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Research Article

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Histopathological Changes in the Placenta in Late Intrauterine Fetal Deaths at a Tertiary Hospital in Bangladesh

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Abstract

Introduction: Meticulous gross and microscopic studies of the singleton placenta alone may provide valuable information regarding the cause of unexplained intrauterine fetal deaths (IUFDs) and can offer potential treatment options for its prevention in future pregnancies.

Objective: To determine the histopathological changes in the placenta associated with late intrauterine fetal death.

Method: A cross-sectional study was carried out in the Department of Pathology, Sir Salimullah Medical College Mitford Hospital, Dhaka, from March 2021 to January 2023. A total of 80 patients aged between 19 and 44 years with late IUFDs were included in this study. The placentas of the dead borns were histopathologically analyzed.

Results: All of the patients presented significant gross and histopathological changes in the placental specimens. A total of 71.3% of them were <30 years of age. Fifty percent of the patients were multipara, and 45% were primi. The gestational age of 61.3% of the patients were within 37-40 weeks, 20% within 28-32 weeks, and 18.8% were within 33-36 weeks. The mean placental weight was 407 gm, and 46.3% of the patients had placental weights within 410-450 gm. A total of 33.8% of the patients had placental diameters within 9-12 cm, and 48.8% had placental diameters within 13-16 cm. Cord insertion was eccentric in 41.3%, central in 45.0% and marginal in 12.5% of the patients. A total of 18.8% of patients had hypocoiled and 10% had hypercoiled cords. Twenty percent of patients had retroplacental hemorrhage. The membranes were greenish yellow in 3.8% of the samples and pale bluish in 2.4% of the samples. The significant microscopic findings were vascular ectasia with congestion in 26.3% of the patients, disorders of villous maturation in 35%, perivillous fibrin deposition in 15.0%, intervillous hemorrhage in 23.8%, subamniotic hemorrhage in 2.5%, microcalcification in 18.8%, infarct with avascular ghost villi in 17.5%, villous edema in 15%, deciduitis in 6.25%, thrombus in 5%, perivillous fibrin deposition in 15%, chorangiosis in 2.5%, villitis of unknown origin in 25% and chronic intervillositis

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in 17.5% of the patients. Maternal and fetal inflammatory responses were present in 26 patients, of whom 46.2% had stage 1 and 38.5% had stage 2 maternal inflammatory responses. A total of 7.7% had stage 1 inflammatory response, and 23.1% had stage 2 fetal inflammatory response.

Discussion: This study revealed that late IUFD is associated with significant placental histopathological abnormalities. Identification of these abnormalities can provide information about the etiopathogenesis of late intrauterine fetal deaths, can play a very important role in medicolegal situations and can guide physicians in the management of patients to prevent further pregnancy losses.

Keywords: Placenta, Late IUFD

Abbreviations: CD: Cluster of Differentiation; DHIS: District Health Information Software; DVH: Distal Villous Hypoplasia; DVM: Delayed Villous Maturation; H & E: Hematoxylin and Eosin; ICD-11: International Classification of Disease; IUFD: Intrauterine Fetal Death; SD: Standard deviation; SPSS: Statistical Package for Social Sciences; VUO: Villitis of Unknown Origin; WHO: World Health Organization.

Introduction

Fetal death is a matter of great distress to both the family and the obstetrician. Regardless of howmuch advancement has been achieved in the field of medical science, pregnancy loss still occurs at an alarming rate worldwide. The International Classification for Diseases 11th revision (ICD-11) classifies fetal death as late fetal death (greater than 1000 g or after 28 weeks) or early fetal death (500-1000 g or 22-28 weeks). Worldwide, approximately 60% of stillborn cases are unexplained in otherwise normal pregnancies according to Lancet Global Health, 2018. According to the World Health Organization, in 2022, the stillbirth rate in Bangladesh was 25 per 1000 births. According to the Emergency Obstetric & Newborn Care Services: Yearly DHIS-2 report by the Ministry of Health & Family Welfare, Bangladesh, from February 2021 to February 2022, a total of 10,777 pregnant mothers were admitted to the Department of Gynecology & Obstetrics, Sir Salimullah Medical College Mitford Hospital, Dhaka for delivery or obstetric complications, and among them the total number of intrauterine fetal deaths was 275.

