

# Microscopic Placental Lesions in Unexplained Intrauterine Fetal Death: A Comparison with Live-Birth Placentas

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## ABSTRACT

**Introduction:** Unexplained intrauterine fetal death (IUFD) remains a significant obstetric challenge, and microscopic placental lesions may provide important evidence of underlying pathological processes that are not apparent clinically or macroscopically. Histopathological examination can identify inflammatory, vascular, and maternal or fetal malperfusion lesions associated with fetal demise. Therefore, this study aimed to assess the pattern of microscopic placental lesions in unexplained IUFD and compare them with those observed in live-birth placentas. **Methods & Materials:** This case-control study was conducted in the Department of Obstetrics & Gynaecology, Sir Salimullah Medical College Mitford Hospital, Dhaka, from July 2021 to June 2022. A total of 100 pregnant women were included in the study using purposive sampling. Data were analyzed using SPSS version 22. **Results:** The study included 100 subjects, with the mean age significantly higher in the IUFD case group than in controls (27.12±5.11 vs. 23.94±4.70 years,  $p=0.001$ ), while irregular ANC was also significantly more common among cases (84.0% vs. 56.0%,  $p=0.002$ ). Histopathological examination showed significantly higher frequencies of acute/chronic inflammation (60.0% vs. 18.0%,  $p=0.001$ ), perivillous fibrin deposition (18.0% vs. 2.0%,  $p=0.007$ ), infarction/necrosis (20.0% vs. 6.0%,  $p=0.037$ ), hemorrhage (24.0% vs. 4.0%,  $p=0.004$ ), and cord thrombosis (14.0% vs. 0%,  $p=0.006$ ) in IUFD placentas. Microscopic calcification was more frequent in cases but did not differ significantly ( $p=0.182$ ). **Conclusion:** The study demonstrated that microscopic placental abnormalities were significantly more frequent in unexplained IUFD than in

live-birth placentas. Acute inflammation was the most common finding (56.0% vs 18.0%), followed by hemorrhage (24.0% vs 4.0%), infarction/necrosis (20.0% vs 6.0%), perivillous fibrin deposition (18.0% vs 2.0%), and cord thrombosis (14.0% vs 0%), with these differences reaching statistical significance ( $p<0.05$ ). Microscopic calcification was also more prevalent in the IUFD group, although the difference was not statistically significant.

**Keywords:** Microscopic Placental Lesions, Intrauterine Fetal Death, Perivillous fibrin

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## INTRODUCTION

Stillbirth remains a major global perinatal health problem, with approximately 1.9 million stillbirths occurring worldwide in 2023, despite substantial reductions in child mortality over the past two decades [1]. A considerable proportion of stillbirths remains unexplained even after maternal, fetal, and clinical evaluation, limiting opportunities for prevention in subsequent pregnancies. The placenta is increasingly recognized as a critical diagnostic tissue in this setting because it integrates maternal vascular, fetal vascular, inflammatory and developmental abnormalities that may precede fetal death. In a large population-based Stillbirth Collaborative Research Network study involving 518 stillbirths and 1,200 live births, multiple placental abnormalities were significantly more frequent among stillbirths, including inflammation (30.4% vs 12.0%), fetal vascular thrombi (23.0% vs 7.0%), retroplacental hematoma (23.8% vs 4.2%), infarction (10.9% vs 4.4%), fibrin deposition (9.2% vs 1.5%), avascular villi (7.6% vs 2.0%) and diffuse terminal villous immaturity (10.3% vs 2.3%) [2].

Microscopic examination is particularly important because many clinically significant placental abnormalities are not reliably recognized by gross inspection alone. Placental maternal vascular malperfusion (MVM), characterized by lesions such as accelerated villous maturation, distal villous hypoplasia, decidual arteriopathy and placental infarction, reflects inadequate maternal perfusion and may produce chronic fetal hypoxia and growth restriction [3,4]. Conversely, fetal vascular malperfusion (FVM), manifested by thrombi, avascular or hypovascular villi and vascular obliteration, indicates obstruction of the fetal placental circulation and has been associated with fetal death [4,5]. A large prospective study conducted in India and Pakistan found MVM in 58.4% of fetal-death placentas compared with 15.4% of term live-birth placentas, corresponding to an adjusted relative risk of 3.88; FVM was also more frequent in fetal-death placentas (19.0% vs 5.0%), with an adjusted relative risk of 4.09 [6]. Inflammatory lesions constitute another important microscopic pathway. Acute chorioamnionitis and funisitis may indicate

