Original Article

A clinicopathological study of the IUGR placenta and its implication in the therapeutic intervention

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Abstract

Background: Ischemia and placental pathology are the two main basic etiopathogenesis behind intra uterine growth retardation (IUGR). Various histomorphological changes are observed in IUGR placenta. **Aim:** To analyse the age distribution, gravidity, socio economic status and maternal causes for IUGR babies. To study the histomorphology of placenta. To correlate the data with the neonatal outcome in terms of fetal weight and apgar score. To suggest treatment modalities based on this. **Settings and Design:** Cross sectional study. **Materials and Methods:** Placenta from the baby born with birth weight less than 10th percentile of normal weight for age and sex were taken up for the study. Appropriate sections were taken and morphology ananlysed. Age of the mother, gravidity, economic class, predisposing factors were retrieved from the records. Baby's weight and the Apgar score were retrieved from the records. **Results:** 80% of the mother was in the age group 21-30 years, 48% were primigravida, 58% belonged to class V socio economic class and 45% of them had no specific etiology. 66% of the placenta had macroscopic abnormality and 60% of the had microscopic abnormality. 51 babies were <5th percentile birth weight and six babies were less than 1. 5kg. There was a positive correlation between reduced placental weight and placental diameter with the fetal weight. When the number of lesions in the placenta is increased, apgar score decreased and infant mortality increased[p<0. 001]. **Conclusion:** Compulsory examination ofall the IUGR placenta are needed to understand the pathogenesis better.
Key words: birth weight, gravidity, age distribution

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INTRODUCTION

The definition of in utero growth restricted (IUGR) or small for date (SFD) is weight less than 10th percentile of the expected fetal weight appropriate for age and sex on ultrasound examination and reversal or absent end diastolic flow in the Doppler study from the umbilical artery.[1] Under nutrition, toxaemia of pregnancy and idiopathic eiteology are the maternal causes for IUGR.[2,3] Ischemia and placental pathology are the two main basic etiopathogenesis behind intra uterine growth retardation (IUGR).[4] IUGR babies have increased perinatal morbidity, increased neuro-developmental impairment and have increased risk of developing diabetes and cardiovascular disease.[5,6] Furthermore recurrence of IUGR in the subsequent pregnancies is also seen.[7] Prevention, treatment and intervention of these complications lack specific strategies. To formulate one understanding the pathophysiology of the IUGR placenta is mandatory.[7]In various studies of placenta of IUGR babies, gross appearance including small placenta due to chorionic regression, marginally inserted umbilical cord, infarction and intervillous thrombus, subchorionic haemorrhage or Breus' mole showing the characteristic nodular appearance and perivillous fibrinoid deposition were observed.[8-11] Various histomorphological changes were observed in the studies of placenta of the IUGR babies. This includesdegenerated syncytiotrophoblastic lining, increase in the number of syncytial knots, fibrin deposits in the intravillous and perivillous areas, hypovascular or avascular villi, villous edema, erythroblastosis, fibrinoid necrosis, intravascular thrombosis and chorionic villitis are the changes seen in

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IUGR placenta.[12] Along with the histomorphological studies, the age distribution, gravidity and socio economic status, maternal causes for IUGR babies were evaluated. These data was correlated with the neonatal outcome in terms of weight and apgar score. These were analysed to understand the pathogenesis and the outcome of it and to suggest treatment modality based on the findings to prevent such occurrence.

MATERIALS AND METHODS

Inclusion Criteria

- Properly fixed placenta from the baby born with birth weight less than 10th percentile of normal weight for age and sex

Exclusion Criteria

- Placentas from mothers with IUGR due to congenital anomaly or infection.
- Placenta from twin pregnancy
- Placenta from premature babies
- Placenta of a mother with an unreliable last menstrual period data and without first trimester scan.
- Placenta that was ill fixed.