The human placenta is a discoid, choriodeciduate organ that acts as a portal connecting the fetus with the uterine wall of the mother via the umbilical cord. The maternal supply of oxygen and nutrients occurs through the placenta via the umbilical circulation in response to fetal demand, whereas its protective function is derived from the ability to mount an inflammatory response to an external stimulus. Despite its undeniable role in human fetal development, the study of the placenta has lagged behind that of the fetus. The placenta can provide a record of both fetal and maternal intrauterine events, acting as the ''black box'' of pregnancy.

Intrauterine fetal deaths may be caused by maternal, fetal and placental factors, but these factors are usually multiple and overlapping. Conditions resulting in placental dysfunction may be recurrent and can manifest in different ways in different pregnancies. The placental factors include umbilical cord and placental disc abnormalities such as retroplacental hemorrhage, circumvallation, marginal cord, true knot, calcification, inflammatory reactions, circulatorycompromise (maternal or fetal), abnormalities in villous maturation, hemorrhage, necrosis, villous edema, perivillous fibrin deposition and other conditions [1-5].

As per the Bangladesh Demographic and Health Survey (BDHS), in 2017-18, only 47% of pregnant women in Bangladesh attended at least four WHO-recommended ANC activities [16]. Therefore, evaluation of gross and histopathological findings in the placentas of unexplained late IUFD cases may help physicians understand their accurate etiopathogenesis to prevent recurrence, to take precautionary measures during further management in future pregnancies and to address accountability issues. Moreover, when medicolegal problems arise, a study of placental histopathology can reveal the exact cause of fetal loss and can act as a legal shield to the doctor from the concerned patient. At the national and regional decision -making levels, identifying causes is important for adopting management strategies for prioritizing medical services according to the person and area needed, thus ensuring proper health care services to the general population of the country.

Although accurate placental examination is necessary in the evaluation of IUFDs and could play an important role in reducing the unexplained IUFD rate, placental examination is not routinely practiced in our country. Surprisingly no previous studies have identified gross and histopathological changes in the placentas of unexplained late IUFDs in Bangladesh.

Methods

This was a cross-sectional, descriptive and observational study. A total of 80 mothers aged 18 years or above with a diagnosis of late IUFD at a gestational age of 28 weeks or above were included in this study. Any late IUFD with known pre-existing maternal conditions such as preeclampsia, diabetes, chronic hypertension, smoking, infections, and antiphospholipid syndrome were excluded from the study, as our sole goal was to identify the factors responsible for unexplained late IUFDs. The study was conducted at the Department of Pathology, Sir Salimullah Medical College, Dhaka, Bangladesh, from March, 2021 to January, 2023.

The placentas were collected from the Department of Obstetrics and Gynecology, Sir Salimullah Medical College Mitford Hospital, Dhaka, immediately after delivery and fixed with 10% neutral buffered formalin for 24 hours. The specimens were subsequently processed and examined at the Department of Pathology, SSMC, for histopathological examination.

Placentas were weighed after the cord and membrane were removed. After meticulous gross examination, 6 blocks were submitted : 1 block to include a roll of the extraplacental membranes from the rupture edge to the placental margin, 2 cross sections of the umbilical cord (one from the fetal end and another 5 cm from the placental insertion end), and 3 blocks each containing a full thickness or upper 3rd or lower 3rd section of placenta parenchyma. The slides were stained with H&E.

Microscopic evaluation of the placenta included evaluation of the maternal and fetal inflammatory response, disorder of villous maturation, vascular ectasia with congestion, villitis of unknown origin, chronic intervillositis, perivillous fibrin deposition, calcification, and villous edema. The presence of findings in 30% or more of the villi was considered significant. Vasculo-syncytial membranes (VSMs) were counted in ten terminal villi in each of ten consecutive high -power fields on 3 slides. Staging of both maternal and fetal inflammatory responses was performed following the criteria described by *Khong, et al.,* (2016) [6]. Both the central and peripheral parts of the placenta were examined, keeping in mind which lesions are considered pathological in which locations (Table 1).

Table 1: Staging of maternal and fetal inflammatory responses according to the Amsterdam Placental Workshop Group Consensus Statement6.

