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DECODING SUBTLE PLACENTAL PATHOLOGY IN LATE-ONSET FGR: A CASE-CONTROL STUDY IN LOW-RISK PREGNANCIES

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Abstract

Background:
Late-onset fetal growth restriction (FGR), diagnosed after 32 weeks of gestation, poses diagnostic challenges due to its subtle clinical presentation and less overt placental pathology compared to early-onset FGR. Distinguishing pathologically growth-restricted fetuses from constitutionally small ones is crucial for improving perinatal outcomes, especially in low-risk pregnancies. Birth of healthy term infant depends on normal placental development with its disturbance causing problems like fetal Growth Restriction (FGR).

Objective:
To compare placental morphological and histopathological features between late-onset FGR and appropriately grown (AGA) fetuses in low-risk pregnancies.

Methods:
A prospective, cross-sectional case-control study was conducted at Fatima Memorial Hospital, Lahore in Maternal fetal Medicine Unit from November 2024 to April 2025. Placentas of ninety-one low-risk pregnancies complicated by late-onset FGR were compared with placentas of 91 gestational age-matched AGA pregnancies. Placentas were examined for gross [morphological] and histopathological abnormalities, including maternal vascular malperfusion, distal villous hypoplasia, infarction, and cord insertion anomalies. Data was analyzed using SPSS 25 with appropriate statistical tests.

Results:
FGR placentas had significantly lower weight (41.75% <10th percentile vs. 4.4% in AGA; $p < 0.0001$) and a higher fetal-placental weight ratio. Marginal cord insertion was more frequent in FGR (97.8% vs. 46.15%; $p < 0.0001$). Histologically, maternal vascular malperfusion (57.14% vs. 9.89%), distal villous hypoplasia (45.05% vs. 6.59%), and infarction/intervillous thrombi (20.88% vs. 2.2%) were significantly more common in FGR placentas. Villous changes related to maternal under perfusion were more prevalent in placentas of fetuses with severe FGR [EFW <3rd percentile] or FGR with EFBW between 3-10th centile with abnormal Dopplers.

INTRODUCTION

Late onset fetal growth restriction (FGR) represents a major cause of perinatal morbidity and mortality affecting a significant number of liveborn infants. (Cetin et al., 2002). The consequences of FGR extend well beyond birth, with established links to increased risks of adult-onset conditions including ischemic heart disease, hypertension, and diabetes, highlighting the critical importance of effective interventions and management strategies (Robinson et al., 2000).

Late-onset FGR, typically diagnosed after 32 weeks of gestation, has different underlying etiological and pathophysiological characteristics as compared to early-onset FGR (Aviram et al., 2018). Crucially, differentiating a pathologically growth-restricted fetus from a constitutionally small but healthy fetus remains a significant clinical challenge, driving the need for advanced diagnostic tools and biomarkers (Deter et al., 2018). A deeper understanding of placental pathology in relation to fetal growth patterns is therefore essential for enhancing prenatal monitoring and reducing perinatal mortality (Gagnon, 2003).

Most common pathophysiological factor associated with early-onset FGR are severe placental dysfunction, particularly maternal vascular malperfusion,whereas,in late-onset FGR these changes are more frequently linked to subtle placental insufficiencies and maternal factors like nutritional deficits or reduced uteroplacental blood flow (Hendrix & Berghella, 2008). Research on placental diseases in late-onset FGR pregnancies have identified lesions indicative of maternal circulation abnormalities, fetal thrombo occlusive disease,and inflammatory responses (Kovo et al., 2013).

The primary objective of this study is to conduct a detailed morphological and histopathological comparison of placentas from pregnancies complicated by severe late-onset FGR (>32 weeks) and gestational age-matched controls with appropriate fetal growth (AGA). Furthermore, we will stratify the FGR placentas based on estimated fetal birth weight (EFBW) centile severity and the presence of abnormal Doppler velocimetry.This would help us to understand and correlate the patterns of histopathological lesions with fetal growth restrictions and abnormal dopplers.