Patient Selection

Placenta from the baby born with birth weight less than 10th percentile of normal weight for age and sex delivered in Madurai medical college hospital was taken up for study

Collection of Samples For Histopathologic Study

All placenta specimens were collected and fixed in 10% neutral buffered formalin for 12 hours.

Grossing

After adequate fixation, placenta was weighed, measured and gross examinations were done. Site of cord insertion, necrotic areas, fibrinous areas, haemorrhage, Beurs' moles and calcification were noted. Tissues were collected from the following sites for the histological examination – at the site of umbilical cord insertion, along the margins in the 12, 3, 6, 9'O' clock position, centre of placenta and area that shows gross pathology such as infracted and calcified area. The sections were processed and stained with eosin and haematoxylin.

Histopathology

Decidual vasculopathy, fetal thrombotic arteriopathy, chorangiosis, inflammation, chorionic villitis, intervillous thrombosis, stromal fibrosis, syncytial knots, basement membrane thickening, necrosis and calcification were noted.

From the records

Age of the mother, her socio economic status, gravidity and maternal diseases were retrieved from the records. These data were correlated with the neonatal out come-that is the weight and apgar score of the infant.

Based on all these the possible treatment modalities are discussed.

RESULTS

Total number of live birth in our hospital was 902 per month. We included 100 consecutive placentas from IUGR babies in our study. The incidence of IUGR babies in our hospital is 0. 9/100 live births. The age distribution of the mother of IUGR babies were as depicted in table 1. 80% of the cases were in the age group 21- 30 years. The mean age of the mother in our study was 22. 5 years[Table: 1]. This was in correlation with the study of Kana Bal, Saubhik Basu, Runa Bal' study in which the mean age was 23. 2 years.[1]

Table 1: Age distribution of the mother of IUGR babies

Age in years	No. of cases
<20	15
21-30	80
>31	5

IUGR was observed mostly in the primipara in our study [Table: 2]. 48% of the cases in our study was primi para. This is in correlation with İlker Günyeli *et al*. study.[13] They also had observed that the IUGR incidence is more among the primi para.

Table 2: Parity distribution

Para	No. of cases
1	48
2	31
3	17
>4	4

Socioeconomic status of these mothers were evaluated. Park had mentioned about the low nutrition and IUGR.[2] So we tried to correlate the socio economic status with IUGR [Table: 3]. And we had observed that 58% of the IUGR babies were born in low so cioeconomic families.

Table 3: Socio economic status of the IUGR mothers

Socio economic status	No. of cases
V	58
IV	30
III	8
II	4
I	0

Mothers were evaluated based on etiology. 45% of the cases had no predisposing factors[Table: 4]. Kotgirwar S *et al* in their study had observed 54% of IUGR cases with no predisposing factors.[14] İlker Günyeli *et al*'s study had included 23% of IUGR cases with no predisposing factors.[13]

Table 4: Etiology based distribution

Etiology	No. of cases
Idiopathic	45
PIH	28

Anemia	14
Heart disease	4
Placenta Previa	2
Chronic maternal disease	4
Miscellaneous	3

Placental weight and the diameter was measured. In 64% of the cases the placental weight was below 400 grams and in 78% of the cases the diameter was less than 12 cm in our study [Table: 5]. Kotgirwar S *et al* in their studyhad observed that the mean placental weight in IUGR cases were 281 ± 24. 69 gms. In their study the placental weight in the control group was 573 ±125. 81 gms. Compared with that placental weight was markedly reduced in IUGR babies. The mean diameter in their study was 13. 56cms.[14] This is in correlation with our study. BazazG *et al* and Mehendale *et al* also had mentioned in their study that placental weight was reduced in IUGR babies.[15, 16] Pooja Dhabhai *et al*, Ganga R Singal *et al*, Londhe *et al*, Figen Barut *et al*, Khadija Qamar *et al*, Gediminas Meèëjus *et al*, Nayereh Ghomian, *et al* and Biswas S *et al* had observed reduction in placental weight in IUGR babies.[9-11, 17-20] Malik *et al* in their study had observed reduction in the dimensions of the IUGR placenta.[21]