Maternal Inflammatory Response	Fetal Inflammatory Response
Stage 1: Acute subchorionitis or chorionitis	Stage 1: Chorionic vasculitis or umbilical phlebitis
Stage 2: Acute chorioamnionitis	Stage 2: Involvement of the umbilical vein and one or more umbilical arteries
Stage 3: Necrotizing chorioamnionitis	Stage 3: Necrotizing funisitis

The data of all the variables were put into the checklists, and statistical analysis was carried out by using the Statistical Package for Social 'IBM SPSS Statistics for Windows, version XXII (IBM Corp., Armonk, N.Y., USA).

Results

Distribution of Patients According to Age and Gestational Age

Among the 80 patients, 57 (71.3%) were in the <30 years age group and 23 (28.7%) were in the ≥30 years age group. The mean age of the patients was 25.7 (± 5.9) years. The gestational age of the majority of the patients (49, 61.3%) was between 37-40 weeks, 16 (20.0%) had a gestational age of 28-32 weeks, and 15 (18.8%) had a gestational age between 33-36 weeks.

Distribution of Patients According to Gravida

Among the 80 patients, half (40 cases, 50%) were multipara, 36 (45%) were primi, and 4 (5%) were grand multipara mothers.

Distribution of Patients According to Placental Weight

Table 2: Distribution of patients by placental weight (n=80).

Placental Weight	Frequency (n)	Percentage (%)
200-250	11	13.8
260-300	2	2.5
310-350	1	1.3
360-400	16	20
410-450	37	46.3
460-500	2	2.5
510-550	11	13.8
Range (in gm) (min--max)	200-550	

Distribution of Patients According to Placental Diamezter

One-third of the patients (27, 33.8%) had a placental diameter ranging from 9-12 cm, 39 (48.8%) had a diameter ranging from 13-16 cm, 12 (15%) had diameter ranging from 17-20 cm, and 2 (2.5%) had a diameter >20 cm. The mean placental diameter of the patients was 13.7 (± 2.9) cm.

Distribution of Patients According to Cord Insertion and Cord Coiling

Eccentric cord insertion was present in 33 (41.3%) patients, central cord insertion was present in36 (45.0%) patients, and marginal cord insertion was present in 10 (12.5%) patients. Only one patient underwent velamentous cord insertion. Cord coiling was normal in 57 (71.3%) patients, while 15 (18.8%) had hypocoiled cords, and 8 (10.0%) had hypercoiled cords.

Distribution of patients according to the color of the membrane

Table 3: Distribution of patients by color of the membrane (n=80).

Color of Membrane	Frequency (n)	Percentage (%)
Normal	75	93.8
Greenish yellow	3	3.8
Pale Bluish	2	2.4

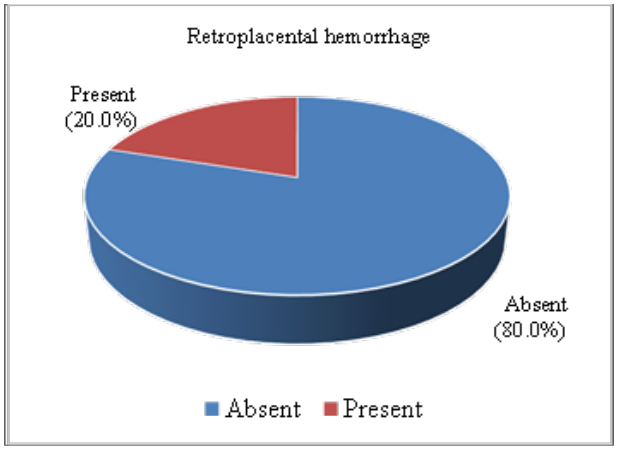

Figure 1: Distribution of patients with retroplacental hemorrhage (n=80).

Figure 2: On the left, photograph showing the marginal insertion of a hypocoiled cord (Case no. 23) and **Figure 3:** On the right, photograph showing greenish discolouration of the membrane (Case no: 39).

