

Role of Placenta in Intrauterine Fetal Demise in a Tertiary Care Hospital of Peshawar, Pakistan

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Abstract

Background: Intrauterine Fetal Demise (IUFD) is the loss of a fetus at or after 20 weeks of gestation. It can be caused by many factors; placental pathologies play a vital role in these cases, but evidence in the literature is limited.

Objective: This study aimed to investigate the specific role of histopathological findings of the placenta associated with IUFDs.

Methods: In this retrospective study, IUFD cases (>20 weeks' gestation) from January 2021 to August 2023 were retrieved from the hospital database. Clinical features such as maternal age, gestational age, and fetal gender were noted. Lesions were categorized as maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), inflammatory lesions, and idiopathic lesions. The contributor to fetal death was classified as primary, secondary, associated minor, incidental, or unknown. Other histopathological findings were also recorded.

Results Placentas of 100 cases of IUFD were observed in total. The mean maternal age was 25 years. Fetal sex distribution included 42 females and 34 males. Relevant obstetric complications included bad obstetric history (n=39), preeclampsia (n=15), intrauterine growth restriction (n=7), oligohydramnios (n=5), pregestational diabetes (n=4), others/ not provided (n=30). Inflammatory lesions and MVM had the highest incidence, at 31% and 30%, respectively, and were identified as the primary contributors to IUFD. In 39 cases, extensive neutrophilic infiltrate was recorded.

Conclusion: Inflammatory lesions and MVM were among the most frequently observed placental histopathological findings in IUFD cases, demonstrating the significant role of placental pathologies in fetal demise.

Key words: IUFD, Placenta, MVM, FVM.

Introduction

By definition, intrauterine fetal demise (IUFD) is defined as fetal death occurring after 20 weeks of gestation and before the onset of labor.¹ It is a disastrous event not only for the parents but also for the caregivers. It is considered the most prevalent and adverse outcome of pregnancy. It affects more than 7000 families daily, which makes

it a global medical concern with psychological, social, and financial repercussions.² An estimated 2 million stillbirths were recorded in 2019 around the globe. Sub-Saharan Africa and South Asia experienced a stillbirth rate of 29 per 1,000 births, which is nearly ten times higher than the rate in high-income countries (3 per 1,000 births)³ In India, the incidence is 32 per 1000 live births; rural areas show a bit more cases than urban populations.⁴ The most common risk factors include cord prolapse, eclampsia, placental abruption, pre-eclampsia, diabetes mellitus, and anemia.⁵

Aside from unexplained deaths, placental pathologies constitute the most common cause of IUFD.⁶ According to a review of more than 40 studies, the placenta was the most common cause of fetal demise in 11% to 65% of cases, with placental abruption being the leading particular cause.⁷ A 2025 study conducted in India demonstrated that among 111 total cases, 64% of IUFDs occurred due to placental pathologies. Preeclampsia and vasculopathies were the most

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Authors Contribution

MT conceptualized the project. RH & MT did the data collection. RH performed the statistical analysis and did the literature search. Drafting, revision & writing of manuscript were also done RH & MT.

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common comorbidities observed in these cases.⁸ Another study from a hospital in Turkey identified hypertensive disorders and diabetes mellitus as the most common causes in the pathogenesis of stillbirths.⁹ Although maternal serum pregnancy-associated plasma protein-A (PAPP-A) levels and uterine artery Doppler indices are evaluated to assess maternal and fetal health, no definitive test exists to directly measure adequate placental function during the first and second trimesters.¹⁰ The only way to know placental pathologies is to perform the histopathological examination of the placenta after fetal death.¹¹ Stillbirths are associated with a variety of placental abnormalities, which must be differentiated from any changes caused by intrauterine retention following fetal demise.^{12,13} Placental pathologies are well recognized as a major contributor to IUFD; nevertheless, evidence within the local population is limited, and the frequency of specific histopathological placental lesions remains poorly characterized. As an autopsy on the fetus is an unusual practice, placental investigation is the only key approach available. Therefore, a comprehensive assessment of placental pathologies may facilitate a better understanding of the etiopathogenesis leading to IUFD and the identification of preventable risk factors. This study aimed to assess and classify placental pathologies according to already established histopathological criteria and to determine their role in IUFD.

Methods

This retrospective study was conducted in the Department of Pathology at Lady Reading Hospital (LRH) in Peshawar, Pakistan. Individual informed consent was waived by the IRB as the

study involved placental specimens and anonymized clinical records.

Data were collected over a period of 2 years and 7 months, from January 2021 to August 2023, through consecutive sampling. Placentas from cases of intrauterine fetal demise (IUFD) at or beyond 20 weeks of gestational age were included. Cases with incomplete clinical or obstetric history were excluded. All eligible cases during the study period were included, resulting in a total of 100 placental biopsies and corresponding histopathological reports retrieved from hospital records.