ascending intrauterine infection, while chronic inflammatory lesions such as villitis of unknown etiology can interfere with placental exchange and vascular function [4,7]. Importantly, placental disease does not necessarily follow a single pathological pathway; vascular injury, inflammatory damage, hemorrhage, thrombosis, and abnormal villous maturation may coexist within the same placenta. In the Stillbirth Collaborative Research Network, 121 of 512 stillbirths (23.6%) were classified as having a probable or possible cause of death attributable to placental disease [8]. The diagnostic value of placental histopathology is substantial. In a standardized evaluation of stillbirth, placental pathology was considered useful in 64.6% of cases, exceeding fetal autopsy (42.4%) and genetic testing (11.9%), demonstrating that placental examination can provide clinically relevant evidence even when no obvious cause is apparent from the clinical history [9]. However, interpretation requires standardized microscopic definitions because postmortem changes following fetal death can mimic true antemortem lesions. The Amsterdam Placental

Workshop Group therefore established standardized terminology and diagnostic criteria for MVM, FVM, delayed villous maturation, ascending infection, and villitis of unknown etiology to improve reproducibility and comparability between studies [10]. Recent evidence further indicates that placental lesions vary according to gestational age and that different histological patterns may characterize different pathways to fetal death. Studies from the Stillbirth Collaborative Research Network have identified gestational-age-specific patterns, including funisitis and increased nucleated fetal erythrocytes in extreme preterm stillbirth and reactive amniocytes and meconium in term stillbirth [11].

METHODS & MATERIALS

This case-control study was conducted in the Department of Obstetrics & Gynaecology, Sir Salimullah Medical College Mitford Hospital, Dhaka, from July 2021 to June 2022. Pregnant women with a gestational age of 28 completed weeks to 40 completed weeks who were admitted to the labour emergency for delivery and fulfilled the eligibility criteria were enrolled using purposive sampling. A total of 100 pregnant women were included in the study. The case

group consisted of women with intrauterine fetal death (IUFD) at 28-40 completed weeks of gestation, confirmed by ultrasonography, while the control group consisted of women within the same gestational age range who delivered viable babies. Women aged 20–40 years were included. Pregnancies complicated by gross fetal congenital malformations, intrapartum stillbirth, antepartum haemorrhage, history of trauma during pregnancy, post-dated or prolonged pregnancy, maternal infection, diabetes mellitus or gestational diabetes mellitus, hypertensive disorders of pregnancy, thyroid disorders, or Rh incompatibility were excluded. Eligible participants were approached before delivery, informed about the objectives of the study, and enrolled after obtaining written informed consent. Following delivery, representative placental tissue and umbilical cord specimens were collected, appropriately preserved, processed, and subjected to routine histopathological examination. Microscopic examination was performed to identify and document inflammation, perivillous fibrin deposition, microscopic calcification, infarction/necrosis, haemorrhage, umbilical cord thrombosis, vascular malformation, delayed villous maturation, accelerated

villous maturation, distal villous hypoplasia, malformed villi, and chorangiosis. Histopathological findings were recorded systematically using a structured data collection form and compared between the IUFD and live-birth groups. Data were analyzed using IBM SPSS Statistics for Windows, version 22. Quantitative variables were expressed as mean ± standard deviation and compared using the unpaired Student’s *t*-test, while qualitative variables were presented as frequencies and percentages and analyzed using the Chi-square test with cross-tabulation. A *p*-value of <0.05 was considered statistically significant. The study protocol was approved by the Ethical Review Committee of Sir Salimullah Medical College Mitford Hospital, Dhaka.

RESULTS

It was observed that almost half (46.0%) of subjects belonged to the age group 20-25 years in the case group and 37(74.0%) subjects in the control group. The mean age was 27.12±5.11 years in the case group and 23.94±4.7 years in the control group. The difference was statistically significant (*p*<0.05) between the case and control groups (Table I).

