Editorial

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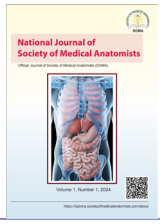

Fetal Autopsy: Insight and Utility

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Fetal anomalies may lead to abortion. The aborted fetus may be an indicator of severe congenital anomaly in addition to other probable causes. Fetal autopsy includes an external and internal examination after demise of fetus for determination of cause of death and finding the fetal anomalies. With the advancement of reproductive medicine, the insight of clinicians and curiosity to find the reason for the failure of treatment is increased. It has enhanced the rate of fetal autopsies in recent years. Finding the cause and anomalies helps to understand the risks for future pregnancies and to the other family members. Causes of fetal death include placental insufficiency (43.6%), fetal causes (35.7%), and maternal reasons (21.4%). Among these, congenital anomalies (28.6%) were the most prevalent cause of death.[1] The common indication of the fetal autopsy includes termination of pregnancy for congenital anomalies, intrauterine death, inevitable abortions, and unexpected stillbirth for understanding the cause of death and detection of congenital anomalies, for detection of genetic diseases, and for detection of markers for gene expression in specific organs.

Congenital Anomalies Causing Fetal Death

Congenital malformations cause significant perinatal deaths (25–30%) in developing countries like India.[2] Mostly multiple congenital anomalies result in fetal death. Some of the reported anomalies include the following:

- Anencephaly, spina bifida, meningocele, rachischisis, encephalocele, agenesis of corpus callosum,
- Agenesis of eyeball, hygroma
- Facial asymmetry, aplasia or oral and nasal cavities, cleft palate, cleft lip
- Situs invertus
- Ectopia cordis, conotruncal malformations, tricuspid atresia, truncus arteriosus, hypoplastic left heart syndrome, premature closure of ductus
- Duodenal atresia, imperforate anus, omphalocele
- Hyperplastic adrenals, polysplenia
- Renal agenesis, distal urethral stenosis, dysplastic kidney, horseshoe kidney
- Clubhand, syndactyly, digital amputation, micromelia,
- Placental agenesis decreased villous vasculature, villous fibrosis, decreased placental maturation, structure massive perivillous fibrin deposition
- Syndromes: Arnold-Chiari malformation, Cantell's petalogy. Fraser syndrome, Meckel-Gruber syndrome, Fryns syndrome, Di George syndrome, amniotic band syndrome, sirenomelia, VACTERAL association, tuberous sclerosis complex, and so on.[3]

Fetal autopsy gives more information than the fetal ultrasound examination in causes of termination of pregnancies based on fetal anomalies.[4] Determination of the cause of death on fetal autopsy is important and may help in counseling and planning for the next pregnancy. It will also help in understanding the developmental aspects of the human and prevention of a similar outcome in the subsequent pregnancy. Fetal autopsy provides significant information in addition to prenatally diagnosed anomalies in cases of termination of pregnancy.

The reduction in the autopsies for perinatal death is observed due to difficulty in gaining consent.[5] Parent's emotions, religious beliefs, disfigurement after autopsy, viscera retention for further analysis, and delay in burial are some hindering factors for the autopsy. Hence, non-invasive or minimally invasive autopsies are also suggested as an alternative to conventional fetal autopsies. These methods include X-ray babygram, postmortem CT scan, post-mortem MRI, biopsy of fetal organs, and placental examination. These may support the findings of antenatal ultrasound, antenatal echography, antenatal CT or MRI scan, amniocentesis, and chorionic villus sampling.

Medicolegal Domain

The fetal autopsy mostly depends on the method of medical termination of pregnancy (MTP). Up to 15 weeks of gestation, MTP is achieved by vacuum aspiration, and it makes the separation of fetal tissue difficult. After this period, MTP is

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achieved by the dilatation and evacuation (D&E) method. Under medical supervision, a medical method using mifepristone misoprostol/gemeprost is also safe for MTP after 12 weeks.[6] In India, up to 20 weeks, one registered medical practitioner (RMP) can take a decision for MTP. Between 20 to 24 weeks, the MTP decision should be taken by two RMP in cases of survivors of the rape case and if there is a risk to the life of the mother. Between 24 to 28 weeks, the medical board decision is required for MTP in cases of substantial fetal abnormalities.

The autopsy should report the viability of the fetus. A dead-born fetus shows the signs of maceration. The live-born fetus should be differentiated using the lung floatation test, the position of the diaphragm on autopsy, and the histopathological findings of lung alveoli. Signs of maturation and viability should be assessed using crown-rump length, the presence of ossification centers in the sternum, calcaneum, talus, and cuboid, and growth of hairs, nails, and eyelashes. In case of unavailability of the preservation and suitable transport method for DNA matching of the sample, the whole fetus should be preserved in rock salt and sent to the genetic laboratories attached to the forensic science lab.

