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Pathology

IMPORTANCE OF FETAL AUTOPSY AND PLACENTAL HISTOPATHOLOGY IN THE EVALUATION OF INTRAUTERINE FETAL DEMISE CASES – A 3 CASE BASED STUDY WITH REVIEW OF LITERATURE

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ABSTRACT **Background:** Intrauterine fetal demise (IUFD) remains a devastating outcome of pregnancy, with significant emotional and clinical implications. Despite advances in prenatal imaging, a substantial proportion of stillbirths remain unexplained without post-mortem evaluation. Fetal autopsy, combined with placental examination, is considered the gold standard in establishing the cause of IUFD.The perinatal mortality rate in India in 2016 was 23/1000 live births. Perinatal mortality includes both intrauterine fetal demise cases and early neonatal deaths. Earlier on, congenital anomalies were being considered to be the most common cause of perinatal mortality. Fetal autopsy plays an important role in determining the cause of death and thereby in helping in counselling the parents in future pregnancies. **Methods:** We report three cases of IUFD referred for post-mortem evaluation at a tertiary care teaching hospital in Eastern Uttar Pradesh, India. Each case underwent systematic external and internal examination, along with detailed placental histopathology. Clinical records were reviewed to correlate maternal factors with autopsy findings. Autopsies were performed according to a standard protocol and categorised using the Cunningham and Hollier classification. **Results: Case 1** Involved a 23-week fetus of a mother with hypothyroidism under treatment; autopsy revealed right renal and adrenal agenesis with hypoplastic left ventricle. **Case 2** A 33-week IUFD in an IVF pregnancy complicated by maternal hypothyroidism and preeclampsia, showed mild hydrops and placental villous fibrosis and haemorrhages intra and perivillous. **Case 3** A 21-week fetus, demonstrated multiple congenital anomalies including absent spleen, renal agenesis, and adrenal agenesis, with placental fibrosis and hemorrhage. Placental lesions were contributory in all three cases, highlighting maternal and fetal interplay in IUFD causation. **Conclusion:** Fetal autopsy, supported by placental histopathology, provides essential diagnostic clarity in IUFD, reduces unexplained stillbirths, and offers crucial guidance for counseling and planning future pregnancies.

KEYWORDS : Intrauterine Fetal Demise, Stillbirth, Fetal Autopsy, Placental Pathology.

INTRODUCTION

Perinatal mortality includes both intrauterine fetal demise cases and early neonatal deaths. Every year more than 3 million perinatal deaths occur worldwide. The perinatal mortality rate in India is 23/1000 live births. (1) Perinatal mortality rate indicates the extent of pregnancy wastage and also the quality of healthcare available to mothers and newborns. (1) Intrauterine fetal demise (IUFD) remains a devastating outcome of pregnancy, with significant emotional and clinical implications. Despite advances in prenatal imaging, a substantial proportion of stillbirths still remain unexplained without post-mortem evaluation. Fetal autopsy, combined with placental examination, is considered the gold standard in establishing the cause of IUFD. Congenital malformations account for10 -15% of perinatal mortality in India. It is also estimated that 3% of neonates have major congenital malformations and 0.7% have multiple congenital malformations in India. (1) It is seen that cases with multiple malformations have a recurrence rate of 25%. Fetal autopsy remains the gold standard for determining the cause of intrauterine and perinatal deaths. (2) Autopsy provides invaluable insights into congenital anomalies, placental disorders, and other causes of death. (2) Three cases of intrauterine deaths referred for autopsy were studied at a tertiary care teaching hospital. Detailed maternal history, antenatal investigations, and fetal autopsy findings were recorded. The cases were analyzed for clinical–pathological correlation. The cause of intrauterine demise (IUD) is essential for accurate counseling and prevention in future pregnancies. While ultrasonography and genetic testing have improved prenatal diagnosis, fetal autopsy continues to be the most comprehensive tool for identifying anomalies and pathological processes. (2) Studies have shown that autopsy findings can significantly alter or add to the clinical diagnosis, particularly in cases of congenital malformations, placental pathology, and unexplained stillbirths.(9,10)

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted in the Department of Pathology, Hind Institute of Medical Sciences. Safedabad. Barabanki. UP. India. Three cases of intrauterine fetal demise referred for medical autopsy between April and May 2025 were included. The study was granted approval by the Institutional Ethics Committee. Maternal history, antenatal records, ultrasound findings, and relevant laboratory results were reviewed. Standard autopsy techniques were employed, including external examination, anthropometric measurements, and detailed internal examination of thoracic and abdominal organs. Placenta and umbilical cord were also assessed grossly. (1) Genetic investigations were not included in this series as per study objectives. Ethical approval was obtained, and written informed consent for autopsy from parents was taken in all cases.

