DOI: 10.7860/JCDR/2014/9226.4920

Original Article

Pathology Section

Foetal Autopsy-Categories and Causes of Death

UROOS FATIMA[1], RANA SHERWANI[2], TAMKIN KHAN[3], SUFIAN ZAHEER[4]

ABSTRACT

Introduction: Intrauterine death(IUD)/ Stillbirth forms a major part of perinatal mortality which thereby is a good indicator of pregnancy wastage as well as quality of healthcare available. The key objectives of autopsy examination are to know the cause(s) of death, elucidation of pathogenic mechanism and quality control of clinical management. The aim of this study was to identify the prevalent causes of IUD, thereby taking appropriate measures to prevent them and decrease the perinatal mortality rate.

Materials and Methods: The study included 14 cases of IUD received for autopsy in the Department of Pathology over a period of five years. Autopsies were performed as per standard protocol and included full anthropometric profile, external examination, gross and microscopic evaluation of different organs and placenta.

Results: Total number of 14 fetal autopsies were performed over a period of 5 years. The causes were broadly classified as fetal, maternal and placental. Placental causes were seen in majority of cases (48.57%) followed by fetal (35.72%) and then maternal (21.42). Most prevalent cause of death was congenital anomalies (28.6%) followed by placental insufficiency (21.4%) and chorioamnionitis (14.2%).

Conclusion: Determination of causes of fetal death would prove beneficial to the clinicians and parents for better management and care in future pregnancies as well as in genetic counseling.

Keywords: Autopsy, Causes, Fetus, Intrauterine death/still birth

INTRODUCTION

Foetus is a product of conception, irrespective of the duration of pregnancy. Upto 9 wk of gestation, it is designated as the embryo. Fetal death is defined as death prior to the complete extraction or expulsion from its mother of a product of conception irrespective of the duration of pregnancy, the death being indicated by the absence of any signs of life. It is divided further as early (<22 wk of gestational age); intermediate (22-27 wk gestational age) and late (≥28 wk gestational age). Of these early are designated as abortions whereas intermediate and late are known as stillbirths [1]. Intrauterine death (IUD)/ stillbirth forms a major part of perinatal mortality which thereby is a good indicator of pregnancy wastage as well as quality and quantity of health care available [2]. Autopsy has been important in medicine since the 15th century and has contributed greatly to the clinical knowledge. Neonatal autopsy has a particular valuable role in the counselling of the families after the loss of an infant as it can help the grieving process, improve parental understanding, and alleviate concerns over prenatal events. Genetic conditions or obstetric factors of relevance to future pregnancies may also be identified [3]. The key objectives of autopsy examination are identification of cause(s) of death, elucidation of pathogenic mechanism and quality control of clinical mechanism [1]. The aim of this study was therefore to identify the prevalent causes of IUD on autopsy thereby taking appropriate measures and offer parental counselling.

MATERIALS AND METHODS

The present study included 14 consecutive cases of fetal autopsy received in the Histopathology section of the Department of Pathology in JNMC(AMU) over a period of five years. Only those cases, where both maternal and fetal records were available along with fetus and placenta were included in the study. Macerated and autolysed fetuses were excluded from the study. Autopsy was performed as per pre-designed protocol followed by the department, after a written consent, which included Name of the mother, Mode of delivery, Sex of the fetus, Anthropometry, External examination, Internal examination of thoracic and abdomino-pelvic cavities as well as removal of viscera, Examination of head & neck, brain and spinal cord, Examination of placenta and umbilical cord. Sections obtained were routinely processed and stained with haematoxylin & eosin. Special stains were used wherever required.

The cases were categorized according to the classification proposed by Cunningham & Hollier [4] as follows:

FETAL (25-40%)

Chromosomal anomalies, Non-chromosomal birth defects, Non-immune hydrops, Infections-viruses/bacteria/protozoa.

PLACENTAL (25-35%)

Abruption, Fetal-maternal haemorrhage, Cord accident, Placental insufficiency, Intrapartum asphyxia, Previa, Twin to twin transfusion, Chorioamnionitis.