Consent and Sample Transport

The parent's consent is essential to carry out a fetal autopsy. It should be obtained in the language which the parent should understand. The autopsy procedure depends on the available sample for the autopsy. The specimen should be transported and examined for the autopsy as soon as possible. For routine autopsy procedures, the fetus should be transported along with the umbilical cord and placenta in 10% formalin. Before fixation in formalin, sample should be collected for karyotyping as it needs live cells. The blood sample should be preserved in EDTA for cell counting, in plain bulb for biochemical analysis and in heparin for karyotyping. For PCR, microarray and other gene analysis, the sample should be transported in nucleic acid stabilization solution or quick freezing. Further, these specimens should be transported in a frozen state at -20^0C to -80^0C or as advised by the kit manufacturer. Multiple freeze-thaw cycles should be avoided.[7]

Autopsy Procedure

The autopsy should begin with a careful review of the clinical history. Photography is one of the essential components of recording external and internal findings. Routine external examinations include weight, crown-to-rump length, crown-to-heel length, foot length, occipitofrontal circumference, and placental and umbilical cord examination.

Use I- or Y- or modified Y-shaped skin incision for internal examination. External examination of skin limbs, head, neck, lips, chest, abdomen, umbilicus, anus, and external genitalia need to be recorded. For central nervous system examination, a median posterior or transverse posterior parietal scalp incision should be given. CNS should be assessed for maturity and malformation. If required specimen should be examined for histological maturation. The internal examination should include an examination of the heart, lungs, major vessels, abdominopelvic viscera, thymus, and diaphragm. If required, a pre-autopsy radiological examination can be done. For detection of infection, lung, blood, or other indicated samples should be preserved. For genetic analysis, skin, muscle, and cardiac blood samples may be used. Fibroblast culture may be required for biochemical/metabolic analysis. Parents need to be informed about the retention of viscera and other samples with the purpose.[8]

Histopathology in Autopsy

Study of histological changes is important for estimation of time of intrauterine fetal demise. These changes include desquamation, brown-red discoloration of the umbilical cord stump, degeneration of umbilical cord vascular smooth muscle, and intravascular karyorrhexis. These changes are followed by putrefaction and abdominal discoloration. Fetal maturation can be best assessed by the histology of the viscera such as lungs, brain, kidney, intestine, and other organs. Approximately 12 hours onwards of fetal death, the maceration of the fetus and histological autolysis start. In intrauterine death, the maceration is sterile, gradual, and progressive. Most of the aborted fetuses are affected by metabolic hypoxic-ischemic changes, especially in myocardium. It occurs due to progressive uterine contractions causing fetal and umbilical cord compressions.[9] It can be best assessed by histological examination of kidneys, intensive liver, pancreas, bronchi, adrenal gland, lungs, and brain.[10] Histological assessment is also useful in cases of neonaticide and live born from stillborn, in addition to lung floatation test.[11, 12]

Genetic Testing

Chromosomal aberrations in aborted fetuses may be detected by karyotyping using lymphocyte culture (if non clotted blood sample is available) or by fibroblast culture. Conventional karyotyping showed many anomalies in aborted fetuses, such as trisomy 21, trisomy 18, Turner syndrome, trisomy 13, triploidy, and so on. The main constraint of karyotyping is it needs viable fetal cells, and it is not useful for detecting smaller chromosomal aberration (<5 MB). For any specific suspected gene abnormality, PCR can be utilized, such as quantitative fluorescence-polymerase chain reaction (QF-PCR), microarray, and next-generation sequencing (NGS).[13] Chromosomal microarray helps to detect the gain or deletion of DNA throughout the human genome (>100 kb), and it does not need viable tissue. Next-generation sequencing is not only useful for fetal death analysis but also the most powerful tool for prenatal testing in fetuses with congenital malformations. It includes prenatal assessment of genomes and exomes (PAGE) and whole-genome sequencing.[14]

Take Home Messages

A fetal autopsy is crucial for understanding developmental failures and probable causes and for planning preventive measures for future pregnancies. The development of fetal body donation program and fetal autopsy center in association with the Departments of Anatomy, Forensic Medicine, Obstetrics & Gynecology, Neonatology, and Pathology may help in the expansion of research in the field of embryology and for exploring measures for perinatal mortality. It may also help in resolving the issue of less availability of adult cadavers for the research.

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