Relevant clinical and obstetric information, including maternal age, gestational age, fetal sex, intrauterine growth restriction, poor obstetric history, gestational diabetes, and other associated obstetric conditions, was obtained from the available records. Gestational age was categorized as early preterm (<34 weeks), late preterm (34 to <37 weeks), and term (≥37 weeks).

Placental slides were independently reviewed by two pathologists. Histopathological lesions were classified according to the placental lesion classification originally described by Redline and subsequently modified by the Amsterdam Placental Workshop Group. The lesions were categorized into maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), inflammatory lesions, and idiopathic lesions (Table-1).

The placental lesions were assessed for their potential contribution to fetal death based on the histopathological criteria described by Manocha et al., which were largely adapted from the Stockholm classification of stillbirth (Table-2). The contribution was assessed as direct, major, minor, or unlikely based on the nature and extent of the placental lesion.¹⁴

Table 1: Classification of placental lesions identified in cases of IUFD.

Category	Placental Lesions
1. MVM	Retroplacental hemorrhage, decidual vasculopathy, intraparenchymal hemorrhage, delayed villous maturation
2. FVM	Thrombi in fetal vessels, avascular villi, chorangiomas, villous stromal vascular karyrrhexis
3. Inflammatory Lesions	Intervillositis, Villitis, Fetal Inflammatory Response (FIR), Chorioamnionitis, Maternal Inflammatory Response (MIR)
4. Idiopathic Lesions	Maternal Floor Infarction (MFI), Massive Perivillous Fibrin Deposition (MPVF)

Table 2: Classification of contributors of fetal death identified in cases of IUFD.

Category	Placental Lesions
1. Primary Contributors	Retroplacental Hemorrhages, Loss of parenchyma (>30%) due to infarcts, diffuse high-grade villitis, Perivillous fibrin deposition, true knots of umbilical cord
2. Secondary Contributors	Extensive decidual vasculopathy, Loss of parenchyma (15-30%) due to infarcts
3. Associated Minor Lesions	Extensive length of the umbilical cord and its torsion, delayed villous maturation
4. Incidental Causes	Chorangioma, focal villitis, intervillitis

Thus, the frequency of specific placental histopathological lesions was assessed separately from their potential contribution to fetal death.

These lesions were also categorized as primary contributors, secondary contributors, associated minor lesions, or incidental causes of death.

Data were collected, analyzed, and interpreted using SPSS version 24. All categorical variables, i.e., gestational age, fetal gender, classification of lesion, death contributor, and obstetric complication, were described in frequencies and percentages, while continuous variables, i.e., maternal age, birth weight, and length of the cord, were summarized in mean and standard deviation.

Results

A total of 100 placentas from IUFD cases were collected and examined in this study. The mean maternal age was recorded as 25 years, which

ranged from 16 to 37 years. Most cases of IUFD were noted during the very preterm period (61%), whereas fewer cases were recorded during late term (26%) and full term (13%) (Table-3). Fetal sex was determined in 76 cases, consisting of 34 male and 42 female fetuses. Poor obstetric history (39%), preeclampsia (15%), intrauterine growth restriction (IUGR) (7%), Oligohydromas (5%), and pregestational diabetes (4%) were the most common reasons associated with IUFD. In 30% of cases no reason was identified or provided.

The length of the placental cords varied from 6 cm to 37 cm, with a mean of 17.27 cm. The mean placental weight was 344 g (range: 85–990 g). Gross placental involvement was observed in 24% of cases, while extensive fibrin deposition, neutrophilic infiltration, and hemorrhage were reported in approximately 25%, 39%, and 11% of cases, respectively.

Table 3: Case-wise spread of principal histopathological findings regarding gestational age.

Histopathological Finding	Very preterm (n= 61) n (%)	Late Preterm (n= 26) n (%)	Term (n= 13) n (%)
MVM	20 (32.8)	5 (19.2)	5 (38.5)
FVM	8 (13.1)	6 (23.1)	3 (23.1)
Inflammatory	20 (32.8)	8 (30.8)	3 (23.1)
Idiopathic	13 (21.3)	7 (26.9)	2 (15.4)
Total	61 (100)	26 (100)	13 (100)

