumvallate placenta rather, marginal placenta is associated in 2.9% of cases.

In contrary to different studies that shows that excessive calcification does not affect fetal growth,our study shows maternal surface calcification present in 38.6% of IUGR cases, in comparision to 7.1% in AGA. Retroplacental hematoma, with or without significant premature separation, is often associated with infarct. The correlation with IUGR is unclear [17, 18]. In our study retroplacental haematoma seen in 10% of IUGR cases wherase only in 2% in AGA.

The observed major histological findings of the placental lesions in the IUGR group are presence of infarct and more extensive deposition of perivillous fibrin [Fig 2]. So-Young Park *et al*, 2003 observed overall incidence of multi infarction tends to be increased in placentas in IUGR (50%) and these were signifcantly higher than those in AGA (0%, p<0.01) [19]. In our study 15.7% cases of IUGR has infarction < 10% area and 34.3% cases has infarction more than 10% area, so in total 50% of cases have infarction which is comparable to previous study [Fig 2]. This is in contrary to study of Masodkar *et al*, 1983 which does not show a single placenta with infarction [19]. The cause of increased perivillous fibrin is unknown, but one possible etiologic factor is failure of the mother to expand her intravascular volume appropriately during pregnancy, leading to a low flow state. As So-Young Park *et al*, 2003 shows intervillous fibrin deposit a significant finding in IUGR (p<0.05), our data also revealed that IUGR is related to more extensive perivillous fibrin deposition 54.3% compared to AGA 1.4%.

In regard to villitis, Salafia *et al*, 1992 has emphasized a wide variation in the incidence, dependent upon numbers of sections, with a 30% and 19% incidence of chronic villitis in IUGR and non-IUGR, respectively. **[20]** In Contrary to So-Young Park *et al*, 2003 who found villitis 8.9% and 8.3% incidence of chronic villitis in IUGR and AGA cases, respectively we observed 14.3% and 1.4% incidence of villitis in IUGR and AGA cases, respectively [Fig 3]. In our study the incidence of acute chorioamnionitis is significantly higher in the IUGR cases (7.1%) than in the AGA (2.9%) group. These results may be related to more frequent incidence of vaginal delivery in the IUGR cases than in the AGA cases in our study. Althabe and Labarrere, 1985 found hemorrhagic endovasculitis associated with IUGR. But in our study not a single placenta in case group is associated with this change. Redline *et al*, 1995 reported that fetal vessel thrombosis was associated with IUGR [21]. Decreased placental reserves also occur when there is chronic obstruction of blood flow in the fetal circulation due to thrombosis in the fetal circulation, or fetal thrombotic vasculopathy. In our study although fetal vessel thrombosis found to be in 5.7% of cases as compared to 0.0% in AGA, it was statistically not significant. However, we observed groups of avascular villi suggestive of fetal thrombotic arteriopathy more frequently in the IUGR cases than in the AGA cases, although there were no statistically significant differences [Fig 3]. Avasthi *et al*, 1991 70% cases of IUGR showed basement membrane thickening and cytotrophoblastic proliferation [22]. Our study showing basement membrane thickening (14.3%) in IUGR cases than AGA (0.0%), but not a single IUGR case showing cytotrophoblastic proliferation. In contrary to study of Masodkar *et al*, 1983 which showed that cytotrophoblastic proliferation was associated in 70% of cases of IUGR [23]. In the study of Mallik *et al*, 1979 the most common finding was syncytial knots seen in 60% of cases and 44% in control group. In our study cases showing syncytial knot in only 11.4% and 1.4% in control group [24]. As study of Mirchandani *et al*, 1978 found combined lesions of fibrinoid necrosis of villous and basement membrane thickening contributed to 36% in IUGR cases [25], Our study shows Fibrinoid necrosis is found to be associated more (15.7%) in IUGR cases than AGA (0.0%) [Fig 4]. We observed groups of avascular villi suggestive of fetal thrombotic arteriopathy more frequently found in the IUGR cases than in the AGA cases, although there is no statistically significant differences [Fig 5].

Other less common placental lesions related to IUGR found in our study are immature villi, intervilli thrombi, succenturiata lobe, chorangiosis [Fig 6]. Findings like acute necrotizing deciduitis, acute chorioamnoinitis are only incidental, has no relation with IUGR shown in pie chat 1.

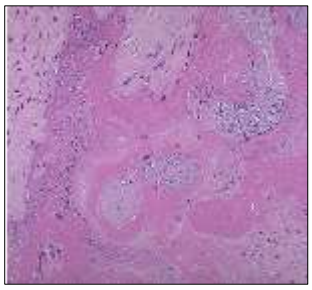


Fig 1: perivillous fibrin deposit.

