



# Fetal Autopsy—A Game Changer!

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## Abstract

Fetal autopsy is one of the most useful investigations that can change or significantly add to the clinical diagnosis despite a prenatal ultrasonographic diagnosis of a fetal abnormality. It is often required to determine the cause of intrauterine death or miscarriages, provide recurrence risk, and is known to alter the final diagnosis and genetic counseling in nearly half of the cases. This article reviews the role of fetal autopsy and discusses its contributory role in confirming the diagnosis and its usefulness in the genetic counseling of cases with risk of recurrence in future pregnancies.

## Keywords

- ▶ fetal autopsy
- ▶ perinatal pathology
- ▶ perinatal autopsy
- ▶ prenatal ultrasound
- ▶ fetal anomalies

## Introduction

The word autopsy in Greek means “seeing with one’s own eyes.” Any autopsy performed on the fetus or neonate is considered to be a “perinatal autopsy” as the perinatal period is generally the period between 28 weeks’ gestation to 1 week of life.<sup>1</sup> Thus, perinatal autopsy or fetal autopsy involves the postmortem examination of a baby following spontaneous or missed miscarriage, intrauterine death, or following termination of a pregnancy. Perinatal autopsy may provide partial-to-complete explanation of the cause for pregnancy loss, can provide a specific diagnosis, or may impart information that may change or add significantly to the clinical diagnosis in nearly half of the cases.<sup>2</sup> Fetal autopsy is the backbone for fetal phenotyping in the molecular era and contributes to the limited data on fetal phenotypes of various genetic disorders. Reverse phenotyping requires detailing of fetal characteristics including dysmorphism that may not be apparent on ultrasound. Thus, fetal autopsy plays an essential role in better understanding of phenotypic–genotypic relationships and complements the field of molecular autopsy in the diagnosis of genetic diseases.<sup>3</sup> Additionally, an autopsy can help in determining the recurrence risk, which is imperative for

counseling regarding the management of future pregnancies. It is, thus, a valuable audit of clinical care and can assist in learning from an adverse event occurring during pregnancy.<sup>2</sup>

## Discussion

### Role of Fetal Autopsy

Fetal autopsy can serve as an ultimate diagnostic tool for the clinician to establish the immediate cause of miscarriage or an intrauterine death or the factors that may have contributed to the same. It facilitates identifying the evidence of diseases, particularly those that may have implications for subsequent pregnancies (e.g., fetal growth restriction, fetal malformations, maternal diabetes, genetic disease).<sup>2</sup> It can help in providing the recurrence risk of a disease and thus enlighten the clinician in the direct management of future pregnancies.<sup>4</sup> It can contribute to the postnatal outcomes for the local or national congenital anomaly registers and can provide the pathology input for clinical review meetings. It also immensely contributes towards auditing (e.g., in antenatal diagnosis, pregnancy, and intrapartum care).<sup>2</sup>

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## Prerequisite to Sending a Specimen for Fetal Autopsy

- Consent form—The fetal tissue is considered in law to be maternal tissue and hence a fetal autopsy should be performed only after obtaining consent from the mother or both the parents.<sup>2</sup>
- Infection screen—The details of maternal antenatal infection screening results should be provided to the pathologist prior to the procedure. All autopsy practices when done using universal precautions are significantly protective against accidental viral transmission in high maternal human immunodeficiency virus prevalent regions.<sup>2</sup>
- Request form—The autopsy specimen should be accompanied by a structured clinical information containing the patient identification details (maternal age, height, weight, and body mass index). The relevant medical history, family history (including consanguinity), and obstetric history (including previous pregnancies/deliveries, previous fetal and neonatal losses, malformations and growth restriction, and any other complications) should be mentioned in the form. The present pregnancy history (including estimated date of delivery, maternal infection screen, copies of antenatal ultrasound report and other relevant antenatal investigations, and detailed history regarding events (hypertension/hemorrhage/pyrexia/rupture of membranes) leading up to delivery or miscarriage, live birth or stillbirth, and any significant neonatal history should be mentioned in the request form.<sup>5</sup>
- The autopsy specimen—The transportation of the fetus with the placenta and the umbilical cord to the perinatal pathology laboratory should take place as soon as the fetus is expelled or delivered out, in a medium containing 10% formalin (1 part formalin to 9 parts of water).<sup>6</sup> The American Board of Pathology does not recognize autopsy of fragmented fetuses obtained from an early trimester termination as adequate to fulfil the criteria for anatomic pathology certification.<sup>7</sup> And before embarking on autopsy, it may be prudent to store fetal samples for further molecular testing that may deem necessary in due course, well before the fetus is submersed in formalin as DNA extraction is challenging from a formalin fixed sample. Similarly, at times maintaining fibroblast cell lines for functional analysis for novel variants or novel genes is important prior to formalin fixation.