Study Procedure

Fetal autopsy examination was performed by a pathologist in the Pathology grossing room after obtaining a request for autopsy by the Obstetrics & Gynecology Consultant and an informed written consent from the parents, after explaining the details of the procedure. (1) The fetus was examined according to the established protocol including anthropometry followed by external and internal examination. External examination was done to rule out skin lesions, cyanosis and congenital anomalies. Internal examination included in-situ

examination of cervical, thoracic, abdominal and pelvic organs, followed by its enbloc removal. This was followed by dissecting them into organ blocks. The anatomical position, size and weight of each organ was measured and recorded. The placenta with membranes and umbilical cord were collected, examined, measured and recorded. All the organs after recognition were stored in 10% buffered formalin. Brain was collected separately in a small bucket in 10% buffered formalin.

Histopathology

Histological sections were obtained from tongue, thymus, thyroid, heart, lungs, liver, spleen, pancreas, stomach, small and large intestines, bilateral kidneys and bilateral adrenals, bladder and umbilical cord, placenta and placental membranes. The formalin fixed paraffin embedded sections were stained by Hematoxylin and Eosin (H&E) stain and reported upon by a senior pathologist. Gross and microscopic autopsy findings were correlated with ultrasound findings and other clinical findings. (1)

Thus, the cases were further categorized into Fetal, Placental and Maternal categories by following the Cunningham and Holler Classification (2,14) as follows:

Fetal: Non- Chromosomal congenital anomalies, non-immune hydrops, infections.

Placental: Placental insufficiency, Chorioamnionitis.

Maternal: Hypothyroidism, Hypertensive disorder, Sepsis.

RESULTS

Case 1

A 30-year-old female(G2P1) with hypothyroidism presented at 23 weeks of gestation with absent fetal movements. Ultrasound revealed intrauterine demise. Autopsy confirmed intrauterine death with features consistent with intrauterine growth restriction. No gross congenital malformations were identified on external examination.

Case 2

A 35-year-old primigravida with a history of hypothyroidism and Rh-negative blood group, conceived through IVF with donor oocytes. At 29 weeks, ultrasound showed absent fetal cardiac activity. Autopsy confirmed macerated stillbirth with no gross malformations. Placenta and cord examination suggested placental insufficiency.

Case 3

A 25-year-old female, (G3P1A1L1), presented at 21 weeks with a fetus diagnosed antenatally to have meningomyelocele and limb deformities. Autopsy revealed a well-developed female fetus with gross abdominal distension and no external neural tube defect. Massive intra-abdominal fluid collection caused pulmonary hypoplasia. Above findings could not be confirmed on antenatal diagnosis. Internal examination showed absent adrenals, absent left kidney and left ureter and malformed urinary bladder with asicitis.

Table 1: Maternal Characteristics

Case	Age	Gestational Age	Gravida/Para	Relevant History
Case 1	30	23 weeks	G2P1	Hypothyroidism under treatment.
Case 2	35	33 weeks	Primigravida (IVF)	Hypothyroidism, non-severe preeclampsia
Case 3	25	21 weeks	G3P1A1	No antenatal care, febrile illness in 1st trimester

Table 2: Fetal Autopsy Findings

Case	Weight	External Findings	Internal Findings
Case 1	242 g	No gross anomalies	Right renal & adrenal agenesis, hypoplastic left ventricle
Case 2	1.2 kg	Mild hydrops (non-immune)	No major malformations, thoraco-abdominal fluid collection.
Case 3	1240 g	Distended abdomen	Absent spleen, unilateral renal agenesis, Absent adrenals, bladder malformation.

Table 3: Placental Pathology

Case	Placental Findings
Case 1	Hemorrhages, fibrin deposition and necrotic foci in chorionic villi.
Case 2	Villous fibrosis, hemorrhage - (Intra & Perivillous) and fibrin deposition.
Case 3	Fibrosis, fibrin deposition, focal hemorrhages and Chorioamnionitis.

Pictures of Article on Important of Fetal Autopsy and Placental Histopathology in the Evaluation of Intrauterine Fetal Demise Cases-A3 Case Based Study with Review of Literature

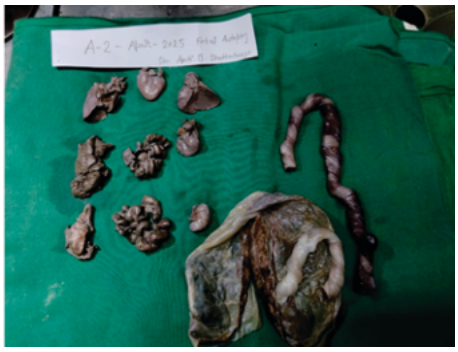

Figure 1- Autopsy Case 2 Gross Dissected Organs

Figure 2- Autopsy Case 3 External View of Fetus with Distended Abdomen and with Placenta.

