



Role of fetal autopsy and its importance in intrauterine fetal death: Histopathological diagnosis

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Abstract

Background & Aims: Intrauterine fetal death (IUFD)/stillbirth accounts for a significant portion of perinatal mortality and is thus a good indicator of healthcare system quality. Autopsy is a well-known specialized surgical procedure used to determine the cause of death. The study's goal is to learn the cause of death, the prevalence of congenital anomalies, and to confirm the diagnosis histopathologically.

Materials & Methods: The study included 32 cases of all terminated pregnancies from 12 to 38 weeks due to abnormal prenatal findings and IUFDs received for autopsy in the department of pathology over a four-year period from 2018 to 2022. Autopsies were carried out in accordance with standard protocol, and included external and internal examinations with photography, as well as gross and microscopic examinations of various organs and the placenta.

Results: Over a four-year period, Abnormalities detected via autopsy are 32 (80%) out of 40 cases, whereas ultrasound findings detected about 11(27.5%) out of 40 cases. Thus, autopsy added to the diagnosis about 47.5%. External anomalies noted in 9 cases and internal anomalies noted in 14 cases. Gestational age of fetuses in intrauterine deaths in our study is early deaths (55%). The most common cause of death was fetal causes (37.5%), followed by placental causes (35%) and two amniotic fluid causes (5%). In congenital causes central nervous system anomalies [(6 cases) which include Arnold Chiari malformation (2 cases), Potter syndrome (1 case), hydrocephalus (3 cases)] were the most common followed by cardiovascular system malformations [(4 cases) which include VSD (2 cases), dextrocardia (1 case), hypoplastic left heart syndrome (1)]. Placental lesions were present in 14 (27.5%) of the cases.

Conclusion: The most common cause of death was congenital anomalies. Though the number of perinatal autopsies has decreased in recent years, fetal autopsies continue to play an important role in determining the cause of disease. It is considered the gold standard for diagnosis, giving parents hope for the future.

Keywords: Fetal Autopsy, Intrauterine Fetal Death, Stillbirth

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Introduction

Intrauterine fetal death (IUFD)/stillbirth accounts for a significant portion of perinatal mortality (1). An autopsy is a common specialized surgical procedure used to determine the cause of death (2). The study's goal is to determine the cause of death, the prevalence of congenital anomalies, and histopathologically confirm the diagnosis. IUFD is classified as early (occurring before 22 weeks of pregnancy), intermediate (occurring between 22 and 27 weeks of pregnancy), and late (occurring after 28 weeks of pregnancy). Early IUFDs are considered abortions, while intermediate and late IUFDs are referred to as stillbirths (3). The post-mortem examination aids in treatment planning and raises awareness for future pregnancies (4). Congenital anomalies are leading causes of neonatal mortality and morbidity (5). Developing countries such as India contribute a significant portion (28%) of the global burden of neonatal mortality due to congenital birth defects (6). Hence, this issue should be addressed by the country's bureaucrats in order to reduce neonatal mortality (7). The primary aim of post-mortem investigation of intrauterine death is determination of cause and mechanism of death, to facilitate counselling of parents, management of subsequent pregnancies and future interventions.

Materials & Methods

The study (diagnostic evaluation study) included 40 cases of all terminated pregnancies from 12 to 38 weeks due to abnormal prenatal findings and IUFDs received for autopsy in the Department of Pathology, SVS Medical College and Hospital, Mahbubnagar, from September 2018 to September 2022.

Inclusion criteria: Fetal autopsies that reach the institution to evaluate the cause. Only cases with complete obstetric history records were included.

Exclusion criteria: New-born autopsies.

The study included the placenta as well as the fetus.

Study protocol included detailed history regarding:

- Maternal
- Fetal
- Placental

- Investigations.

Fetal

- 1) Anthropometric measurements
- 2) Detailed photography
 - Serve as a record for litigation purposes
 - Help ascertain diagnosis of a malformation syndrome
 - Depict and preserve anatomic relationships of visceral lesions which otherwise are destroyed after dissection and evisceration.
 - Assist in identifying tissues submitted for microscopic examination.
- 3) Any meconium stain, congenital anomalies should be noted.

Placental:

- 1) Received or not
- 2) If received, short/ long cord, hemorrhagic, necrosed, infarction, etc.

Maternal:

- 1) Age of the mother
- 2) Gravidity
- 3) Previous history of abortions, still births, termination of pregnancy, neonatal death and mode of delivery
- 4) Obstetric history: Any prior pregnancies, if present live children and fetal demise, hospitalization charts, and complications of delivery should be recorded.
- 5) Medical history
- 6) Consanguinity
- 7) Sexual partners, etc.