## The Components of Fetal Autopsy

This includes the details of the clinical review, taking a radiograph in all cases but recommended especially in cases of skeletal pathology, photographs, external fetal examination, removal of individual organs, removal of the brain, and sampling of tissues for histological evaluation. Fetal brain examination can be done only after fixation. Special studies are conducted as per need including tissue for genetic testing, metabolic studies, microbiology cultures, and electron microscopy. This is followed by provisional anatomic

diagnosis, recording of gross and histologic findings. A thorough review of all ancillary studies (genetic, metabolic, and microbiology) is done. A placental examination is done, and the placental pathology results are incorporated. In the end, a final autopsy report should consist of the anatomic diagnoses, summary of clinical history, gross description, microscopic description, and clinicopathologic correlation, all put together.<sup>1</sup>

- Imaging—A radiograph of the whole fetal body is a must. The abnormalities detected in radiography contributed to diagnosis in 0.9% of the cases. Ossification center is used as an index of bone maturation. Findings such as metaphysitis of the long bones can be suggestive of congenital syphilis. Presence of cerebral calcifications on radiographs may be seen in toxoplasma and cytomegalovirus infection. Imaging can also detect abdominal or vascular calcification. Radiography of the skull and limbs is essential in suspected cases of trauma and also has a major role in the diagnosis of cases of skeletal dysplasia.<sup>8</sup> Additionally, postmortem arteriography is essential in suspected vascular abnormalities. Performing a postmortem ultrasound and magnetic resonance imaging (MRI) can contribute to additional information especially in cases where the conventional autopsy is declined by the parents.<sup>9</sup> Photographs, especially digital photographs, of whole body, face and facial profile, and limbs and extremities can help in the diagnosis of specific anomalies. Printed photographs can be useful for easy comparison with reference books. Use of photographs of malformations can serve immensely in counseling the couple and also in record keeping.<sup>8</sup>
- Metabolic autopsy—In a suspected case of death secondary to a metabolic disorder, metabolic autopsy should be performed within hours of death to procure tissue for the diagnosis. Lamentably, this produces substantial stress on the family and healthcare team as it requires mobilization of significant resources and places. However, the yield of a new diagnosis of a metabolic disorder in these cases is 18% with the highest yield for patients with lactic acidosis and limited premortem workup. The use of postmortem blood and fibroblast cell lines proved similar limited success at identifying metabolic disorders. Hence, the cost-benefit ratio of a true metabolic autopsy is unclear. Additionally, the postmortem blood spots can be stored for extended neonatal screening.<sup>9-11</sup>
- Genetic analysis—The American College of Obstetricians and Gynecologists recommends use of perinatal autopsy, placental examination, and microarray for cytogenetic analysis in the workup of all stillbirth cases. Microarray has shown higher detection of genetic abnormalities with 8.3% for microarray versus 5.8% for karyotype. Microarray, being a DNA-based study, has the benefit of detecting genomic gains and loss with more sensitivity and thus it is better than karyotype for the study of macerated stillborn and requires viable cells, unlike the karyotype. However, microarray can be complicated by associated genomic findings by detection of variants of unknown significance