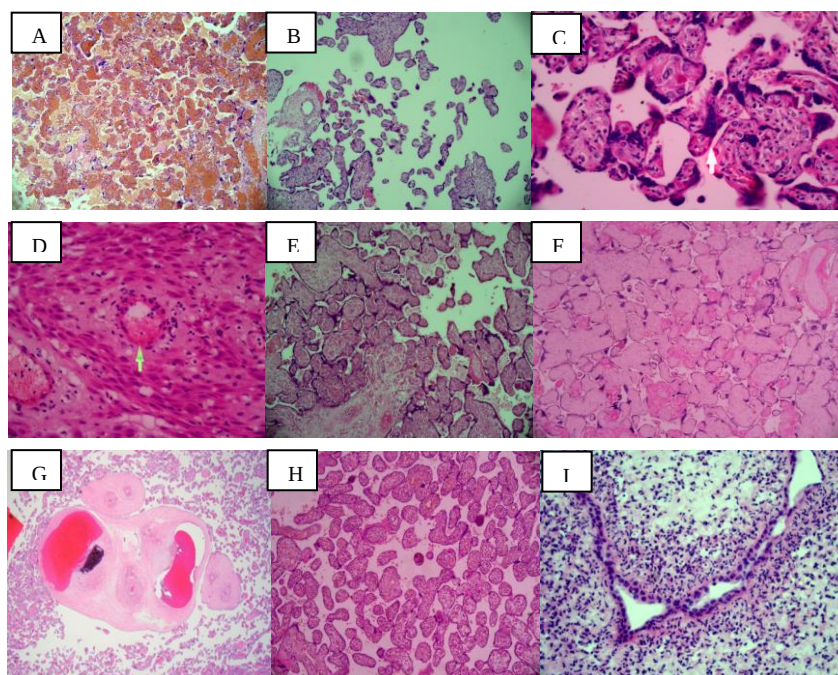


Figure 1: Composite Microphotograph of H&E group showing Retroplacental Haemorrhage (A), Distal Villous Hypoplasia (B), Accelerated Villous maturation (C), Acute Atherosclerosis (D), Villous Stromal-Vascular karyorrhexis (E), Avascular villi (F), Intramural Fibrin Deposition (G), Delayed Villous Maturation (H), acute Chorioamnionitis (I) in Placenta of IUFD cases.

Table 4: Contributors across different gestational ages leading to fetal death.

Fetal Death Contributors		Very Preterm (<34 weeks) n (%)	Late Preterm (34– <37 weeks) n (%)	Term Gestation (≥ 37 weeks) n (%)
Primary causes (n=60)	Retroplacental hemorrhage	20 (32.8)	3 (11.5)	2 (15.4)
	$>30\%$ parenchymal loss	13 (21.3)	5 (19.2)	1 (7.7)
	Combined (retroplacental hemorrhage + $>30\%$ parenchymal loss)	8 (13.1)	6 (23.1)	2 (15.4)
Secondary contributors (n=26)	15–30% parenchymal loss	10 (16.4)	5 (19.2)	6 (46.2)
	Extensive decidual vasculopathy	2 (3.3)	3 (11.5)	0 (0)
Associated minor lesions (n=8)	Delayed villous maturation	2 (3.3)	3 (11.5)	2 (15.4)
	Abnormal torsion of umbilical cord	1 (1.6)	0 (0)	0 (0)
Incidental causes (n=6)	Chorangioma	2 (3.3)	1 (3.8)	0 (0)
	Focal villitis	1 (1.6)	0 (0)	0 (0)
	Intervillositis	2 (3.3)	0 (0)	0 (0)
	Total	61 (100)	26 (100)	13 (100)

Placental histopathological findings were identified in 88% of the 100 cases, while the remaining 12% were idiopathic. Inflammatory lesions (31%) followed by MVM (30%) were observed frequently. Only 17% of cases had a finding of FVM. Of these 30 cases of MVM, in 7% of the cases, FVM and MVM are observed in combination. Isolated inflammatory lesions and isolated MIR were observed in 39% and 24%, respectively, while inflammatory lesions in combination with MIR (29%), FIR (4%), villitis, and deciduitis (4%) were also reported.

Primary Contributors were most common among all gestational ages, causing fetal death. Isolated retroplacental hemorrhage was reported in 25% of the cases, extensive parenchymal loss is seen in 19% of cases, and a combination of retroplacental hemorrhage and parenchymal loss was identified in 16% of the fetal deaths. Of the total 26 cases of Secondary Contributors, 21 cases were reported with 15-30% parenchymal loss, remaining 5 cases were classified as extensive deciduous vasculopathy. Delayed villous maturation and abnormal cord torsion were categorized as minor contributors to fetal demise, occurring in 7% and 1% of cases, respectively. Other incidental findings included chorangioma (3%), focal villitis (1%), and intervillositis (2%). Table-4 describes various contributors in different groups of gestational ages leading to fetal death.