Table 5: Placental indices in IUGR babies

No. of cases	Placental weight			Placenta diameter	
	200-300 gms	301-400 gms	>400 gms	10-15cm	16-20cm
	14	64	22	78	22

Microscopic examination of the placenta revealed placental infarcts[Figure 1] [60%] and syncytial knots[58%] in higher frequency in our study [Figure 2]. Mardi K *et al* in their study had observed increase in the incidence of infarction, intervillous fibrin deposition, stromal fibrosisand syncytial knotting in IUGR placenta.[8] Perivillous fibrin deposition were observed in Katzman PJ's study.[22] Vander Veen F *et al* in their study had observed villous hyperplasia and focal syncytial necrosis.[23] Egbor M *et al* in their study had observed loss of villous volume.[24] Burton GJ and Sankar *et al* had observed increase in the syncytial knots in their study.[25, 26] This correlated with our study. Increase in the oxidative stress was quoted as the reason behind the increased knots and thickened basement membrane.[25, 26]

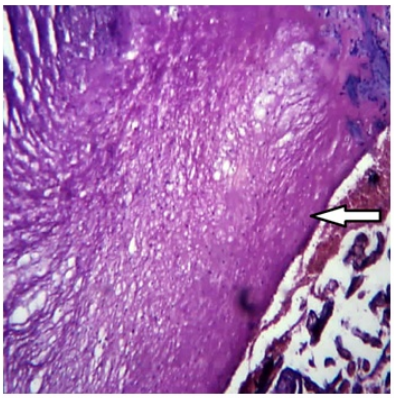

Figure 1

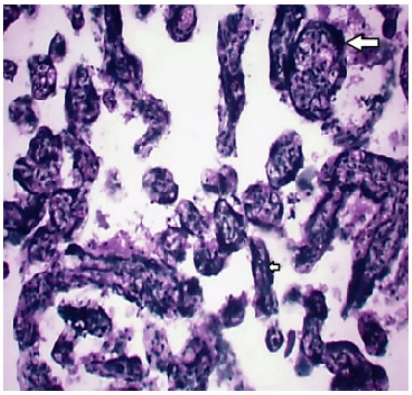

Figure 2

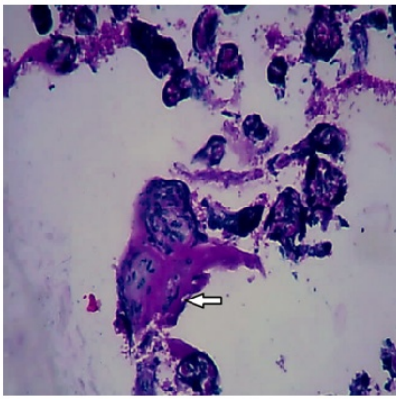

Figure 3

Legend

Figure 1: Shows areas of necrosis in the placenta[arrow][10xHandE].

Figure 2: Shows syncytial Knots[Big arrow] and remnant of the syncitiotrophoblast[Small arrow][10x HandE].

Figure 3: Shows Perivillous fibrin deposits[10x HandE].

DISCUSSION

Placenta is the document of the intra uterine life.[27] Although definite morphological changes are seen in placenta, debates are going on whether the placental pathogenesis is the primary factor, a co mormid factor or an external agent is acting through the placenta. Maternal causes like diabetis, hypertension, pre ecalmpsia, smoking are associtated with IUGR and they are the minor contributing factors. Idiopathic etiology is found in the majority. Analysis of these idiopathic placentas were tried to pinpoint the pathogenesis of IUGR. Considerable loss of villi and functional loss is implicated in the pathogenesis of IUGR. This affected the placental volume thereby restricting fetomaternal exchange and contribute to reduced placental oxygen transfer, thereby restricting fetal growth and development. As the placenta grows, interstitial extravillous trophoblast (EVT) transform the proximal myometrial portions of the spiral arteries creating a ventouri effect, where high-volume maternal blood is allowed to flow into the fetal circulation at low pressure. When this physiological event fails there is altered inter-villous blood flow [that is increase in the