Methodology

A prospective, cross-sectional study was conducted in the Maternal Fetal Medicine Unit of Fatima Memorial Hospital, Lahore,from January 2022 to December 2024 after taking ethical approval for institutional review board.This prospective case control study was conducted to evaluate placental morphological and histopathological findings in low-risk pregnancies complicated by late-onset fetal growth restriction (FGR) and to compare these changes with placental findings of fetuses born appropriate for gestational age . The study cohort comprised low-risk pregnant women referred with late-onset FGR, diagnosed after 32 weeks of gestation using ultrasound criteria, including estimated fetal weight (EFW) <3rd centile or EFBW <10th centile with umbilical artery pulsatility index (PI) >95th centile, or cerebroplacental ratio (CPR) <5th centile. The control group included low-risk pregnant women with appropriately grown fetuses. EFW was calculated using the Hadlock formula based on biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). A sample size of 91 participants was recruited using non-probability, consecutive sampling based on WHO sample size calculation, assuming a 6.25% prevalence of umbilical cord torsion with a 95% confidence level and 5% margin of error. Exclusion criteria included multiple gestation, hypertensive disorders, diabetes, fetal anomalies, antepartum hemorrhage, and maternal systemic illness. Fetal surveillance was carried out with serial ultrasound monitoring of growth and Dopplers every 1–2 weeks. Delivery was individualized based on fetal wellbeing, but not extended beyond 39 weeks; early delivery was offered in cases with absent end-diastolic flow, severe FGR, or abnormal Dopplers. Following delivery, placental morphologic features such as placental weight, cord and membrane insertion were recorded. Placentas were fixed in 10% formalin and processed using standard histopathological techniques, including paraffin embedding, H&E staining, and systematic sampling from the placental parenchyma, cord, and membranes. Histological evaluation included assessment of villous infarction, hypoplasia, intervillous thrombi, fibrin deposition, trophoblastic basal membrane thickening, and syncytial knots.

Data was analyzed using SPSS version 25. Frequencies and percentages were calculated for categorical variables, while means and standard deviations were computed for continuous variables. Histological changes were stratified by maternal age, parity, and gestational age. Characteristics of late-onset FGR infants were compared with AGA term infants using the chi-square test of independence, Fisher's exact test, and Welch's two sample t-test assuming unequal population variances. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 182 women were included in the study, comprising 91 cases of late-onset FGR and 91 term AGA infants.Table 1 shows demographic characteristics with no significant difference between both the groups. Neonates in the FGR group had significantly lower birth weights and placental weights (2204 ± 378 g vs. 3100 ± 426 g; p = 0.0000).Table 2 shows morphological and histopathological differences between the two groups.. Placental weight below the 10th percentile was present in **41.75**% of FGR cases compared to **4.4**% in AGA infants (*p* = 0.0000).Marginal membrane insertion was significantly higher in FGR (97.8% vs. 46.15%; p = 0.0000), whereas umbilical cord insertion patterns and abnormal vessel numbers did not differ significantly. Histopathological findings showed significantly higher rates of composite maternal vascular supply lesions (57.14% vs. 9.89%; p = 0.0000), distal villous hypoplasia (45.05% vs. 6.59%; p = 0.0000), and infarction/intervillous thrombi (20.88% vs. 2.2%; p = 0.0002) in the FGR group.Table 3 shows stratification of FGR cases by estimated fetal birth weight revealed that distal villous hypoplasia, infarction, fibrin deposition, and villitis were most common in the <3rd percentile group, suggesting a link between severity of growth restriction and extent of placental pathology