Investigations:

- 1) Ultrasonography
- 2) TIFFA scan

Autopsies were performed in accordance with standard protocol, which included external and internal examination with photography, gross and microscopic evaluation of various organs, and examination of the placenta. After taking written consent from the parents, the autopsy was performed according to a predesigned protocol, which included the mother's name, any relevant history, mode of delivery, fetal sex, anthropometry, as well as external and internal

examination of the head and neck, brain, spinal cord, placenta, and umbilical cord. The sections were processed routinely and stained with hematoxylin and eosin (H & E Staining).

Microscopic Examination:

With the exception of malformations, the macroscopic appearance of fetal organs does not give specific information. Apart from identifying a cause or mechanism of death, microscopic examination can also help in assessment of gestational age.

The cases were categorized according to the classification proposed by Cunningham and Hollier as follows:

FETAL (25-40%)

Chromosomal anomalies, non-chromosomal birth defects, nonimmune hydrops, infections-viruses/bacteria/protozoa.

PLACENTAL (25-35%)

Abruption, fetal maternal hemorrhage, cord accident, Placental insufficiency, Intrapartum asphyxia, Previa, twin to twin transfusion, and Chorioamnionitis.

MATERNAL (5-10%)

Diabetes, Hypertensive disorders, Trauma, Abnormal labor, Sepsis, Acidosis, Hypoxia, Uterine rupture, Post-term pregnancy, Drugs, Antiphospholipid antibodies, and Unexplained.

All categorical data was recorded in Microsoft Excel sheets and analyses were performed by

frequency/percentages.

Results

Over a four-year period, 32 cases of fetal autopsies were included in the study. The mean maternal age group is 24.6 years. Male fetuses are the most commonly affected, accounting for 30 cases (75%) of the total, with female fetuses accounting for 10 cases (25%).

In our study, external anomalies noted in 9 cases and internal anomalies noted in 14 cases. External malformations mainly involved were limb malformations, open spina bifida, hydrocephalus with frontal bossing, potter facies. Of the 14 cases with internal anomalies, CNS and CVS defects were the most common. Most of the cases were intrauterine fetal deaths i.e., 38 cases (95%), and the remaining were medically terminated pregnancies due to abnormal targeted imaging for Fetal Anomalies (TIFFA) scan, which included 2 cases (6.3%).

Most of the fetal deaths were early fetal deaths (less than 22 weeks of gestational age) in 22 cases (55%), followed by late fetal deaths (more than 27 weeks gestational age) in 10 cases (25%), and intermediate fetal deaths (in between 22 to 27 weeks of gestational age) in 8 cases (20%). Currently, the legal limit of viability was considered to be around 24 weeks (35).

In our study, 12 cases had attained viability.

The mothers were of primi to gravida 4, of all these cases primi mothers are 20 cases.

Table 1. Percentage of mothers against their gravidity

Pregnancy status	Number	Percentage
First pregnancy (Primi) (G1)	20	50%
Second pregnancy (G2)	13	32.5%
Third pregnancy (G3)	3	7.5%
Fourth pregnancy (G4)	4	10%
Total	40	100%

The comorbid conditions associated with the mother include maternal hypothyroidism (3 cases) and one case

of Rh-negative pregnancies. In 3 cases, there was a history of consanguinity.

History of spontaneous abortion was present in 19 cases. Recurrent history of abortions (three successive pregnancy losses) in one case.

Placenta not received in 7 cases. Breech presentation in one case. Mothers with live children were 9 cases.

Umbilical cord with normal vessels in all cases except in one case i.e., single umbilical artery (one artery and one vein). Cord entanglement was in 2 cases.

Specimen received is well preserved in 17 cases, whereas macerated and autolysed in 22 cases, and fresh and unfixed in one case.

Past history of molar pregnancy was in one case, and severe oligohydramnios in another case. The delivery mode of first delivery in most of the cases are vaginal delivery, whereas elective caesarean delivery was in one case. Autopsy provided a final diagnosis in 32 out of 40 cases (80%).