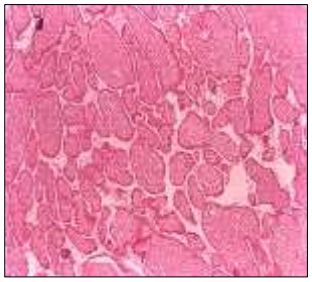


Fig 2: villous infarct

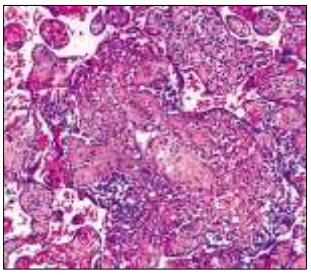


Fig 3: Vilitis

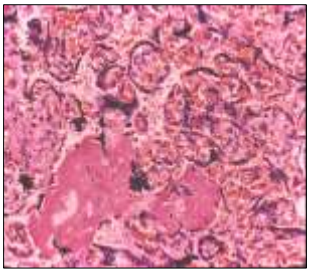


Fig 4: Fibrinoid necrosis

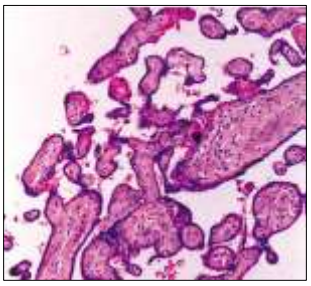


Fig 5: Avascular villi

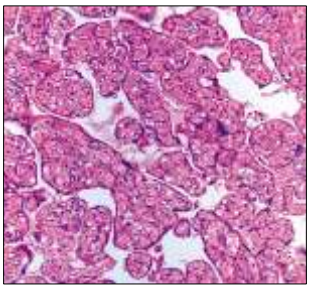


Fig 6: Chorangiosis

Conclusion

Gross and histological changes can be the cause of IUGR, but single lesion or multiple lesions leading to the causation of IUGR is unclear. Though IUGR fetuses are more frequently associated with morphologically abnormal placentas, it could not be conclusively decided whether this abnormal gross morphology actually contributed to the intrauterine growth restriction. Relationships of all placental lesions to IUGR are independent of each other. Some histological changes of placenta are the cause or effect of IUGR is unclear. Although the cause of IUGR pregnancies is heterogeneous, careful clinicopathologic correlations in individual cases are necessary in the interpretation of placental lesions of IUGR, and the total burden of several placental lesions may be more important than a single histologic feature.

References

1. Benirschke K. The placenta: How to examine it and what you can learn-Contemp Obstet Gynaecol, 1981; 17:117-119.
2. Hoffman H, Bakketeig I. Heterogeneity of intrauterine growth Retardation and recurrence risks. Semin Perinatol, 1984; 8:15-24.
3. Fernando Arias. Practical guide to high risk of pregnancy and delivery, Third edition, p86-87
4. Towner DR, Shaffer LG, Yang SP, *et al*. Confined placental mosaicism for trisomy 14 and maternal uniparental disomy in association with elevated second triemester maternal serum human chorionic gonadotropin and third triemester fetal growth restriction. Prenat Diag, 2001, 21:395.
5. Yücesoy G, Ozkan S, Bodur H, Tan T, Calişkan E, Vural B, *et al*. Arch Gynecol Obstet. 2005; 273(1):43-9.
6. Fox H. The pattern of villous variability in normal placenta. Journal of Obstetrics and Gynaecology of British common wealth, 1964; 71:749-758.
7. Fox H. Pathology of the placenta. 2nd ed. London (UK): WB Saunders, 1997.
8. Lewis SH, Perrin E. Pathology of the placenta, 2nd ed. New York: Churchill Livingstone, 1999.
9. Yaget S, Zacut D. In utero ponderal index as a prognostic factor in the evaluation of intrauterine growth retardation. Am J Obstet Gynecol, 1987; 157:415-419.
10. Thomson AM, Billewicz WZ, Hytten FE. The weight of the placenta in relation to birth weight. Journal of Obstetrics and Gynaecology of British Commonwealth, 1969; 76:865-872.
11. Elchalal U, Ezra Y, Levi Y, Bar-Oz B, Yanai N, Intrator O, *et al*. Sonographically thick placenta: a marker for increased perinatal risk—a prospective crosssectional study. Placenta. 2000; 21(2–3):268-72.
12. Biswas S, Ghosh SK. Early Hum Dev. 2008; 84(6):357-62.
13. Sepulveda W, Rojas I, Robert JA, Schnapp C, Alcalde JL. Prenatal detection of velamentous insertion of the umbilical cord: a prospective color Doppler ultrasound study. Ultrasound Obstet Gynecol. 2003; 21(6):564-9.
14. Gediminas Meèëjus. Influence of placental size and gross abnormalities on intrauterine growth retardation in high-risk pregnancies: Acta medica lituanica. 2005; 12(2):14-19.
15. Bjøro K Jr. Gross pathology of the placenta in intrauterine growth retardationAnn Chir Gynaecol. 1981; 70(6):316-22
16. Sandstedt B: The placenta and low birth weight M. In Grundmann E (ed): Peinatal pathology. New York,Springer-Verlag, 1979.
17. Scott JM, Jordan JM. Placental insufficiency and the small – for-date's baby. Am J Obtet Gynecol, 1972; 113:823.
18. So-Young Park, Moon Young Kim, Yee Jeong Kim, Yi Kyeong Chun Hye Sun Kim, Hee Sook Kim, Sung Ran Hong, *et al*. The Korean Journal of Pathology. 2002; 36:30-7.
19. Masodkar AR, Kalamkar LR, Patki PS. Histopathology of placenta and its correlation with foetal outcome. J Obstet Gynec India, 1983, 294-300.
20. Salafia CM, Vintzileos AM, Silberman L, Bantham KF, Vogel CA. Placental pathology of idiopathic IUGR at term.

Am J Perinatol, 1992.
21. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. Hum Pathol 1995; 26:80-5.
22. Avasthi K, Midha U, Sabharwal BD, Devi K. Histopathology of placenta and its correlation with foetal outcome. J Obstet Gynec India, 1991; 41:317-323.
23. Verkauskiene R, Albertsson Wikland K, Niklasson A. Variation in size at birth in infants born small for gestational age in Lithuania. Acta Paediatr 2002; 91(3): 329–34.
24. Mallik GB, Mirchandani JJ, Bazaz Malik G, Chitra S. Placenta in intrauterine growth retardation. J of Obstet and Gynec India, 1979; 29:805-810.
25. Mirchandani JJ, Mallik GB, Chitra S. Villous fibrinoid necrosis and basement membrane thickening in toxaemia of pregnancy and in intrauterine growth retardation J Obstet Gynec India, 1979; 29:407-411.