Discussion

The present study examined placental morphological and histopathological changes in low-risk pregnancies complicated by late-onset fetal growth restriction (FGR) and compared them to placentas from gestational age-matched, appropriately grown fetuses (AGA).The findings of our study revealed significant, albeit often subtle, placental changes in pathological growth restriction, even in the absence of overt maternal risk factors. This study strengthens the understanding of the complex link between placental dysfunction and FGR.(Shao et al., 2021; Silver, 2018). The predominant lesions indicative of maternal vascular malperfusion (MVM) – such as composite MVM lesions and distal villous hypoplasia – strongly implicates compromised placental perfusion as a primary pathological mechanism underlying late-onset FGR (Bos et al., 2018). This vascular insufficiency leads to fetal adaptations that prioritize vital organs perfusion at the expense of overall growth. The significantly higher proportion of placentas weighing below the 10th percentile in the FGR group (over 40% vs. 4.4% in AGA) underscores the critical role of adequate placental mass in supporting fetal growth potential. (Marchand et al., 2022). This was further supported by an elevated fetal-placental weight ratio in FGR cases, reflecting disproportionate fetal demands relative to placental capacity—an established marker of placental insufficiency.

Clinical and Macroscopic Findings

- Although maternal demographic variables (age, BMI, and parity) did not differ significantly between groups,however birthweight was markedly reduced in the FGR cohort than the control group. **Maulik et al, found placental weights to be 631g in the control group and 409g in the IUGR group with the differences being statistically significant.The findings of both the studies are comparable.** . Morphologically, marginal cord insertion was more frequent in the FGR group (97.8% vs. 46.15%).

- **HISTOPATHOLOGICAL ABNORMALITIES**
- The most prevalent **histopathological abnormalities** seen in the FGR group were
- **Composite maternal vascular malperfusion lesions (57.14% in FGR vs. 9.89% in AGA; p < 0.0001)**
- **Distal villous hypoplasia (45.05% vs. 6.59%; p < 0.0001)**
- **Infarction and intervillous thrombi (20.88% vs. 2.20%; p = 0.0002)**

These findings show that vascular insufficiency is the predominant pathology in late-onset FGR. Distal villous hypoplasia and infarcts directly impair the nutrient exchange, leading to fetal undernutrition and hypoxia. Syncytial knot frequency did not differ significantly, suggesting it lacks diagnostic specificity for FGR in this context. Similarly, fibrin deposition, accelerated villous maturation, and villitis were not significantly elevated in FGR, indicating that inflammatory and degenerative processes may play a lesser role in this low-risk cohort with late-onset restriction.

Stratification by Severity and Doppler Histopathological:
Severity correlated with both lower estimated fetal weight (EFW) centiles and abnormal Doppler velocimetry. Among the severely growth-restricted fetuses (EFW <3rd percentile), nearly half exhibited distal villous hypoplasia and 16% had infarction. Similar lesions were observed in fetuses with EFW between the 3rd-10th percentile only if accompanied by abnormal Dopplers.This highlights the complementary value of integrating Doppler assessment with fetal biometry for predicting underlying placental pathology. It aligns with evidence that late-onset FGR often features preserved umbilical artery Doppler but abnormal cerebroplacental ratio or middle cerebral artery flow, indicating central redistribution – a sign not always captured by umbilical artery indices alone.

Interpretation and Clinical Relevance: Collectively, these findings reinforce that late-onset FGR in low-risk pregnancies is predominantly a vascular disorder characterized by a spectrum of placental insufficiency. The consistent presence of lesions like MVM, infarction, and villous hypoplasia confirms that significant placental pathology can occur without traditional risk factors or gross abnormalities. However, the heterogeneity in histological findings – with some FGR placentas lacking significant lesions – underscores the diagnostic challenge and suggests that placental dysfunction can sometimes be functional rather than overtly structural. Therefore, placental histopathology should be integrated with antenatal Doppler and serial growth assessment to refine diagnosis, improve risk stratification, and guide management decisions for borderline and late-onset FGR cases.

Limitations: Several limitations warrant mention. The single-center design may impact generalizability. While standardized protocols were used, some interobserver variability in histopathological assessment is inherent. Finally, the lack of long-term neonatal outcome data precludes correlation of placental findings with postnatal health trajectories, an important avenue for future research.