Table 2. Causes of stillbirth

Categories	Number of cases	Percentage
Fetal	15	37%
Placental	14	35%
Maternal	1	3%
Amniotic fluid	2	5%
Unclassified	8	20%
Total	40	100%

Table 3. Abnormal cases detected in the study

Categories	Causes	Number of cases	Percentage
Fetal (15)	Congenital anomalies	14	43.75%
	Infections	1	3.1%
Placental (14)	Placental insufficiency	11	34.4%
	Umbilical cord	3	9.4%
Amniotic fluid (2)	Amniotic fluid	2	6.25%
Maternal (1)	Hydrops fetalis	1	3.1%
Total	-	32	100%

Abnormalities detected via autopsy are 32 (80%) out of 40 cases, whereas ultrasound findings detected about 11 (27.5%) out of 40 cases. Thus, autopsy added to the diagnosis about 47.5%. Placental histopathology was done in 33 (82.5%) of the cases. Placental lesions were present in 14 (27.5%) of the cases. Placental infarction was seen in one case. Placental necrosis and

calcification found in four cases. In two cases, placental examination showed chorioamnionitis.

Some of the interesting cases in the present study include Arnold-Chiari syndrome, Potter syndrome, diaphragmatic hernia, dextrocardia, hypoplastic left heart syndrome, ventricular septal defect, single umbilical artery, chorangioma of placenta, and CMV (Figures 1, 2 and 3).



Fig. 1. a. Arnold-Chiari syndrome, Lemon sign. b. Arnold-Chiari syndrome, Ultrasonography showing lemon sign. c. Arnold-Chiari syndrome, Meningomyelocele. d. Potter syndrome, Potter facies. e. Potter syndrome, talipes equinovarus. f. Potter syndrome, imperforate anus. g. Potter syndrome, liver hemangioma.

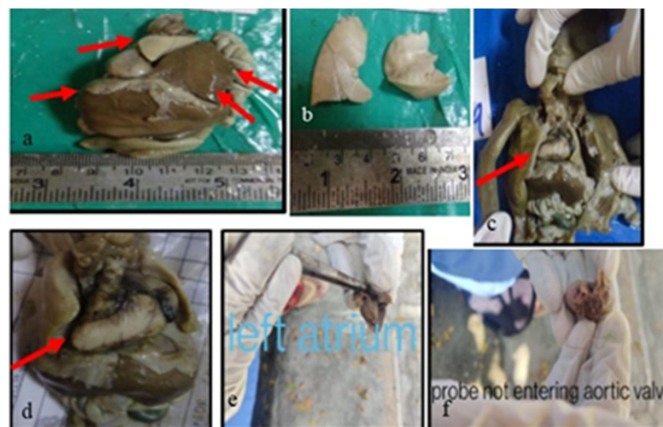


Fig. 2. a. Diaphragmatic hernia, arrows pointing towards diaphragm, intestines, Liver and Lung. b. Hypoplastic Lung. c and d. Dextrocardia, Apex of the heart pointing towards Right. e and f. Hypoplastic left heart syndrome.

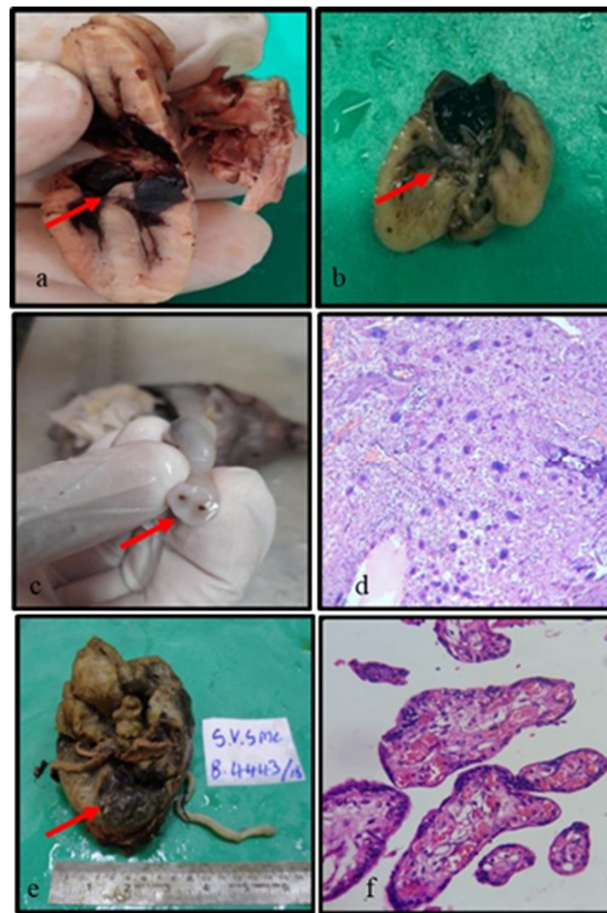


Fig. 3. a & b. Ventricular septal defect. **c.** Single umbilical artery (showing one Artery and one Vein). **d.** CMV (showing large giant cells in placenta). **e.** Gross image of placenta showing the lesion. **f.** Capillaries proliferation

Discussion

Perinatal autopsy remains the gold standard (8) technique for determining the cause of death in IUFD and confirming the anomalies detected on ultrasound (USG). In this study, 27.5% of all the USG findings correlated with autopsy.

