Placental changes in idiopathic intrauterine growth restriction

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Abstract
Introduction
Placenta is the maternal–foetal contact zone. The placenta of ‘idiopathic’ intrauterine growth retardation babies may hold the key to the aetiology of growth restriction. It was noted by most workers that in cases of intrauterine growth retardation placentas, there were some abnormal positions of insertion of umbilical cords, placental weight and volume were significantly lower than the controls and they also had smaller diameters. The greater placental coefficient in intrauterine growth retardation indicates that though both placentas and babies in intrauterine growth retardation had less weight, placental sizes were not relatively less. This article aims to review literature to identify any morphological and structural peculiarities of placenta that might contribute to development of idiopathic intrauterine growth retardation.

Discussion
Light microscopy suggested that syncytiotrophoblastic lining was more degenerated and a number of syncytial knots increased in intrauterine growth retardation placentas than that of the control placentas. X cells were present in both the cases, though more in intrauterine growth retardation. Intra-villous and perivillous fibrin deposition were markedly increased in intrauterine growth retardation; also there were more hypovascular/avascular villi and large areas of infarction.

Conclusion
Review of the literature to establish any relationship between placental histomorphometric changes and intrauterine growth retardation suggests that intrauterine growth retardation pregnancies are associated with reductions in villous tree elaboration, particularly affecting the volume and surface area of terminal and intermediate villi, thereby restricting surface area over which foeto-maternal exchange may occur. Thus, placental oxygen transfer might be reduced, thereby restricting foetal growth and development.

Introduction
The placenta is the vital organ for maintaining pregnancy and promoting normal foetal development. It is elaborated by both maternal and foetal tissues to serve as an instrument for transfer of essential elements. The foetus and the placenta share the same genetic make-up, therefore, are expected to have parallel growth potentials. Maturation-associated increase in the placental nutrient transfer capacity improves placental efficiency, permitting an increase in the number of grams of foetal weight supported by every gram of placental mass. Not surprisingly, ‘placental insufficiency’ is invoked commonly in cases of impaired foetal growth.

The most important cause of neonatal loss is the low birth weight. A low birth weight baby is defined by the ninth revision of International Classification of Diseases of World Health Organization (1977) as one whose birth weight is 2500 g or less, irrespective of gestational age. After correlating both birth weight and gestational age they are classified into two groups: pre-term and intrauterine growth retardation (IUGR) or small-for-date (SFD).

There are many well-established causes of IUGR, such as maternal disorders like pre-eclampsia, foetal intrauterine infections, congenital malformations, chromosomal anomalies, etc., but in the cases of idiopathic IUGR, there is no obvious foetal or maternal cause. The placentas of these ‘idiopathic’ IUGR babies might hold the key to the aetiology of the growth retardation, though the contribution of placental changes remains controversial.

This paper reviews the significance or importance of morphological, histological and quantitative histomorphometric changes of placentas associated with IUGR.

The methodical study of growth rate of normal foetuses and their placentas to ascertain the interrelationship through the stages of intrauterine life was first undertaken by Hamilton and Girmes, and Boyd and Hamilton. While correlating certain morphological and histological findings of placenta with IUGR, the comments of Macpherson can be kept in mind that it is fanciful to assume that every adverse perinatal outcome is associated with an abnormal placenta, and equally fanciful to expect that every abnormal placenta will result in a poor perinatal outcome. Sinclair observed that placental weight increased linearly as gestation progressed. He was unable to account for great microscopic variability among placentas. According to Little, placental co-efficients

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(placental weight: foetal weight) between 0.10 and 0.18 were to be considered normal. Any value <0.08 were to be considered abnormally small and more than 0.2 abnormally large. Gruenwald and Minh⁶ had observed 1232 deliveries and opined that placental weight did not determine the size of the baby, though the weight must be considered as one of the several factors affecting placental function and adequacy.