MATERNAL (5-10%)

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

RESULTS

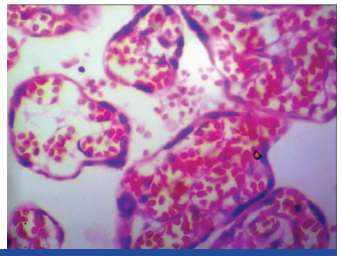
In the study 14 cases of fetal autopsy were included over a period of five years. Mean maternal age was 24.4 y. Mode of delivery in most cases was vaginal (10 cases). The other four were lower segment caeasarean section (LSCS).

Categories	Causes	No.of cases	Percentage(%)
Fetal (35.7%)	Congenital Anomalies	4	28.6
	Infection	1	7.1
Placental (43.6%)	Cord accident	1	7.1
	Placental Insufficiency	3	21.4
	Chorioamnionitis	2	14.3
Maternal (21.4%)	Trauma	1	7.1
	Pre-eclampsia/PIH	1	7.1
	Sepsis	1	7.1
	Total	14	100

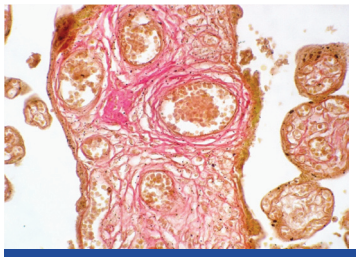
[Table/Fig-1]: Distribution of cases in various categories and causes of fetal death

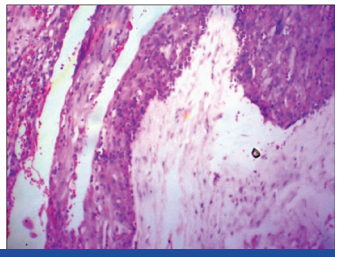
S. No.	Causes of fetal death	Gross & Microscopic Findings in Fetus on Autopsy	Gross & Microscopic features in Placenta and Cord
1.	Congenital abnormalities (4 Cases)	1) Multiple congenital anomalies syndrome -Facial asymmetry with one eye ball: Cystic swelling on left side of the head: Aplasia of oral and nasal cavities; Bilateral axillary cutaneous horns; Ectopia cordis; Omphalocoele M/E-benign cystic teratoma -Pulm . edema; severe atelectasis with hyaline membrane disease in lung. -pericardial fibrosis in heart; congestion, edema and spongiosis in brain	Placenta showed extreme eccentric attachment of cord and microscopically extensive areas of infarction [Table/Fig-3] and focal areas of chorangiosis [Table/Fig-4] were seen.
		2) Bilateral renal agenesis with syndactyly, truncus arteriosus imperforate anus. Hyperplastic adrenals were seen microscopically.	Placenta with varying degree of maturation, decreased villous vasculature, Giant trophoblastic villi and knots; occasional hydropic villi and stromal villous fibrosis [Table/Fig-5]. -Findings commonly seen in trisomy 16(trisomy D type)
		3&4) Anencephaly with spina bifida ; multiorgan developmental cystic anomalies in one case	Placenta showed chorangiosis; mildchorioamnionitis [Table/Fig-6]; decreased syncytiovascular membranes of variable maturity Placenta showed chorangiosis; mildchorioamnionitis [Table/Fig-6]; decreased syncytiovascular membranes of variable maturity
2.	Infection (1case)	Gross-unremarkable (UR) M/E-most of the parenchymal organs showed heavy interstitial mononuclear inflammatory infiltrate	Cord showed mild focal mononuclear inflammation with intervillious infiltrate
3.	Cord Accident (1 case)	Asphyxial death Tight cord seed encircling the neck with cyanosis of lips and nails. M/E-Pathological changes seen predominantly in lungs and brain. Lung: Primary atelectasis with incompletely distended alveoli; air spaces contained fluid and epthelial squames derived from aspirated vernix caseosa. Brain: Periventricular haemorrahage, cystic degeneration and focal neuronal degeneration.	Unremarkable
4.	Placental insufficiency(3cases)	Features of IUGR	Varying maturity of placenta, increased syncytial knots [Table/Fig-7], decreased vasculature, infarction, necrosis [Table/Fig-7],fibrosis, dystrophic calcification and basement membrane thickening [Table/Fig-8]. Cord showed presence of 2 vessels in one case.
5.	Chorioamnionitis (2 cases)	Gross & M/E-non-specific, except mild non-specificinflammation in lung sections	Gross-areas of fibrinous deposites and infarction, M/E-funisitis and villitis
6.	Trauma (1 case)	Non-specific	Large retroplacental blood clot was seen suggestive of abruption
7.	Pre-eclampsia/ PIH (1 case)	Features if IUGR Histology-UR	Placenta showing features of vascular insufficiency mainly infarct, calcification and chorangiosis
8.	Sepsis (1 case)	Gross-UR M/E-mild non-specific inflammation seen in sections of lung, heart and liver	Features of inflammation