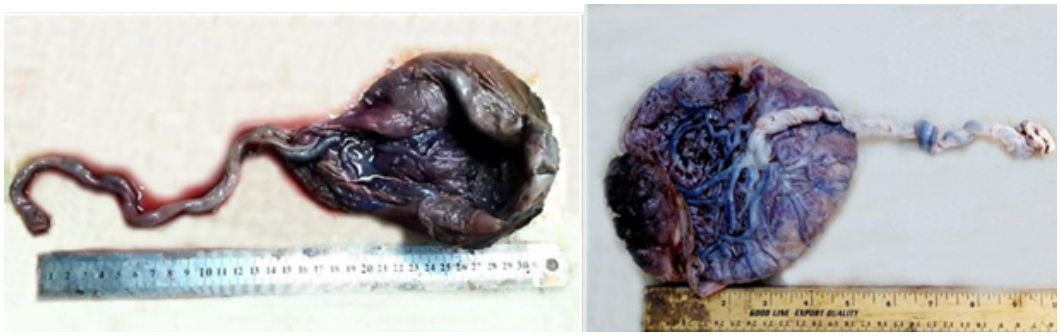

Figure 4: On the left, photograph showing the velamentous insertion of the cord (Case no.78) and **Figure 5:** On the right, photograph showing hypercoiled cord (Case no: 18).

Distribution of patients according to microscopic findings

Table 4: Distribution of patients by microscopic findings (n=80).

Microscopic Findings	Frequency (n)	Percentage (%)
Maternal & fetal inflammatory response	26	32.5
Disorder of villous maturation	28	35
Vascular ectasia with congestion	21	26.3
Villitis of unknown origin	20	25
Intervillous Hemorrhage	19	23.8

Microcalcification	15	18.8
Infarct with ghost villi	14	17.5
Chronic intervillositis	14	17.5
Villous edema	12	15
Perivillous fibrin deposition	12	15
Deciduitis	5	6.25
Thrombus	4	5
Subamnionic Hemorrhage	2	2.5
Chorangiosis	2	2.5
Increased syncytial knot	2	2.5
Simple cyst	1	1.3
Squamous metaplasia	1	1.3
Placenta increta	1	1.3
No changes	2	2.5

Distribution of patients with maternal and fetal inflammatory responses according to stage

Table 5: Distribution of patients by maternal and fetal inflammatory response (n=26).

Inflammatory Response	Frequency (n)	Percentage (%)
Stage 1 Maternal	12	46.2
Stage 2 Maternal	10	38.5
Stage 3 Maternal	1	3.9

Figure 6: On the left, photograph showing a histological section of a thrombus in an Umbilical artery (Case no: 51, H&E, 40X).

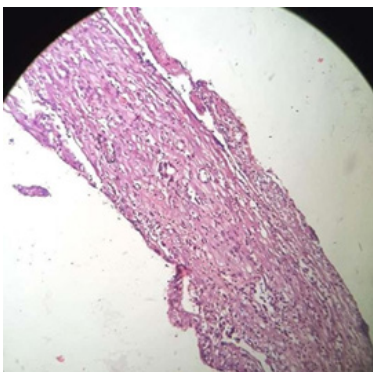

Figure 7: On the right, photograph showing a histological section of a patient with chorionitis (Case. no: 56, H&E, 40X).

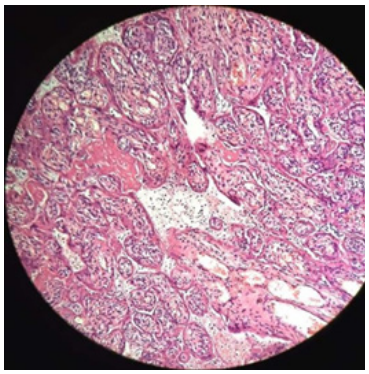

Figure 8: On the left, photograph showing a histological section of villitis and intervillositis (Case no: 53, H&E, 40X).

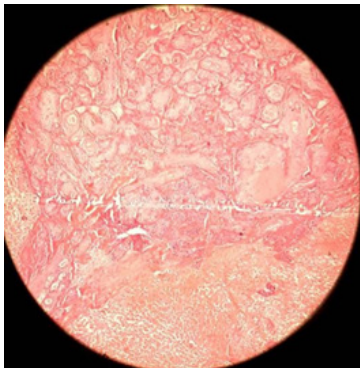

Figure 9: On the right, photograph showing a histological section of the infection (Case no: 54, H&E, 40X).

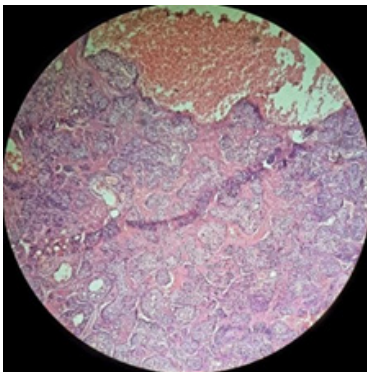

Figure 10: On the left, photograph showing a histological section of perivillous fibrin deposition (Case no: 38, H&E, 10X).