Discussion

This study was based on the evaluation of 100 pregnancies with IUFD over a period of 2 years and 7 months (from January 2021 to August 2023) at a tertiary care hospital in Peshawar, Pakistan. In this study, a slight female preponderance is reported. Early PT cases were reported more than

half from late PT and full-term cases. Among different risk factors, poor obstetric history (39%) and preeclampsia (15%) were the most common.

In 2018, a study conducted in India examined 100 placentas from cases of fetal demise. The average maternal age was 26 years in this data set. They reported fetal demise most commonly during the very preterm period (65%); the mean gestational age was 30 weeks, and the male-to-female ratio of fetuses was 1:1.7. Among obstetric complications, the most common included preeclampsia (39%), restrained intrauterine growth, and pre-gestational diabetes 7% each, poor obstetric history, and oligohydramnios (6% and 5%, respectively). The average weight of the placenta was 256 g. Upon histopathological examination, the highest incidence was recorded for MVM (40%); if combined with FVM, isolated inflammatory and FVM cases were recognized in 12% and 6%, respectively. Primary contributors to fetal demise were the most prevalent across all gestational ages (51%). Secondary contributors, associated minor lesions, and incidental findings were observed in 21%, 11%, and 9% of cases, respectively. Fetal hypoxia was evident in 35 cases.¹⁴

A Turkish study reported a maternal mean age of 29.47 years at the time of fetal demise. In that study, of the 92 cases evaluated, 56.52% were female fetuses with a mean weight of 1,654 g. The most common causes included idiopathic cases (31.5%), fetal anomalies (21.9%), and preeclampsia/eclampsia (14%).⁹ Another study from India, conducted in 2015, reported the rate of IUFDs to be 36 per 1,000 births. They recorded anemia in about 74.4% of cases, while other maternal complications included hypertension (32.8%), diabetes, cardiac diseases, hyperpyrexia (2.4%), and infective hepatitis (0.8%).¹⁵ A 2016 study conducted in London evaluated 1,064 IUFD cases,

of which 307 (32%) presented with placental abnormalities at the time of fetal demise. The most common cause was ascending genital tract infection, accounting for 176 of 307 cases (57%). Other causes included specific placental lesions (20%), placental abruption (12%), fetal growth restriction (6%), and preeclampsia (5%). Among 60 cases of placental lesions, most were due to MVM (n=42). The remaining lesions included fetal vascular malperfusion (FVM; n=9), massive perivillous fibrin deposition (n=6), and chronic histiocytic intervillitis (n=3).¹⁶

A total of 60 IUFD cases were analyzed in a study where the mean maternal age was 30 years, and the mean gestational age at fetal demise was 30 weeks. Furthermore, in that study, 58.33% of cases occurred during the early-term period, and no post-term fetal deaths were reported. Hypertensive syndrome (21.67%) and obesity (13.33%) were the most common maternal pathologies. Upon histopathological examination, infarctions were the most common finding, affecting more than 36% of the cases. Placental or fetal tissue infection (25%) and placental abruption (18.33%) were also observed among the cases. This study was done in Serbia in 2023.¹⁷

Another study from India, conducted in 2023, involved 114 patients with IUFDs who were diagnosed through ultrasound and clinical examinations. Most of the females (46%) were between the age group of 21-25 years, and 73% had 28-36 weeks of gestational age. Among the causes, maternal causes were the most common (68.4%), followed by placental (27.2%) and fetal causes (4.4%). Specific maternal causes included hypertension (55.1%), anemia (21.7%), and gestational diabetes (11.5%), mainly. The prominent gross placental findings included calcification (54.4%), infarction (37.7%), and retroplacental hemorrhage (26.3%). On histopathological examination, the observed lesions included perivillous fibrin deposition (n=75), syncytial knots (n=53), intervillous hemorrhage (n=50), cytotrophoblastic proliferation (n=45), increased vascularity (n=32), fibrinoid necrosis (n=21), hydropic villi (n=9), and villitis (n=7).¹⁸

Conclusion

In conclusion, placental pathologies play a crucial role in the pathogenesis of IUFD. Inflammatory lesions and MVM were identified as the most frequent pathologies in this study, highlighting their significance in fetal demise. Advanced technologies for early detection and preventive strategies must be identified to manage

this condition, thereby reducing the burden of IUFD and improving pregnancy outcomes. A major limitation of the present study is the lack of fetal autopsies, which restricts the comprehensive evaluation of fetal causes of IUFD.

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Availability of Data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: The Institutional Review Board of Lady Reading Hospital, Peshawar approved the study via letter no. 228/LRH/MTI dated 04/09/2023.

Conflict of Interest: None declared.

Declaration: The authors confirm and guarantee that all images, figures, photographs, and other visual materials submitted with the manuscript are original, authentic, and shall be fully responsible for any copyright claim, infringement, dispute, or legal liability arising from the use of such materials.

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