Table I  
Distribution of the study subjects according to age (n=100).

| Age in years    | Case (n=50) |      | Control (n=50) |      | p value |
|-----------------|-------------|------|----------------|------|---------|
|                 | n           | %    | n              | %    |         |
| 20-25           | 23          | 46.0 | 37             | 74.0 |         |
| 26-30           | 16          | 32.0 | 9              | 18.0 |         |
| 31-35           | 9           | 18.0 | 3              | 6.0  |         |
| >35             | 2           | 4.0  | 1              | 2.0  |         |
| Mean±SD         | 27.12±5.11  |      | 23.94±4.7      |      | 0.001s  |
| Range (min-max) | 20-40       |      | 20-40          |      | -       |

s=significant; *p* value reached from the unpaired *t*-test.

It was observed that the majority (84.0%) of subjects had irregular ANC in the case group and 28(56.0%) in the control group.

The difference was statistically significant (*p*<0.05) between the case and control groups (Table II).

Table II  
Distribution of the study subjects according to ANC (n=100).

| ANC       | Case (n=50) |      | Control (n=50) |      | p value |
|-----------|-------------|------|----------------|------|---------|
|           | n           | %    | n              | %    |         |
| Irregular | 42          | 84.0 | 28             | 56.0 | 0.002s  |
| Regular   | 8           | 16.0 | 22             | 44.0 |         |

s= significant; *p* value reached from the Chi-square test.

The differences in inflammation, perivillous fibrin deposition, infarction/necrosis, hemorrhage, and thrombosis of the cord of

placenta were statistically significant (*p*<0.05) between case and control groups (Table III).

**Table III**  
Distribution of the study subjects according to microscopic findings of placenta of IUFD and live birth (n=100).

| Microscopic findings          | Case<br>(n=50) |      | Control<br>(n=50) |       | p value |
|-------------------------------|----------------|------|-------------------|-------|---------|
|                               | n              | %    | n                 | %     |         |
| Inflammation                  |                |      |                   |       |         |
| Acute                         | 28             | 56.0 | 9                 | 18.0  | 0.001s  |
| Chronic                       | 2              | 4.0  | 0                 | 0.0   |         |
| Absent                        | 20             | 40.0 | 41                | 82.0  |         |
| Perivillous fibrin deposition |                |      |                   |       |         |
| Present                       | 9              | 18.0 | 1                 | 2.0   | 0.007s  |
| Absent                        | 41             | 82.0 | 49                | 98.0  |         |
| Microscopic Calcification     |                |      |                   |       |         |
| Present                       | 7              | 14.0 | 3                 | 6.0   | 0.182ns |
| Absent                        | 43             | 86.0 | 47                | 94.0  |         |
| Infarction/necrosis           |                |      |                   |       |         |
| Present                       | 10             | 20.0 | 3                 | 6.0   | 0.037s  |
| Absent                        | 40             | 80.0 | 47                | 94.0  |         |
| Hemorrhage                    |                |      |                   |       |         |
| Present                       | 12             | 24.0 | 2                 | 4.0   | 0.004s  |
| Absent                        | 38             | 76.0 | 48                | 96.0  |         |
| Thrombosis of cord            |                |      |                   |       |         |
| Present                       | 7              | 14.0 | 0                 | 0.0   | 0.006s  |
| Absent                        | 43             | 86.0 | 50                | 100.0 |         |

s=significant; ns= not significant; p value reached from the Chi-square test.