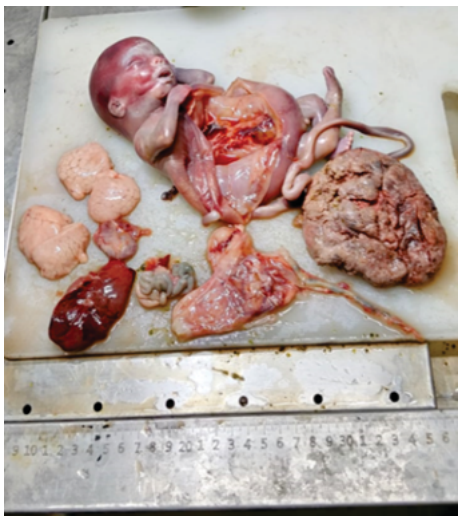

Figure 3 - Autopsy Case 3 Fetus with Dissected Organs Showing Absent Adrenals, Absent Left Kidney and Left Ureter and Showing Abnormal Urinary Bladder with Attached Right Ureter. Distended Abdomen Contained Ascitic Fluid.

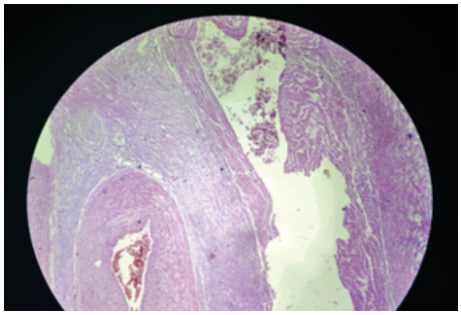

Figure 4 – Microscopic Picture of Umbilical Cord Showing One Umbilical Artery and Vein (case 1).

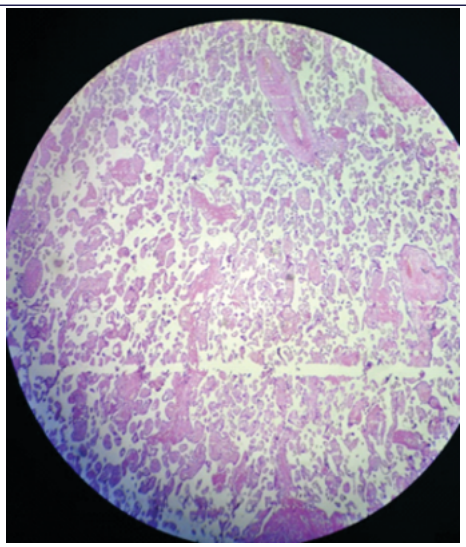

Figure 5 – Placenta Microscopic Picture Showing Fibrin Deposits in and Around Villi (Case 1)

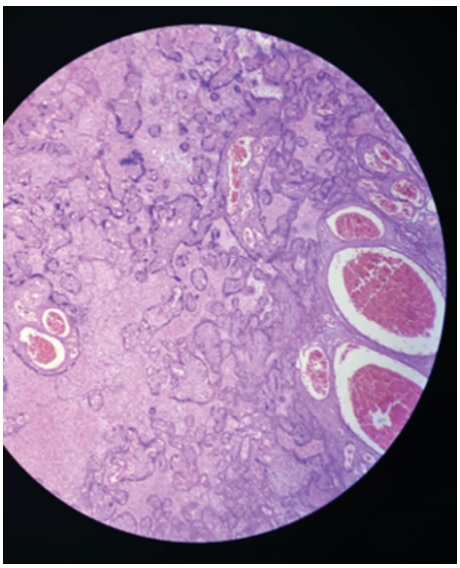

Figure 6 – Placenta: Microscopic Picture Showing Intravillous and Intervillous Haemorrhages and Fibrin Deposition (Case 2.)