Wigglesworth⁷ demonstrated that placental infarct of more than 5% area had been a key factor in causing low birth weight. Histological examination revealed considerable regional variations in villous structures from both normal and abnormal pregnancies. Changes like increased fibrin deposition both within and between the villi, thinning of syncytium and increased syncytial knots and proliferation of Langhans cells were noted in placentas having insufficiency. In normal placentas (Figure 1), syncytiotrophoblastic lining of the villi are thinned out and aggregated as syncytial knots in most areas of all placentas. At places, there were no trophoblastic lining. Plenty of intravillous cytotrophoblasts were seen within villous stroma. Intravillous fibrin depositions were present at places. At some places, mostly in the marginal and subchorionic areas, perivillous fibrin depositions were noted. Many villi were completely entrapped in the perivillous fibrin. These villi had incomplete syncytiotrophoblastic lining. Few large extravillous cytotrophoblasts, also termed as X cells, were entrapped in the fibrin deposits.

In mature placenta, typical layering of basal plate is not expected. Chorionic plates are observed to have multi-layered structure, consisting of amnionic epithelium, compact layer, spongy layer, followed by a compact layer of chorionic mesoderm that is separated from the Langhans fibrinoid stria by a basement membrane (Figure 2). Chorionic plates were lined by Langhan’s layer of fibrinoid, which in turn was lined by syncytiophoblast towards the intervillous spaces. Many villi were entrapped in this layer, and few extravillous cytotrophoblast cells (X cells) were also seen. Aherne and Dunnill⁸ dealt with quantitative aspects of placental structure. They worked out volume proportions of villi and total surface areas using point counting.
and linear intercept methods. They observed that at term, abnormally small infants’ placentas had reduced mean volumes. There was a significant deficit of parenchyma; the mean values for villous surface area and foetal capillary surface area in the placentas of abnormally small infants were significantly lower than normal. They suggested that stunting might occur due to primary placental hypoplasia.

Thomson et al.\textsuperscript{9} remarked that placental weight was a poor indicator of placental adequacy. SFD babies did not have relatively small placentas. The observation was based on records of 52,004 singleton births over a period of 18 years.

Increased villous fibrosis and syncytial knotting was reported by Mehrota et al.\textsuperscript{10} in placentas of mothers having anaemia and subsequently low birth weight babies. In another observation by Agboola\textsuperscript{11}, presence of low haematocrit was associated with higher placental weight and lower foetal weight. Histologically, more villous fibrosis was seen as compared with normal control group. After studying undernourished pregnant Indian women, Mirchandani et al.\textsuperscript{12} observed that placentas were significantly smaller in mature IUGR babies. Syncytial knotting (Figure 3), trophoblastic basement membrane thickening, villous stromal fibrosis, fibrinoid necrosis, severe degree of intervillous fibrin deposition completely or partially filling up the intervillous spaces (Figure 4) were noted by them in the placentas of IUGR foetuses.

Benirschke and Driscoll\textsuperscript{13} observed that the histological findings of placentas included marked increase in fibrin deposits in the decidual floor with encasement of many villous tips (Figure 5). There was an increase of extravillous trophoblasts (X cells). Ermocila and Altshuler\textsuperscript{14} also found increased proliferation of X cells in IUGR.

According to Bjoro\textsuperscript{15}, velamentous insertion of cord, single umbilical artery and placental infarct occurred more frequently in placentas with IUGR. In a study by van der Veen and Fox\textsuperscript{16}, placentas of idiopathic IUGR revealed excess of villous cytotrophoblastic cells and endarteritis.

**Figure 3:** Chorionic villi showing a faintly positive PAS stain in the villous core and basement membrane of the trophoblasts. Cytotrophoblast cells (arrowhead) seen within the villous stroma. Syncytial lining is present at places. Syncytial knots (arrows) are plenty. Stain used: PAS. Magnification ×400.

**Figure 4:** Microphotograph showing that perivillous fibrin deposition (arrow), red in colour, has partially replaced trophoblastic lining of villi (v) in an IUGR placenta. Few villi (v) are seen to be entrapped in the fibrinoid. Stain used: Masson’s trichrome. Magnification ×100.
of large stem villous arteries. They suggested that these changes were due to uteroplacental ischaemia, and pathogenesis of IUGR was due to restriction of nutrition supply to the foetus because of inadequate physiological changes of spiral arteries.