In the present study, total fetal autopsies were 40, which in 32 (80%) out of them, abnormality was detected.

Our study highlights the importance of fetal autopsy in cases of stillbirths and IUFDs. We identified that fetal causes and placental causes are associated with major causes of fetal death.

Both most prevalent and most common cause of death in our study are fetal causes (37.5%), later followed by placental causes in 14 cases (35%), and two amniotic fluid causes (5%). In fetal causes, congenital causes are in 14 cases and infectious in one case. In placental causes, placental insufficiency seen in 11 cases, followed by cord anomalies in 3 cases. Maternal causes include one case. Amniotic fluid causes include 2 cases. Unclassified which include no abnormalities detected during the autopsy include 8 cases. Although several conditions have been linked to stillbirth and specific associated risk factors are widely known in many cases, it is difficult to define the precise etiology

and a significant number of stillbirths are still unexplained (9-12).

In congenital causes, central nervous system (CNS) anomalies [(6 cases) which include Arnold Chiari malformation (2 cases), Potter syndrome (1 case), hydrocephalus (3 cases)] were the most common, followed by cardiovascular system (CVS) malformations [(4 cases) which include VSD (2 cases), dextrocardia (1 case), hypoplastic left heart syndrome (1)]. The frequently encountered CNS syndromic anomaly in our study was Arnold–Chiari II malformation with myelomeningocele (2 cases), and one case of potter syndrome. Others include congenital diaphragmatic hernia, single umbilical artery, chorangioma of placenta, multiple congenital defects, etc. In cases of fetal malformation, only a complete autopsy will detect all abnormalities, which may be crucial in providing appropriate counseling to the family for a subsequent pregnancy (13, 14).

In this study, 34% of all USG findings correlated with autopsy. Faye Petersen et al. (15) reported that fetal autopsies performed by an experienced pathologist in collaboration with clinical specialists could identify the cause of death of the fetus in 94% of cases. In this study, autopsies were used to diagnose approximately 80% of the cases.

Pasztor et al. (16) provided exact cause of death in 57.9% cases in their study on identification of causes of still birth through autopsy and placental examination reports. Davies and Arroyo (17) were able to ascertain the cause of perinatal death by autopsy alone in 47.6%.

Fatima Uroos et al. (19) presented data on their analyses of 14 cases of stillbirths. In their study, mean maternal age group is 24.4 years which was almost similar to our study i.e., 24.6 years. In this study affected ones are mostly male fetuses about 75%, whereas in Thakur S et al. (18) it is 54%. Autopsy showed external anomalies in 16 of 100 cases, whereas internal anomalies were noted in 8 cases in Thakur S et al.

In our study external anomalies noted in 9 cases and internal anomalies noted in 14 cases. External malformations mainly involved are limb malformations, open spina bifida, hydrocephalus with frontal bossing,

potter facies. Of the 14 cases with internal anomalies CNS and CVS defects are most common.

Gestational age of fetuses in intrauterine deaths in our study is early deaths (55%) Thakur S et al. (18) was early deaths (37%), whereas in Fatima Uroos et al. (19) was late deaths (64.3%). The most prevalent cause of death was congenital anomalies (4 cases, 28.6%) followed by placental insufficiency (3 cases, 21.4%) and then chorioamnionitis (2 cases, 14.3%).

Placental causes were implicated in highest number of cases (43.6%) in Fatima Uroos et al., whereas in our study, the most prevalent and most common cause of death was fetal causes (37.5%). Most common cause of death in this study was fetal causes (37.5%), whereas in Thakur S et al. (18) and Fatima Uroos et al. (19), was placental causes with 68.6% and 43.6%, respectively.

In our study, fetal causes included congenital anomalies and infections. Congenital malformations remain a common cause of perinatal death and account for 25-30% in developing countries like India (20); whereas in this study 93.3% were found with congenital anomalies. Arnold-Chiari malformation is characterized by downward displacement of cerebellum and brainstem into the spinal cord and is divided into three types in that, type II is the most common form. This was true even in this study. The histological hallmark of CMV infection is a chronic lymphoplasmacytic infiltrate (21) and this is one of the major causes of chronic villitis. The fetal and neonatal disease in this case has many manifestations including stillbirth which was evident in one of our cases in which the mother came out to be serologically positive for CMV, though viral inclusions could not be demonstrated in the placenta or fetus.