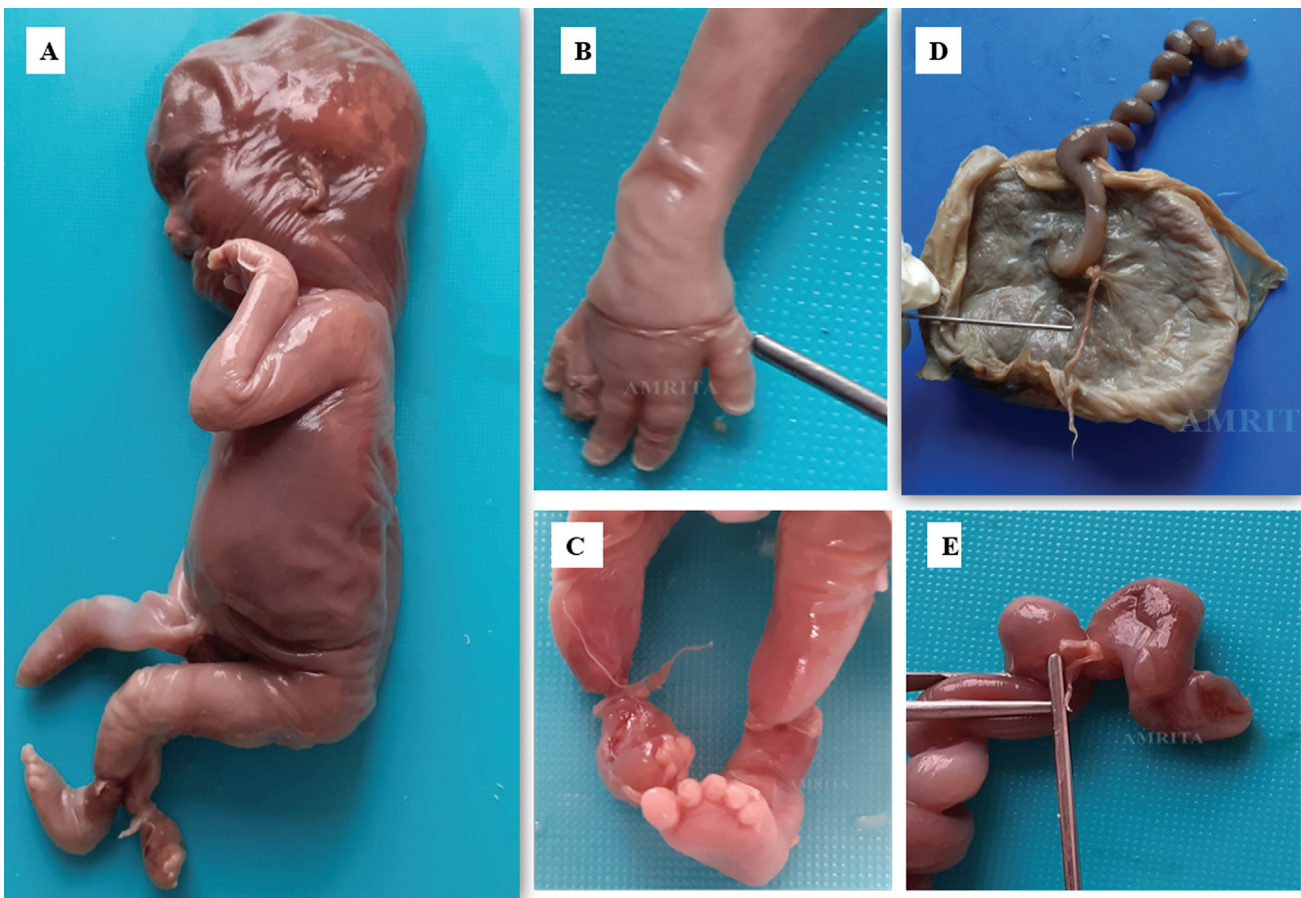
or novel changes contributing to fetal death, in which cases genetic counseling is mandatory.<sup>12–14</sup>

- Limited autopsy—It is the limited examination of the autopsy specimen in cases where consent for a full autopsy is not given. It includes external examination of the body with X-ray, photography, and genetics or placental examination only (with genetic testing if indicated). Autopsy limited to one or more body cavities or an open or needle biopsy of specific internal organs (if indicated) or imaging (computed tomography [CT], MRI) alone or with targeted biopsies is included under limited autopsy.<sup>15–17</sup>

### Information Provided by Perinatal Autopsy

Perinatal autopsy provides information regarding the adequacy of intrauterine growth (in comparison to the gestational age based on information obtained from multiple body measurements, body and organ weights, and bone lengths) and the fetal maturity (based on findings from external, internal examination and primary ossification centers), and estimates the time and cause of intrauterine death based