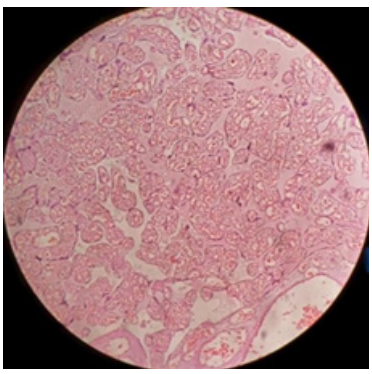

Figure 11: On the right, photograph showing a histological section of a patient with chorangiosis (Case no: 27, H&E, 10X).

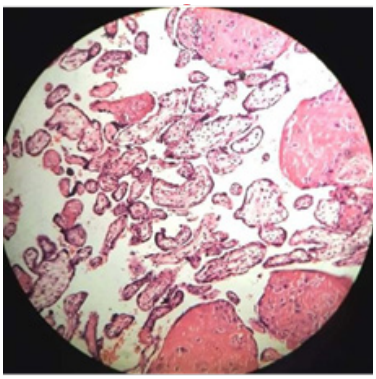

Figure 12: On the left, photograph showing a histological section of a severe case of delayed villous maturation (Case no: 53, H&E, 40X).

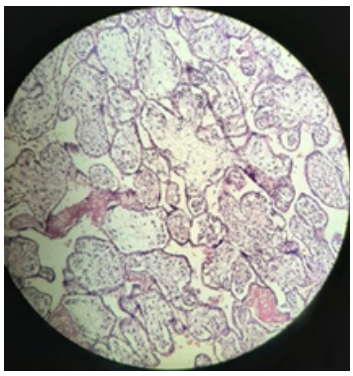

Figure 13: On the right, photograph showing a histological section of villous edema (Case no: 37, H&E, 40X).

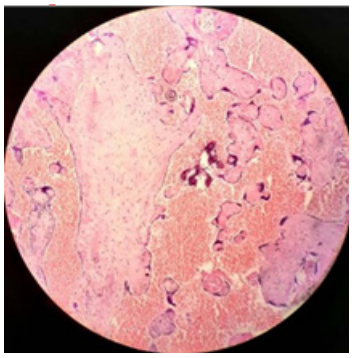

Figure 14: On the left, photograph showing a histological section of an intervillous hemorrhage and calcification (Case no: 45, H&E, 40X).

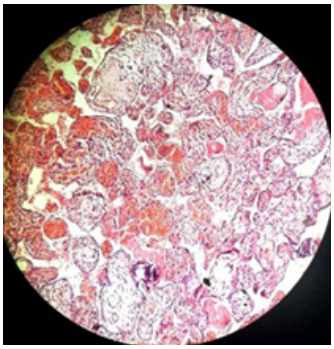

Figure 15: On the left, photograph showing a histological section of an intravillous hemorrhage and calcification (Case no: 30, H&E, 40X).

Discussion

Placental pathology in fetal death is now considered a research priority to gain insights into the causes and mechanism of fetal death, as approximately 60% of total fetal loss cannot be connected to any identifiable antepartum etiology7 and cannot be readily accessed by doctors or midwives. The aim of the current study was to categorize fetal deaths by different gross and histopathological findings to analyze the underlying mechanisms and to determine how many unexplained fetal deaths remain unexplained after examination of the placenta.

In this study, the mean age of the mothers was 25.7 ± 5.9 years, with ages ranging from 19-45 years. Among the 80 patients, the majority (57 patients, 71.3%) were in the <30 years age group. Both *Aminu, et al.,* (2014) [8] and *Lema, et al.,* (2020) [9] revealed that advanced maternal age was a factor for stillbirth, which contradicts the findings of the current study. However, *Borade, et al.,* (2018) [5] reported that IUFD was more common in mothers aged 21-25 years. This was in accordance with the studies of *Patel, et al.,* (2016) [10] and *Dave, et al.,* (2016) [11], all of which are similar to the current study.