Davies et al. observed that IUGR placentas were smaller in weight, volume and area. Marginal insertion of cord was a significant finding. Increased numbers of villi with fibrinoid necrosis were also noted.

Teasdale did quantitative analysis of placentas in IUGR. He observed that these placentas were 45% smaller than controls and had significantly less surface area of exchange between mother and foetus. Mainly, the peripheral capillary area, villous surface area and intervillous space volume were found to be less. Total numbers of cells were also seen to be markedly decreased, placental membrane showed 51% decrease in trophoblastic mass or cellular content. These findings suggested that, in idiopathic IUGR, the placental morphological changes were bound to produce placental insufficiency and foetal growth retardation. It was revealed by him that microvilli were often distorted and reduced in number in idiopathic IUGR.

In another quantitative structural study of placenta by Boyd and Scott, lower total placental volumes in IUGR were revealed. With light microscopic study, they observed lower volume of parenchyma, reduced villous surface area and increased volume proportion occupied by foetal capillaries in these placentas in comparison to control groups.

Terminal villi deficiency has been interpreted as a result of reduced foetal capillary growth in the villous periphery (Kaufmann et al.)

They suggested that due to the lack of terminal villi, there might be reduction of exchange surface and increase in materno-foetal diffusion distance. Hypercapillarization was suggested by Bacon et al. and Scheffen et al. to be induced by hypoxia. In IUGR with preserved end-diastolic flow in umbilical arteries, these changes were frequently seen.

It was postulated by Xu that the development of IUGR was related to smaller functional areas of the placenta. In their histomorphometric study of placentas in IUGR, they noted that the ratio of parenchymal tissue, absolute villi components and surface area values and villous capillaries were significantly smaller in IUGR placentas than the control ones.

Markedly increased number of X cells (Figure 6) were found to be associated with placentas of IUGR by Vernof et al. These X cells were found in close proximity of affected villi. Histological evidence of placental infarction, characterized by large conglomeration of necrotic villi, was found by Laurini et al. to be significantly associated with IUGR.

In a study of placentas from preterm IUGR infants, Salafia et al. concluded that placentas of asymmetric IUGR infants were characterized by decreased foeto-placental weight ratio, decreased placental weight, increased number of infarcts located throughout the placental area as compared with that of the placentas of AGA infants. Histological evidence of abruptio placenta, increased proliferations of extravillous cytotofothoblast (X cells) and avascular terminal villi were found. Extensive perivillous fibrin deposition, villous stromal fibrosis, syncytial knotting and increased incidence of chronic villitis were noted in cases of symmetric IUGR. They opined that though single placental infarct was more common at term, presence of many placental infarcts was significantly related to IUGR.

Beebe et al. studied 1252 placentas of different categories, and concluded that histological evidence of placental ischaemic changes and infarction were significantly increased in cases of IUGR as compared with normal babies.

The study conducted by Dawson et al. revealed that main microscopic

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**Figure 5**: Microphotograph of IUGR placenta showing massive perivillous fibrin deposit (arrow), red in colour, near the basal plate (B). The villi (V) are green in colour, avascular and sclerosed. Stain used: Masson’s trichrome. Magnification ×100.
findings of IUGR placentas included shrunken fibrosed villi with decreased number of capillaries per villus, prominent cytotrophoblasts, increased fibrin and syncytial knots and increase in stromal fibrosis.

Oliveira et al.\textsuperscript{29} found that the placentas in IUGR had significantly greater incidence of choioamnionitis, placental infarction and extensive perivillous fibrin deposition. They were lighter and had smaller diameters. Placental index (placental weight: foetal weight) was also significantly greater, indicating that placental impairment was relatively less.

Katzman et al.\textsuperscript{30} found massive perivillous fibrin deposition strongly associated with IUGR. Similar views were given by Bane and Gillan\textsuperscript{31}.