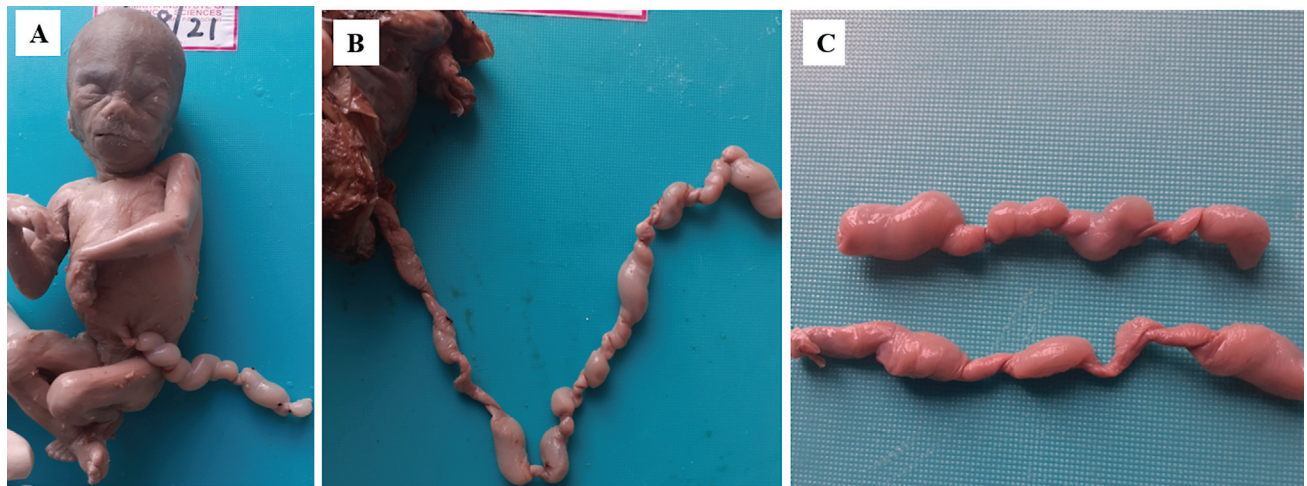
on external (►Fig. 1), internal, and histological maceration changes. It also helps in characterization of fetal congenital anomalies, any variations from normal, and gives the differential diagnosis of known syndrome,<sup>1</sup> fetal anemia, fetal growth restriction by elevated brain:liver ratio,<sup>18</sup> and sequences and defects that may or may not relate to the cause of death. It provides evidence of infection based on gross, histologic, microbiologic, and molecular analysis. It can provide histologic evidence of fetal stress and placental pathology (►Fig. 2). The placental findings in stillbirth related to the cause of death include features of placental insufficiency, fetal vascular obstruction, or an umbilical cord pathology (►Fig. 3). Additionally, a mid-trimester placental examination can enlighten the cause of preterm delivery in previable fetuses. Inherited thrombophilia, a risk factor for stillbirth, may present with findings of impaired implantation, impaired placentation, placental thrombosis, and placental insufficiency by infarction or abruption. Antiphospholipid antibodies, a cause for stillbirth, can also result in placental insufficiency through abnormal placental development or damage caused by placental inflammation, thrombosis, or infarction.<sup>1</sup>



**Fig. 1** Case 1: A 24-year-old primigravida at 17 weeks of gestation presented with an antenatal ultrasound suggestive of intrauterine fetal demise, the cause of which could not be determined on ultrasound examination. The fetus was subjected to fetal autopsy. (A, B) On external examination, the fetus showed whitish-gray bands of tissue running across the dorsal surface of right palm. (C) The same band of tissue seen above the level of ankle joint bilaterally causing near amputation. (D) The same seen adhered to the fetal surface of the placenta and (E) was also seen constricting the umbilical cord. As the rest of the autopsy including internal examination was negative, the cause of death was determined to be amniotic band syndrome. Thus, it helped to counsel and reassure the couple that it is a condition with no risk of recurrence.<sup>20</sup>



**Fig. 2** Case 2: A 29-year-old primigravida at 18 weeks of gestation was diagnosed as a case of fetal demise, early onset fetal growth restriction, and oligohydramnios with normal kidneys on ultrasound scan. (A) Autopsy showing a growth restricted fetus with severe wasting of all muscles on external examination. (B) Internal examination showing small liver. (C) Placental examination showing a firm pale gray-white appearing basal plate and (D) the same firm and gray-white area on cut-section. (E, F) Hematoxylin and eosin-stained section of placenta showing extensive fibrin deposition in the intervillous space. Avascularity and fibrosis of the villi are also noted. The above findings were suggestive of massive perivillous fibrin deposition involving 80% of the placenta. Massive perivillous fibrin deposition is a severe placental lesion of unknown etiology. In most cases, a pathologic immune reaction associated with increased perinatal morbidity and mortality and recurrence risk of 14–50% is noted. It is also associated with recurrent spontaneous abortions, fetal growth restriction, intrauterine fetal demise, and neurological impairment.<sup>21</sup> Here, autopsy could enlighten the cause of death as well as it could shed light on the reproductive future of this couple.



**Fig. 3** Case 3: A 32-year-old second gravida with a history of one full-term delivery and no risk factors at 20 weeks of gestation in the current pregnancy reported for anomaly scan which showing a fetus with intrauterine demise. The autopsy specimen (A, B, C) showing excessive coiling of the umbilical cord suggestive of umbilical cord stricture.<sup>22</sup> Here, an autopsy helped in ascertaining the cause of death and counseling the couple.