pressure and increase in velocity]. Along with this, reperfusion injury occurs due to unstable flow leading on to diabetic vasculopathies that are seen in IUGR placenta.[29] Microscopically this is exhibited as fibrinoid deposits in the spiral artery walls, accumulation of foam cells, and persistence of muscularized distal segments. Perivillous fibrinoid deposits prevents feto maternal exchange leading on to growth retardation. Reperfusion injury induce cyclins to arrest the dividing cytotrophoblast. This is microscopically seen as impaired syncytial fusion, wave-like syncytial knotting, distal villous hypoplasia, apoptosis, focal necrosis and reduction in the villi reducing the energy transfer.[30, 31] Syncitial knots are usually formed in the last trimester as the syncitiotrophoblast loose the nuclei and form an aggregate thus facilitating easy diffusion of metabolites. In IUGR babies more such knots are formed to compensate the compromised nutrient supply. High volume blood flow lead on to auto thrombosis of the placenta and one such casuality is the spiral artery thrombosis leading on to infarction. Thrombosis in the fetal part of the placenta lead on to hemoconcentration and abnormal increase in the peripheral capillary formation in the distal villi and decreased exchange and acidosis.[32] Resulting hypovasularity lead on to stromal fibrosis. Immune mediated injury of the placenta is also implicated in the pathogenesis. Plasma cell, macrophage, and leukocytes are found in the IUGR placenta. Increased macrophages in the intervillous spaces termed Chronic inter-villositis (CIV) is associated with IUGR and it is also seen in recurrent IUGR cases.[33] Villitis of unknown etiology (VUE) in which there are increased macrophages and lymphocytes in the inter villous spaces are associated with recurrent IUGR.[34] Fibrinoid necrosis observed in the IUGR placenta had immune deposits in it. Grigoriadis C *et al* in their immuhistochemical study of the Hofbauer cell in the placenta had observed that 87. 5% of the normal term placenta and 100% of the IUGR placenta harbour these cells.[35] Probable inflammatory role of these cells was suggested in their study. All these studies point towards the immune background for IUGR. Glial cell missing-1 (GCM1) gene is responsible for the asymmetric division of the cytotrophoblast. Other genes like fibroblast growth factor and heparin also regulate the cytotrophoblast. mRna synthesis is detected in the syncitiotrophoblast and its role in eclampsia is established. But their role in IUGR placenta is in nascent stage. More work is needed in this direction to identify the complex pathogenesis of IUGR placenta. Gross pathology seen in IUGR include chorion regression syndrome where membrane part of the placenta are formed more compared to the frondosum part.[36] Reduced placental length and reduced placental weight is also associated with IUGR. Marginal insertion of the cord is also observed in IUGR placenta. Marginally inserted cords are more prone for rupture leading to growth retardation and sometimes fetal loss.[9] Circumvallate placenta, velamentous insertion of the cord and placenta previa is associated with IUGR.[37] Grossly visible infarct and calcifications are observed in IUGR placenta. Infarcts are caused by maternal platelet aggregation and thrombus formation due to unknown etiology and it is associated with recurrent IUGR.[11] Investigation to predict IUGR include low pregnancy-associated placental protein A (PAPP-A), high HCG, high Inhibin, elevated AFP and raised serpina. Ultrasound analysis of the placental morphology reveals chorionic regression in the first trimester in IUGR placenta.[38] Doppler studies show altered wave forms and reversalof flow in IUGR placenta. On the treatment aspect, low dose asprin is an option. But it did not change the major pathology associated with IUGR. There is still no strong evidence to use steroids for IUGR. Heparin trials were undertaken with promising results. It seemsto have effect on the serpin protein. This is independent of its anti-coagulantproperty.[39] More trials and studies are needed for the standardtreatment protocol toprevent infant mortality in IUGR babies.