Conclusion

Late-onset FGR is associated with significant but subtle placental pathology primarily involving maternal vascular malperfusion. These lesions are more common and severe in fetuses with abnormal Doppler findings and greater degrees of growth restriction. Histopathology, when combined with clinical and Doppler data, can enhance the diagnostic distinction between constitutional smallness and true FGR, thereby informing surveillance and delivery strategies to improve perinatal outcomes.

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[Insert acknowledgments here]

Declaration of Interest

[Insert declaration of interest here]

REFERENCES

Aviram A, Giltvedt MK, Sherman C, Kingdom J, Zaltz A, Barrett J, Melamed N. The role of placental malperfusion in the pathogenesis of preeclampsia in dichorionic twin and singleton pregnancies. Placenta. 2018 Oct 1;70:41-9.

Baschat AA. Neurodevelopment following fetal growth restriction and its relationship with antepartum parameters of placental dysfunction. Ultra- sound Obstet Gynecol 2011;37(5):501e14.

Baschat AA. Fetal growth restriction e from observation to intervention. J Perinat Med 2010;38(3):239e46.

Crovetto F, Triunfo S, Crispi F, et al. First- trimester screening with specific algorithms for early- and late-onset fetal growth restriction. Ultrasound Obstet Gynecol 2016;48:340-8

Curtin WM, Krauss S, Metlay LA, Katzman PJ. Pathologic examination of the placenta and observed practice. Obstetrics & Gynecology. 2007 Jan 1;109(1):35-41.

Deter RL, Lee W, Sangi-Haghpeykar H, Kingdom J, Romero R. Third trimester growth restriction patterns: individualized assessment using a fetal growth pathology score. The Journal of Maternal-Fetal & Neonatal Medicine. 2018 Aug 18;31(16):2155-63.

Faye-Petersen OM, Heller DS, Joshi VV. Handbook of Placental Pathology, 2nd (edn.).

Gagnon R, Van den Hof M. The use of fetal Doppler in obstetrics. Journal of Obstetrics and Gynaecology Canada: JOGC= Journal D'obstetrique et Gynecologie du Canada: JOGC. 2003 Jul 1;25(7):601-14.

Gardosi J, Kady S, McGeown P, *et al.* Classification of stillbirth by relevant condition at death (RECODE): population based cohort study. *BMJ* 2005; **331**: 1113–1117

Hendrix N, Berghella V. Non-placental causes of intrauterine growth restriction. InSeminars in perinatology 2008 Jun 1 (Vol. 32, No. 3, pp. 161-165). WB Saunders.

Kovo M, Schreiber L, Ben-Haroush A, Cohen G, Weiner E, Golan A, Bar J. The placental factor in early-and late-onset normotensive fetal growth restriction. Placenta. 2013 Apr 1;34(4):320-4.

Laurini R, Laurin J, Marsål K. Placental histology and fetal blood flow in intrauterine growth retardation. Acta obstetricia et gynecologica Scandinavica. 1994 Jan 1;73(7):529-34.

Mardi K, Sharma J. Histopathological evaluation of placentas in IUGR pregnancies. Indian journal of pathology & microbiology. 2003 Oct 1;46(4):551-4.

Maulik D, Evans JF, Ragolia L. Fetal growth restriction: pathogenic mechanisms. Clinical obstetrics and gynecology. 2006 Jun 1;49(2):219-27.

Munim S, Nawaz FH, Ayub S. Still births – eight years experience at Aga Khan University Hospital Karachi, Pakistan. The Journal of Maternal-Fetal and Neonatal Medicine, March 2011; 24(3): 449–452.

Pardi G, Marconi AM, Cetin I. Placental-fetal interrelationship in IUGR fetuses: a review. Placenta. 2002;23:136-41.

Robinson JS, Moore VM, Owens JA, McMillen IC. Origins of fetal growth restriction. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2000 Sep 1;92(1):13-9.

Salafia CM, Charles AK, Maas EM. Placenta and fetal growth restriction. Clinical obstetrics and gynecology. 2006 Jun 1;49(2):236-56.