Birth defects are currently the leading cause of infant mortality accounting for 20% of all infant deaths (22). Placenta, membranes, and cord abnormalities known to cause fetal deaths constitute about 25-35% of the causes of fetal deaths (23). Shepard et al. (24) undertook 20 years analysis of aborted specimen and found that 19% of the fetuses had a localized defect.

It is well noted in literature that a considerable percentage of stillbirths is associated with placental pathologies, and that, placental investigations assist in

determining the cause of stillbirth (24-27). Placenta examination, performed by expert pathologists, can detect significant lesions and allows to clarify the pathophysiology of many adverse outcomes. It also may assist to determine the cause of death (27). In the study of Reggiani Bonetti et al. (28), placental anomalies were observed in 21% of the cases, whereas in this study, about 35% fetal deaths are due to placental abnormalities.

Placental histopathology was done in 83% of the cases. Placental lesions were present in 68.6% of the cases. Placental infarction was seen in 14 cases. Placental hemorrhage was found in 14 cases. In Thakur S et al. study, placental examination showed chorioamnionitis in 12 cases. However, in our study, placental histopathology was done in 33 (82.5%) of the cases, and lesions were present in 14 (27.5%) of the cases. Placental infarction was seen in one case. Placental necrosis and calcification found in four cases. In two cases, placental examination showed chorioamnionitis.

Maternal causes include hypothyroidism, pre-eclampsia, diabetes mellitus, Rh negative mothers, etc. In this study, two cases were found with hypothyroidism and one with Rh negativity. Though few cases are not fatal and only have a small contribution to fetal deaths, maternal factors may be underestimated because pathologies with a strong maternal component often are attributed to fetal or placental causes. Hypertensive disorders and diabetes are the two most commonly cited maternal diseases, associated with 5-8% of stillbirths (28). Causes like trauma, infection, cord accident are preventable causes, which if taken care of, would lead to a favorable outcome in future pregnancies. Even congenital abnormalities due to exposure to a known teratogen or poor glycemic control are preventable. Though a higher degree of recurrence is associated with maternal medical disorders like hypertension, appropriate clinical intervention either preconceptionally or early pregnancy may improve the outcome in subsequent pregnancies. In our study, one case of hydrops fetalis is noted; hydrops indicates the

presence of heart failure, anemia, hypoproteinemia, or a combination (29).

Our study's data showed a higher percentage of associated pathology, which can be explained by systematic analyses of cases in a dedicated unit.

Pekkola et al. (30) did a standardized post-mortem examination and a re-evaluation of the results of 214 antepartum singleton stillbirths (from 2003 to 2015). They reported that the cause truly remained unexplained in only 10.7% of the cases.

Uroos Fatima et al (31) studied 14 cases of IUD. Placental causes were in (48.57%), followed by fetal (35.72%) and maternal (21.42). The common prevalent cause of death was congenital anomalies in (28.6%), followed by placental insufficiency in (21.4%) and chorioamnionitis in (14.2%) .

Shanmuga Priya S et al studied of 168 fetuses for 3 years, in which 42 terminated after detecting an anomaly in ultrasonogram and 126 were spontaneous fetal losses. All fetuses with malformations confirmed by ultrasound were compared with autopsy findings. Fetal autopsy provides a definite final diagnosis in 100% of cases. Fetal autopsy correlated with the ultrasound findings (32).

Venkataswamy C et al (33) studied a total of 66 fetuses, which includes 17 IUD, 49 terminations due to congenital malformations, and increased risk for chromosomal abnormality. The most common anomalies were central nervous system (neural tube defect) followed by the genitourinary system. Autopsy confirmed prenatal ultrasound in all cases except three. Complete agreement between USG findings and autopsy were seen in 17 cases (39.7%).

However, in our study autopsy has revealed the cause of death in 32 (80%) out of 40 cases, even though with complete scrutiny, the cause of death is unexplained in 8 cases (20%).

In some cultures, post-mortem examination is refused due to cultural or religious reasons and some are refused due to monetary reasons (31).

Conclusion

Though the number of perinatal autopsies has

decreased in recent years, fetal autopsies continue to play an important role in determining the cause of disease and are considered the gold standard for diagnosis and providing hope to parents in cases of congenital anomalies with a low risk of recurrence. Counseling about the utility of fetal autopsies and genetic testing is critical for increasing autopsy consent rates. Hence, the combination of autopsy and genetic studies provides future hope for expecting parents.

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Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Conflict of interest

The authors have no conflict of interest in this study.

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