CONCLUSION

Multiple placental pathologies are associated with IUGR. Not all institutions are equipped with pathologists trained in placental pathology. Mandatory placental examinations will lead on to more understanding of the pathogenesis. This will go a long way in reducing the infant morbidity and mortality.

REFERENCES

1. Kana Bal, Saubhik Basu, Runa Bal. Histology of Placenta in Intrauterine Growth Restricted Pregnancy. Journal of Evolution of Medical and Dental Sciences 2014; 3(64); 14037-14043.
2. Park K. Park's textbook of preventive and social medicine. 19th ed. M/sBanarsidas bhanotPublishers Jabalpur, India. 2007; 427 - 8.
3. Cetin I, Alvino G. Intrauterine Growth Restriction: Implications for Placental Metabolism and Transport- A Review Placenta. 2009; (30): 77- 82.
4. Suska P, Vierik J, Hand zi I etal Incidence of maceroscopic changes in the placentas in IUGR in neonates. Bratist lek Lisly 1989;90: 604-1
5. Mandruzzato G, Antsaklis A, Botet F, Chervenak FA, Figueras F, Grunebaum A, Puerto B, Skupski D, and Stanojevic M, Intrauterine Growth Restriction Recommendations and guidelines for perinatal practice, J Perinat Med, 2008; 36, . 277-281.
6. Barker DJP. Fetal Growth Restriction: a WorkshopReport. Clin Sci 1998; 95, 115-128.
7. Tyson R, Barton C. The intrauterine growth restricted fetus and placenta evaluation. Semin Perinatol 2008; 32 (3): 166 - 71.