## Value of Perinatal Autopsy

In a systematic review published in 2017, the prenatal ultrasound findings were confirmed by fetal autopsy in 70% cases, provided additional information in 22% and disagreement in only 9% cases, with 3 false positivity in 3.2% and false negativity in 2.8% cases; and in the remaining, further details about the reasons for disagreement were not described. In 0.3% cases, autopsy could not be performed because of autolytic events.

Central nervous system anomalies showed highest agreement (79.4%) between prenatal ultrasound diagnosis and autopsy, while limb anomalies showed lowest agreement between ultrasound and autopsy findings (23%). Genetics showed 79.2% correlation followed by genitourinary anomalies (76.8%), skeleton (76.6%), heart (75.5%), thorax (69.7%), gastrointestinal system (62.6%), and multiple fetal anomalies (37%). Approximately 22% of fetal anomalies were missed by prenatal ultrasound, but detectable with autopsy. In about 2 to 3% of cases, the additional findings obtained by autopsy changed the final diagnosis and genetic counseling especially with regard to the risk of recurrence in subsequent pregnancies. Contrarily, in 18% cases, the additional findings were of no clinical significance to the index case and future pregnancies. Additionally, autopsy was of particular value, in 5% cases missed by prenatal ultrasound due to poor visualization as in unfavorable fetal position, maternal obesity, oligo-anhydramnios, or operator inexperience.<sup>5</sup> Despite all of the above, in a prenatally diagnosed case of fetal aneuploidy, an autopsy is of little value in terms of management of future pregnancies.<sup>18</sup> It was also found that the highest rate of discordance between prenatal ultrasound and fetal autopsy was found with the presence of multiple fetal anomalies, probably due to the excessive attention paid by the sonographer to the part with major anomaly. Missed anomalies need not always be considered an error of perinatal autopsy as it could also be due to the postmortem changes of fetal anatomy as in collapse of ventriculomegaly and small posterior fossa anomalies at autopsy or due to the autolytic changes that would have occurred in the specimen.

Literature quotes a drastic improvement in the correlation between prenatal ultrasound and postnatal findings in the last two decades due to the advancement in technology, the ultrasound resolution as well as the operator's skills as evident from the high concordance in the diagnosis of genitourinary anomalies (79%) when compared to studies at the beginning of this century.

However, there is still paucity of literature on large series showing correlations of prenatal ultrasound and fetal autopsy and there is also a lack of uniformity in the studies regarding the gestational age of autopsy specimen due to the difference in the termination laws and health policies in each country.<sup>5</sup>

## Recent Advances

There is a low level of uptake for fetal autopsy by the community, reported well below the recommended 75%

and this is attributed to several procedural, psychological, and cultural barriers from the parental perspective as well as numerous professional barriers. This can be overcome to a larger extent by a realistic noninvasive alternative including a cross-sectional imaging technique, such as postmortem CT or MRI. Other modalities including postmortem ultrasound have also shown to have reasonable diagnostic accuracy rates, with the added benefit of being more readily accessible and affordable and can also be used to guide further tissue sampling.<sup>19</sup>

## Conclusion

Despite the recent less-invasive autopsies, the conventional fetal autopsy remains the gold standard for establishing the cause of death when combined with the genetic workup. Hence, it would be prudent to focus on breaking the psychosocial and clinical barriers toward conventional autopsy.<sup>1</sup> To help parents make a decision and give an informed consent for fetal autopsy, it is essential that we, clinicians, provide information with greater clarity. The clinicians, obstetricians, and midwives should be well educated about the potential risks and benefits of autopsy and its alternatives and should be armed with the ability to guide and support the parents through personalized and sensitive approaches. It is important to have a perinatal pathologist in loop during the counseling sessions after the diagnosis of a fetal abnormality, so that the parents are encouraged for an increased uptake of autopsy facility.<sup>18</sup> A team involving the obstetrician, neonatologist, the geneticist, and the perinatal pathologist is useful to review every perinatal death and evaluate a complete picture of care for the patients. Thus, a multidisciplinary approach to the interpretation of autopsy findings can be valuable not only to that particular individual involved but also to prompt additional research and encourage practice changes that can reduce perinatal mortality.

### Patient Consent

Written informed consent was obtained from the patients for participation and publication of this study.

### Ethics Approval

This was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Authors' Contributions

All authors contributed to the study's conception and design. All authors have read and approved the final manuscript.

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### Conflict of Interest

None declared.

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