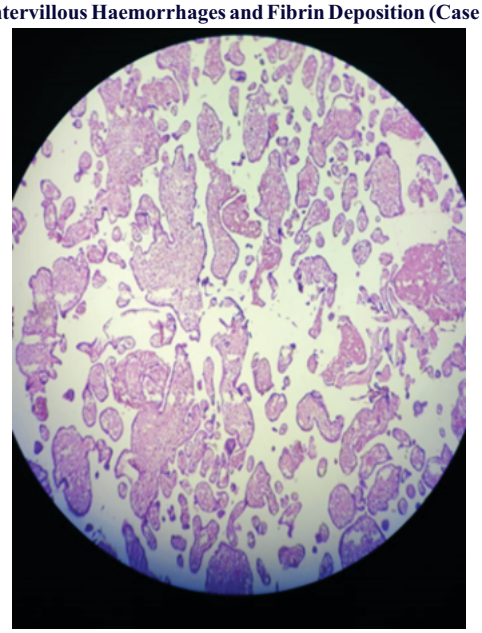

Figure 7 – Placenta Microscopic Picture Showing Fibrin Deposition, Fibrosis and Reduced Number of Villi (Case 3.)

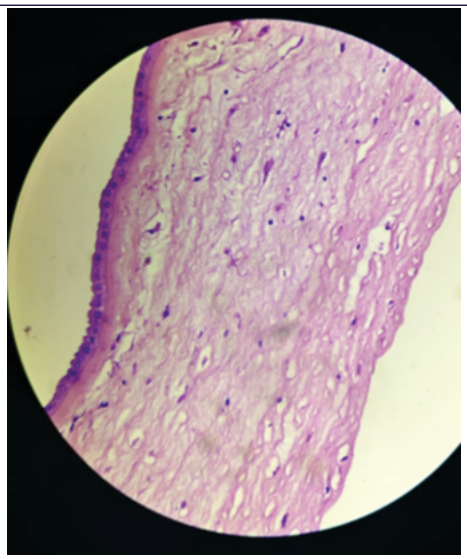

Figure 8 – Placental Membrane Microscopic Picture Showing Evidence of Chorioamnionitis (Case 3)

DISCUSSION

The three cases demonstrate the multifactorial etiology of IUFD. Maternal hypothyroidism played a central role in two cases, contributing to placental insufficiency and subsequent fetal hypoxia. In the third case, multiple congenital malformations were the primary cause of IUFD. (2)

Placental pathology was contributory in all three cases, consistent with global evidence that placental lesions are the leading identifiable cause of stillbirth. Autopsy findings provided additional diagnostic yield, identifying anomalies missed antenatally and correlating with maternal conditions.

The combined approach of fetal autopsy and placental histology thus reduced the number of unexplained IUFD cases and guided clinicians in counseling families about recurrence risks and preventive measures for future pregnancies. Fetal autopsy plays a vital role in establishing the cause of intrauterine deaths. In the present series, each case highlighted different contributory factors: maternal hypothyroidism, Maternal hypothyroidism with IVF conception, and major congenital anomalies (6,7). Autopsy provided confirmation of clinical suspicions and added details about fetal morphology and organ involvement. (2) Earlier studies have shown that placental lesions, cord abnormalities, and fetal malformations account for a large proportion of stillbirths.(6,7) Our observations align with these findings and demonstrate the utility of systematic autopsy in perinatal pathology. Importantly, the exclusion of genetic analysis in this series emphasizes the independent value of autopsy in identifying structural causes of death.

Placental examination enables a surgical pathologist to diagnose diseases of the mother, fetus and the new born. Conditions like chorioamnionitis, condition of subclinical reduced uterine blood flow, subclinical gestational diabetes mellitus and potential recurrent reproductive failure can be detected. (2) Thus, placenta serves as a diary of gestational life for both the mother and fetus.

Placenta is a readily accessible specimen, which can provide a record of cumulative effects of pregnancy-related events and changes within the intrauterine environment. IUFD is multifactorial and as pregnancy progresses, the causes of IUFD are increasingly likely to be extrinsic to the fetus. Placental lesions are important contributors to antepartum IUFD across all gestational ages. There is increasing evidence to show that placental pathology may be the cause of IUFD in pregnancies at or above period of gestation (POG) of 24 week(14) Further, it remains viable for several days after IUFD and can provide information regarding other underlying pathology leading to fetal demise. The placental specimen is collected immediately after delivery and is transported to the histopathology laboratory in 10% buffered formalin. Placental weight and size of the disc, cords and membranes are recorded. Inspection of fetal surface is done for colour, consistency and translucency of the membranes. Vessels are inspected for the presence

of thrombi or calcification. Presence of subchorionic fibrin plaques and deposits are noted for. The umbilical cord is examined for the presence of vessels and its point of insertion into the disc. The maternal surface is examined for any significant areas of disrupted cotyledons, fibrosis, infarct or retroplacental hematoma. Serial sectioning of the placental disc from the maternal surface through to the fetal surface looking for infarcts, hemangiomas or other lesions is done.