Salafia CM, Minior VK, Pezzullo JC, Popek EJ, Rosenkrantz TS, Vintzileos AM. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. Am J Obstet Gynecol. 1995;173:1049-57.

Shamim A, Khan HO, Rana JS, Ahmed KA. Intrauterine growth restriction: a perspective for Pakistan. JPMA. The Journal of the Pakistan Medical Association. 1999 Feb 1;49(2):50-2.

Smith NM. Broadsheet number 56: Mechanisms of fetal loss. Pathology. 2000;32:107-15.

Fan M, Wu H, Sferruzzi-Perri AN, Wang YL, Shao X. Endocytosis at the maternal-fetal interface: balancing nutrient transport and pathogen defense. Frontiers in Immunology. 2024 Jun 18;15:1415794.

Zimmermann P, Eiriö V, Koskinen J, Kujansuu E, Ranta T. Doppler assessment of the uterine and uteroplacental circulation in the second trimester in pregnancies at high risk for pre-eclampsia and/or intrauterine growth retardation: comparison and correlation between different Doppler parameters. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of

Boss AL, Chamley LW, Brooks AE, James JL. Differences in human placental mesenchymal stromal cells may impair vascular function in FGR. Reproduction. 2021 Oct 1;162(4):319-30

Gagnon R, Van den Hof M. The use of fetal Doppler in obstetrics. Journal of Obstetrics and Gynaecology Canada: JOGC= Journal D'obstetrique et Gynecologie du Canada: JOGC. 2003 Jul 1;25(7):601-14.

Tables

Table 1.quantitative variables in FGR

Characteristics	Late Onset FGR n=91	Term AGA n=91	p-value (of difference between groups)
Maternal age (mean ± sd)	27.33 ± 4.18	26±5.23	0.0598
Gravidity (mean ± sd)	2.02 ± 1.21	3.02±2.11	0.0001 *
Parity (mean ± sd)	0.81 ± 0.94	0.84±0.74	0.4967
BMI [kg/m2] (mean ± sd)	25.5 ±4.5	24.8±3.2	0.2283
Smoking n %	1 (0)	0 (0)	1.0000
Birth weight [gr] (mean ± sd)	2204 ± 378	3100±426	0.0000 *
Birth-weight percentile (mean ± sd)	3.5 +/- 2.9	53 +/- 28	0.0001 *

Table 2. morphological and histopathological feautres in cases and controls

Characteristics	Late Onset FGR (n %) n = 91	AGA term infants (n %) n = 91	p-value (of difference between groups)
Placental weight <10th centile	38 (41.75)	4 (4.40)	0.0000 *
Fetal Placental weight ratio (mean ± sd)	6.22 ±2.86	6.1±1.8	0.7353
Umbilical cord insertion			
Central	85 (93.41)	88 (96.70)	0.4941
Eccentric	6 (6.59)	1 (1.10)	0.1231
Number of abnormal umbilical vessels	4 (4.40)	1 (1.10)	0.3644
Membrane insertion			
Marginal	89 (97.80)	42 (46.15)	0.0000*
Circummarginate	2 (2.20)	1 (1.10)	1.0000
Composite maternal vascular supply lesion	52 (57.14)	9 (9.89)	0.0000 *
Syncytial knots	8 (8.79)	12 (13.19)	0.4771
Distal villous hypoplasia	41 (45.05)	6 (6.59)	0.0000 *
Infarction and intervillous thrombi	19 (20.88)	2 (2.20)	0.0002 *
Accelerated villous maturation	2 (2.20)	8 (8.79)	0.1039
Fibrin deposition	10 (10.99)	4 (4.40)	0.1643
Chorionic villitis	9 (9.89)	4 (4.40)	0.2496

Table 3.stratification according to birth weight

FGR n=91	Syncytial knots	Distal villous hypoplasia	Infarction and intervillous thrombi	Accelerated Villous Maturation	Fibrin deposition	Chorionic villitis
EFBW <3rd centile = 68	6	31	11	1	5	6