Fox (1976, 1981 and 2000)\textsuperscript{32} conducted several studies and observed that in the majority of cases of IUGR, the small foetus could not be explained by so-called ‘placental insufficiency,’ for which there was little morphological or other evidences. In 2003, he also observed that placenta from cases of idiopathic IUGR were considered to be smaller, but placental–foetal weight ratios were usually normal. Very extensive perivillous fibrin deposition, maternal floor infarction, widespread thrombosis of foetal arteries might be associated with IUGR but such lesions were found on only a small minority of placentas from growth retarded foetuses. Histological examination of placentas in IUGR revealed no constant or diagnostic findings.

In placental stereological studies by Mayhew et al.\textsuperscript{33,34}, the exchange surface areas of peripheral (terminal and intermediate) villi and their foetal capillaries were estimated. They observed that IUGR (with or without PE) was associated with reduced surface areas and this was the principal factor leading to a smaller membrane diffusive conductance in these placentas.

Ansari et al.\textsuperscript{35} and Egbor et al.\textsuperscript{36} also observed that in idiopathic IUGR, the surface areas of terminal villi were significantly (p < 0.001) reduced, also their volumes were reduced. Biswas et al.\textsuperscript{37} had similar observations and commented that since the surface area of the villi presents the interface between maternal and foetal circulation, its reduction might be the cause of idiopathic intrauterine growth restriction of the foetus.

Discussion
The author has referenced some of its own studies in this paper. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Contradictory histological and morphological findings were recorded by various authors.

Velamentous insertion and marginal insertion of cord was a significant finding in the placentas of IUGR fetuses\textsuperscript{15,17}. Biswas and Ghosh\textsuperscript{38} found that in the majority of IUGR cases, positions of insertion of umbilical cords were eccentric whereas in the control group, the majority was central.

Placental weights and volumes of IUGR group were lower than those of the controls. It was observed that placental coefficient was significantly greater in IUGR than normal-weight babies\textsuperscript{29}; though both placentas and babies in IUGR had less weight, placental sizes were not relatively less. In fact, these placentas were functional, and even tried to compensate the abnormal morphology\textsuperscript{32}.

On light microscopic study of the histological sections of the placentas of both control and IUGR group, marked regional variations of structures of chorionic villi, the intervillous spaces, basal and chorionic plates were noted. In the chorionic villi, syncytiotrophoblastic linings...
were thinned out in most of the areas of control placentas, whereas in IUGR placentas, the linings were thinned as well as disrupted. Villous cytrophoblast cells were seen at places along the margins of villi in both the groups. In IUGR placentas, they were more numerous and even present within the villous stroma. Syncytial knottings were present in both groups, but they were more prominent and their numbers were increased in IUGR placentas. Though intravillous fibrinoid depositions were present at places in term control placentas, in IUGR cases they were more frequently observed. Few X cells were found entrapped in these intravillous fibrinoid. Replacement of degenerated trophoblastic linings of villi by perivillous fibrin depositions were positively correlated with IUGR. These perivillous fibrin deposits might be acting as a barrier between foetal and maternal circulation, thereby reducing the transfer of the essential nutrients to the foetus, thus causing IUGR.

The number of X cells in basal plate markedly increased in the placentas of IUGR babies. Many workers like Brosens and Khong reported that the muscle and elastic coats of the placental bed arteries were replaced by fibrinoid.

The diffusion of different elements from mother to foetus or vice versa occurs at the presenting surface of villi containing foetal vessels and maternal blood present in the inter-villous space. The findings of lower surface area of villi in IUGR compared with control placentas suggest less oxygen and nutrients reaching foetuses of IUGR group.

The mean total volumes of villi (terminal and intermediate) of IUGR placentas were found to be significantly lower than that of control placentas by some workers. But, both Aherne and Dunnilla, and Biswas et al. observed that the volume proportions of chorionic villous tissue of IUGR did not differ significantly from those of normal pregnancies.

Conclusion
From this review, it can be said that though IUGR foetuses were more frequently associated with morphologically and histologically abnormal placentas, it could not be conclusively decided whether these abnormalities contributed to the intrauterine growth restriction. Quantitative, rather than qualitative changes of placental structure might be responsible for the phenomenon. Many more quantitative histomorphometric studies have to be undertaken by researchers to come to a definite conclusion regarding placental changes as cause of idiopathic IUGR.

References

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Review


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