Histopathological evaluation is performed by pathologist on routine hematoxylin and eosin-stained sections using standard definitions established by the Amsterdam Placental Workshop Group.

The lesions are further classified as maternal vascular malperfusion (MVM) or fetal vascular malperfusion (FVM), inflammatory lesions or idiopathic lesions. The term MVM is used when retroplacental hematoma, decidual vasculopathy, delayed villous maturation and intraparenchymal hematoma are noted. Fetal vascular malperfusion is used in the presence of avascular villi, villous stromal vascular karyorrhexis, occlusive and nonocclusive thrombi in fetal vessels and chorangiomas (fetal vascular lesion). Inflammatory lesions are characterized by the presence of chorioamnionitis (maternal inflammatory response, MIR), fetal inflammatory response (FIR), villitis, intervillositis, and deciduitis. Idiopathic conditions are those in which no other abnormalities can be recognized. Gross findings are confirmed microscopically and all observations are recorded. (9,10,11)

IUFD occurs as a result of a complex process involving the mother, the fetus as well as the placenta. Hence, a comprehensive analysis of all these factors is necessary to determine the cause of fetal demise. Increased risk of IUFD is seen in advanced maternal age, presence of chronic maternal illness, poor socioeconomic status and multiple gestations. (9)

Following IUFD, regardless of etiology, the placenta undergoes certain post-mortem changes due to cessation of fetal blood flow, alteration of maternal perfusion, maternal inflammatory response to non-viable products and labor changes associated with separation of placenta. Cessation of blood flow leads to endothelial karyorrhexis, loss of luminal integrity, and extravasation of erythrocyte fragments onto the villous stroma, which over time ultimately results in avascular villi. Muscular fetal vessels in stem villi and the chorionic plate also undergo obliteration. Initially, following IUFD, maternal perfusion persists but over time, it diminishes and results in ischemic changes including villous fibrosis with diminished cellularity, and replacement of the maternal intervillous space by fibrin. (9) In cases of IUFD prior to the initiation of labour, there may be changes secondary to placental separation during the third stage of labor such as presence of adherent retroplacental blood and recent placental infarction noted microscopically. (14) Grossly, the cases IUGR show focal calcification and multiple grey white areas of infarction Microscopically, presence of distal villous hypoplasia is noted. Also noted are features of infarction and increased vascularity indicating presence of prolonged fetal hypoxia. (10,11)

Predominance of placental inflammatory lesions points towards presence of modifiable causes that can be addressed directly. An evaluation of placental features can not only identify the cause of IUFD but also, possibly help prevent recurrence in following pregnancies by allowing timely initiation of screening and management. The identification of a probable cause and patient education regarding the same may also motivate the patient to seek early and proper antenatal care in subsequent pregnancies. (11,12,13)

Summary

Importance of Fetal Autopsy and Placental examination in Intrauterine Fetal Demise Cases. Intrauterine fetal demise (IUFD) is a devastating pregnancy outcome with significant emotional and clinical impact. Fetal autopsy, combined with placental histopathology, is the gold standard in identifying causes of IUFD. This study presents 3 cases from a tertiary care teaching hospital in Eastern Uttar Pradesh, India.

Placental Pathology

Present in all 3 cases. Common lesions being villous fibrosis, hemorrhage, fibrin deposition, necrosis.

Key Messages

1. Maternal hypothyroidism contributed significantly to IUFD in two cases.
2. Multiple congenital anomalies were the primary cause in one case.
3. Placental lesions were contributory in all cases.
4. Autopsy findings reduced diagnostic uncertainty and guided parent counselling and management of future pregnancies.

CONCLUSION

1. Fetal autopsy with placental histopathology remains indispensable in IUFD evaluation. By revealing structural anomalies, placental pathology, and maternal influences, autopsy helps provide clarity in cases that would otherwise remain unexplained. Greater awareness and acceptance of fetal autopsy are essential to improve outcomes and parental counseling in tertiary care settings. Fetal autopsy remains an indispensable tool in perinatal pathology. It not only provides answers regarding the cause of intrauterine death but also assists in parental counseling and management of future pregnancies. Routine incorporation of autopsy into clinical practice is strongly recommended, especially in cases of unexplained stillbirth.
2. Fetal autopsy, with placental histopathology, is indispensable for IUFD evaluation.
3. Provides diagnostic clarity, reduces unexplained stillbirths, and aids in future pregnancy planning.
4. Greater awareness and acceptance of fetal autopsy is needed in tertiary care practice.

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