EFBW 3-5 centile with abn dopplers= 16	1	7	6	1	3	2
EFBW 5-10th centile with abn dopplers=7	1	3	2	0	2	1

Figures

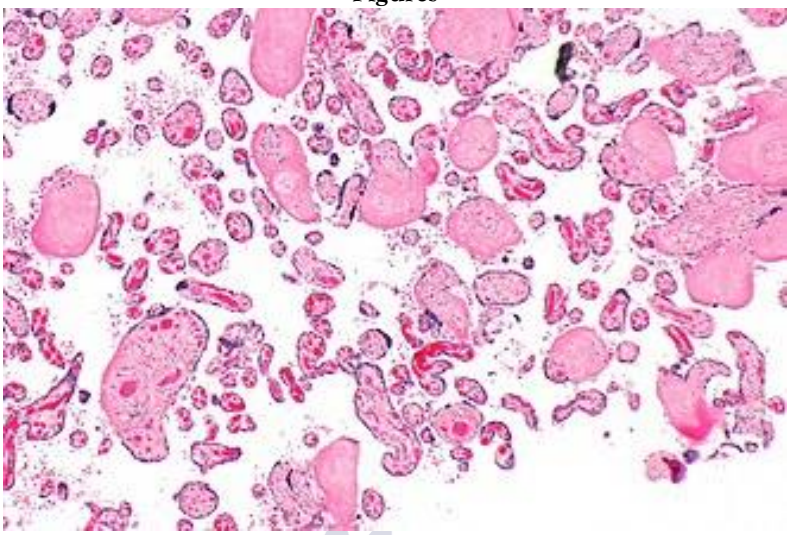

Figure 1. Distal Villous Hypoplasia

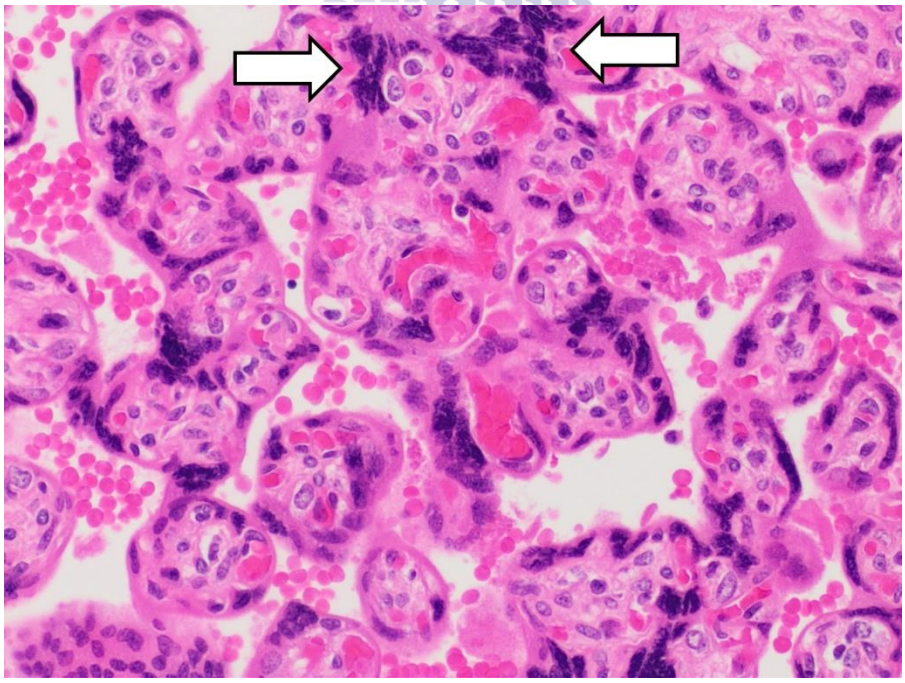

Figure 2. Increased syncytial knots

Figure Captions

Figure 1. Distal Villous Hypoplasia

Figure 2. Increased syncytial knots.