**DISCUSSION**

Maternal age is noted to be a risk of stillbirth [12]. In the UK, Aminu et al. revealed that advanced maternal age was a factor for stillbirth [13]. Another study conducted in Nigeria highlighted that advanced maternal age was associated with an increased risk of developing stillbirths obtained by Suleiman et al [14]. In the present study, it was observed that 46.0% of subjects belonged to the 20-25 years age group in the case group and 50.0% of subjects in the control group. The mean age was 27.1±5.1 years in the case group and 23.9±4.7 years in the control group. The mean age was significantly ( $p<0.05$ ) higher in the case group. In Tanzania, Ghana, and Canada, Chuwa et al. Badimsuguru et al. and Huang et al. did not find a significant association between maternal age and risk of stillbirths [15,16,17]. Regarding the antenatal checkup in this study, it was observed that 84.0% of subjects received ANC irregularly in the case group and 56.0% in the control group. On the other hand, 16.0% and 44.0% of patients received regular ANC in the case and control groups, respectively. Irregular ANC was significantly ( $p<0.05$ ) higher in the case group. Lema et al. mentioned in their study that mothers who did not attend or had one visit to ANC during pregnancy had a 6.96 times higher risk of developing stillbirth when compared to those with at least four visits, and this was statistically significant ( $p<0.05$ ) [12]. The investigators found a strong association between maternal education and number of ANC attendance with an increased risk of stillbirth. Lack of adequate antenatal care is the most important issue that needs urgent attention. Regular ANC not only detects complications but also helps in their management, and feto-maternal morbidity and mortality can be prevented [18].

Ananthan et al. reported that the most common placental findings in stillbirths were abnormalities of the foetal villous capillaries, inflammatory lesions, villitis and foetal circulatory disorders [19]. These included terminal villous immaturity, chorionic plate acute vasculitis, acute and chronic diffuse villitis, foetal vascular thrombi in the chorionic plate, and avascular villi. Notably, the prevalence of terminal villous immaturity and hypoplasia, acute diffuse villitis, and fibrin deposition was more than 30.0% in their study, reflecting the causality associated with stillbirth. Similarly, maternal complications such as placental abruption and gestational diabetes were significantly associated with stillbirths. Regarding the association of placental histomorphology with intrauterine foetal death in this study, it was observed that acute inflammation was observed in 56.0% and 18.0% in the case and control groups, respectively. Acute inflammation was significantly ( $p<0.05$ ) associated with intrauterine foetal death. Histopathology of the placental lesions indicates acute and severe placental insufficiency, thereby causing stillbirth [20]. Lema et al. study results agree with a systematic review conducted in the UK by Ptacek et al. who reported several placental lesions to be associated with stillbirth; these included fetal thrombotic vasculopathy, endovasculitis, cord abnormalities, and delayed villous maturation [12,20]. The investigators also found inflammatory abnormalities such as choriomanionitis, villitis, and endovasculitis to be associated with stillbirth. Significantly, the researchers noted a wide spectrum of placental pathology and placental abnormalities in classification systems for identifying the cause of death in stillbirths. Lema et al. also agree with another report done by

Goldenberg et al. in the USA, which highlighted acute chorioamnionitis and other inflammatory lesions to be common in stillbirth and early preterm delivery.<sup>12,21</sup> This could be explained by an increase in infections in the placenta that is linked with causal pathology that precipitates labour leading to stillbirth and preterm deliveries. The placenta could be directly infected, leading to reduced blood flow to the foetus. Moreover, maternal infections of the genital tract or elsewhere may precipitate the preterm labour that the foetus is unable to tolerate, as a result of stillbirth [21]. The current study confirms a significant relationship between placental histopathological abnormalities and stillbirths.

**LIMITATIONS**

The study had certain limitations. As the participants were recruited from a single hospital in Dhaka, the findings may have limited applicability to the wider Bangladeshi population. The relatively brief study duration and small sample size may also have restricted the strength and generalizability of the results. In addition, fetal autopsy was not performed after delivery, which may have prevented identification of some fetal pathological conditions that could have contributed to the cause of death.

**CONCLUSION**

The study concluded that microscopic placental lesions were significantly more common in unexplained IUFD than in live-birth placentas, particularly acute inflammation (56.0% vs 18.0%), hemorrhage (24.0% vs 4.0%), infarction/necrosis (20.0% vs 6.0%), perivillous fibrin deposition (18.0% vs 2.0%), and cord thrombosis (14.0% vs 0%)

( $p < 0.05$ ). Microscopic calcification was also more frequent in IUFD, although the difference was not significant.

## RECOMMENDATION

Routine gross and microscopic examination of the placenta should be incorporated into the evaluation of unexplained IUFD, with particular attention to inflammatory, hemorrhagic, thrombotic and infarctive lesions. Standardized placental histopathological assessment may improve identification of otherwise unrecognized causes of fetal death and provide useful information for counseling regarding future pregnancies.

## FUNDING

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## CONFLICT OF INTEREST

None declared

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