8. Mardi K, Sharma J. Histopathological evaluationof placentas in IUGR pregnancies. Indian J PatholMicrobiol 2003;46(4): 551-4.
9. Londhe, pradeep s. *et al* Placental morphometry in relation to birth weight of full term newborn babies. , National journal ofintegrated research in medicine. 2012; 3(1): 67-72.
10. Gediminas meèëjus, Influence of placental size and gross abnormalities on intrauterine growth retardation in high-riskpregnancies, Acta medica lituanica. 2005: 12 (2): 14–19
11. Ghomian, nayereh *et al* Iranian journal of pathology;winter2014; 9 (1), p9
12. Madazli R, Somunkiran A, Calay Z, Ilvan S, AksuMF. Histomorphology of the placenta and the placental bed of growth restricted fetuses and correlation withthe Doppler velocimetries of the uterine and umbilicalarteries. Placenta 2003; 24(5): 510–6.
13. İlker Günyeli, Evrim Erdemoğlu, Serdar Ceylaner, Sema Zergeroğlu, Tamer Mungan. Histopathological analysis of the placental lesions inpregnancies complicated with IUGR and stillbirths incomparison with noncomplicated pregnancies. J Turkish-German Gynecol Assoc 2011; 12: 75-9
14. KotgirwarS, AmbiyeM, Athavale S, Gupta V, Trivedi S Study of gross and histological features of placenta in intrauterine growth retardation. J. Anat. Soc. India 2011;60(1) 37-40
15. BazazG, MirchandaniJJ, Chitra S. placenta inIUGR. J obstet Gynecol 1979; 29: 805-10.
16. Mehendale SS, Vasanthi L, Godbole pv. Placental histopath with IUGR Indian J obstetGynecol 1988;1: 38-4.
17. Pooja Dhabhai, Ghanshyam Gupta, . Placental weight and Surface area in IUGR cases. Innovative Journal of Medical and Health Science2014; 4()6: 198-200
18. Ganaga R Singal *et al*, Placental Morphometry inRelation to Birth Weight of Full Term Newborn 2013;2(5)
19. Khadija Qamar, Liaqat Ali Minhas, Muhammad Yunus Khan. Histological study of human placenta inultrasonically determined cases of intrauterine growthretardation, Pakistan Armed Forces Medical Journal 2009, 3
20. Biswas S, Ghosh SK. Gross morphological changes ofplacentas associated with intrauterine growth restriction offetuses: a case-control study. Early Human Develop 2008; 84(6): 357-62.
21. Malik G, Mirchandani J, Chitra S. Placenta in IUGR. J obstet gynecol 1968;70: 805-10.
22. Katzman PJ, Genest DR. Maternal floor infarction and massive perivillous fibrin deposition: histological definitions, association with intrauterine foetal growth restriction, and risk ofrecurrence. Pediatr Dev Pathol. 2002; 5 (2): 159-64.
23. Van der Veen F, Fox H. The human placenta in idiopathic intrauterine growth retardation: lightand electron microscopic study. Placenta. 1983; 4 (1): 65-77.
24. Egbor M, Ansari T, Morris N, Green C, Sibbons P. Morphometric placental villous and vascularabnormalities in early and late-onset pre-eclampsia with or without fetal growth restriction. BrJ Obstet Gynaecol 2006; 113580-9.
25. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences ofconversion of the maternal spiral arteries for uteroplacental blood flow during humanpregnancy. Placenta. 2009; 30: 473–482.
26. Sankar KD, Bhanu PS, Kiran S, Ramakrishna BA, Shanthi V. Vasculosyncytial membrane inrelation to syncytial knots complicates the placenta in preeclampsia: a histomorphometricalstudy. Anat Cell Biol. 2012; 45: 86–91.
27. Althshuler G, Russell P, Ermochilla R. The placental pathology of small for gestational age infants. Am J obstet. Gynecol. 1975; 121: 351 - 59.
28. Burton GJ, Jauniaux E, Charnock-Jones DS. The influence of the intrauterine environment on human placental development. Int JDev Biol 2010;54(2–3): 303–12.
29. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological andphysiological consequences of conversion of the maternal spiralarteries for uteroplacental blood flow during human pregnancy. Placenta 2009;30(6): 473–82.
30. Ray JE, Garcia J, Jurisicova A, Caniggia I. Mtd/Bok takes a swing: proapoptotic Mtd/Bok regulates trophoblast cell proliferationduring human placental development and in preeclampsia. CellDeath Differ 2010;17(5): 846–59.
31. Soleymanlou N, Jurisica I, Nevo O, *et al*. Molecular evidenceof placental hypoxia in preeclampsia. J Clin Endocrinol Metab2005;90(7): 4299–308.
32. Proctor LK, Toal M, Keating S, *et al*. Placental size and the prediction of severe early-onset intrauterine growth restriction in women with low pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 2009;34(3): 274–82.
33. Contro E, deSouza R, Bhide A. Chronic intervillositis of theplacenta: a systematic review. Placenta 2010;31(12): 1106–10.
34. Feeley L, Mooney EE. Villitis of unknown aetiology: correlationof recurrence with clinical outcome. J Obstet Gynaecol2010;30(5): 476–9.
35. Grigoriadis C, Tympa A, Creatsa M, Bakas P, Liapis A, Kondi-Pafiti A, Creatsas GHofbauer cells morphology anddensity in placentas from normal andpathological gestationsRev Bras Ginecol Obstet. 2013; 35(9): 407-12
36. Saraswat L, Bhattacharya S, Maheshwari A. Maternal and perinatal outcome in women with threatened miscarriage in the first trimester: a systematic review. BJOG 2010;117(3): 245–57
37. BenirschkeK, Kaufmann P, Baergen R. Pathology ofthe Human Placenta. 5th ed. New York Springer 2006.
38. Pardi G, Cetin I, Marconi AM, *et al*. Diagnostic value of blood sampling in fetuses with growth retardation. N Engl J Med 1993;328(10): 692–6.
39. Sobel ML, Kingdom J, Drewlo S. Angiogenic response of placental villi to heparin. Obstet Gynecol 2011;117(6): 1375–83.

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