In the present study, half of the 80 patients (40 cases, 50.0%) had multiple pregnancies, 36 (45.0%) were primi, and only 4 (5.0%) were grand multipara patients. These findings are similar to those of the study of Gunyeli (2011)7, where the mean gravidity was 2.60±1.90.

In the present study, the gestational age of the majority of the patients (49 patients, 61.3%) ranged from 37-40 weeks, 16 patients (20.0%) had a gestational age of 28--32 weeks, and 15 (18.8%) had a gestational age ranging from 33--36 weeks. However, *Borade, et al.,* (2018)5, *Prasanna, et al.,* (2015)12 and *Dave, et al.,* (2016) [11] reported an increased prevalence of IUFD in preterm fetuses. In the present study, the mean placental weight was 407 gm (mean ± SD = 407±93.8), whereas the majority of the patients (37 cases, 46.3%) had placental weights ranging from 410-450 gm, and 16 patients (20%) had placental weights ranging from 360-400 gm. Twenty-seven patients (33.8%) had placental diameters ranging from 9-12 cm, while the majority (39 patients, 48.8%) had placental diameters ranging from 13-16 cm (Table 2). *Kamarkar, et al.,* (2018) [13] reported that, the average placental weight of IUFDs was 510.1 g, and the average diameter was 15.44 cm. This interpretation supports the current study.

In the present study, central cord insertion was present in 36 (45.0%) patients, eccentric cord insertion in 33 (41.3%) patients, and marginal cord insertion in 10 (12.5%) patients. Only one patient had velamentous cord insertion. Cord coiling was normal in 57 (71.3%) patients, while 15 (18.8%) had hypocoiled, and 8 (10.0%) had hypercoiled cords. *Owino, et al.,* (2014) [14] reported that the majority (86.3%) of patients had central cord insertion. Among the 80 patients, the color of the membrane was normal in 75 (93.8%) patients, while it was greenish yellow in 3 (3.8%) patients and pale bluish in 2 (2.4%) patients (Table 3). Sixteen (20.0%) patients had retroplacental hemorrhage (Figure 1). Similarly, *Borade, et al.,* (2018) [5] reported retroplacental hematoma in 28.28% of cases.

In the present study, 28 (35%) patients presented with disorders of villous maturation, vascular ectasia with congestion was present in 21 (26.3%) patients, villitis of unknown origin was present in 20 (25.0%) patients, chronic intervillositis was present in 14 (17.5%) patients, and perivillous fibrin deposition was present in 12 (15.0%) patients. Moreover, findings such as intervillous hemorrhage 19 (23.8%), subamniotic hemorrhage 2 (2.5%), microcalcification 15 (18.8%), infarct with avascular ghost villi 14 (17.5%), villous edema 12 (15%), deciduitis 5 (6.25%), thrombus 4 (5%) and chorangiosis 2 (2.5%) are worth mentioning (Table 4). These findings correspond with other similar studies [1,4,5].

Lema, et al., (2020)9 agreed with *Ptacek, et al.,* (2014) [15], who reported fetal thrombotic vasculopathy, endovasculitis, cord abnormalities, choriomanionitis, villitis, and endovasculitis and delayed villous maturation as significant lesions in IUFDs, similar to the findings of the present study.

In the present study, a maternal and fetal inflammatory response was present in 26 patients, 12 (46.2%) patients had a stage 1 maternal inflammatory response, and 10 (38.5%) had a stage 2 maternal inflammatory response. On the other hand, 2 (7.7%) patients had stage 1 inflammatory response, and 6 (23.1%) had stage 2 fetal inflammatory response (Table 5). This aligns with the results of *Ananthan, et al.,* (2019) [4].

Conclusion

This study was undertaken to determine the gross and histopathological changes in the placentas of late intrauterine fetal deaths. In this study, various patterns of gross and histopathological changes in the placenta were clearly associated with almost all cases of late intrauterine fetal death. Currently, no such study is available in our country. With respect to this issue, this study will yield highly gainful assistance and help both histopathologists and obstetricians unriddle the facts regarding unexplained pregnancy losses.

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Author Contributions

Saba S prepared the research protocol and was responsible for data collection, arranging the data analysis and preparing the manuscript. Begum S, Ferdous J N and Billah M were responsible for conceptualizing the study and assisted in protocol development, manuscript preparation and proofreading. Ara J, Adhikary P and Hazari T J helped in grossing.

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Conflicts of Interest

None.

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