[Table/Fig-2]: Morphological features in foetus, placenta and umbilical cord on autopsy (M/E-Microscopic examination;NS-Non-specific;UR-unremarkable)



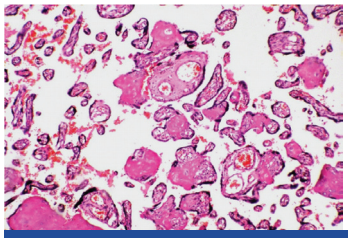
[Table/Fig-3]: Gross- Placenta showing extensive infarction
[Table/Fig-4]: H&E stained section showing increased number of vessels in the villi-Chorangiosis (400x)

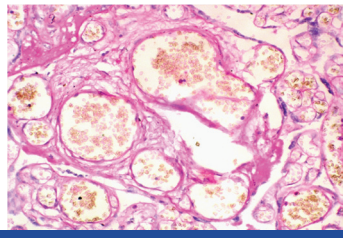




[Table/Fig-5]: VG stain showing increased stromal fibrosis(pink) (400x)
[Table/Fig-6]: H&E stained section showing neutrophilic infiltrate in the membranes-Chorioamnionitis (100x)

Most of the fetal deaths in our study were late fetal deaths, 9 cases (64.3%), 2 cases (14.28%) were intermediate and 3 cases (21.4%) were early. The no. of cases in various categories and causes of fetal death have been shown in [Table/Fig-1]. 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%).





[Table/Fig-7]: H&E stained section showing increase syncytial knots and fibrinoid necrosis (100x)
[Table/Fig-8]: PAS stain showing basement membrane thickening (400x)

One case of fetal autopsy with generalized mononuclear inflammation was suspected for some viral aetiology with multisystem involvement. The mother later came out to be CMV positive. The two cases with chorioamnionitis gave history of some form of manual interference during the early weeks of pregnancy. The case with maternal sepsis had a history of high grade fever with pleural effusion and ascites.

Various histomorphological features in fetus, placenta and the umbilical cord have been tabulated in [Table/Fig-2].

DISCUSSION

Faye Petersen and their colleagues [5] found that fetal autopsies performed by an experienced pathologist in collaboration with clinical specialists could identify the cause of death in 94% cases. Some type of fetal abnormalities like congenital anomalies, infection, non-immune hydrops, malnutrition etc. account for 25-40% of all stillbirths [6,7]. Pasztor et al., were able to provide exact cause of death in 57.9% cases in their study on identification of causes of still birth through autopsy and placental examination reports. In the first half of third trimester placental insufficiency perdominated as cause

of death whereas umbilical cord complications occurred around term [8].

The reported incidence of major congenital malformations in stillborn is highly variable. Congenital malformations remain a common cause of perinatal death and account for 25-30% in developed countries like India [9]. In all 3% neonates have a major congenital malformation and 0.7% has multiple congenital defects. Cases with multiple congenital malformations were specific to autosomal recessive single gene disorder that have recurrence risk of 25% [9]. Majority of stillbirths attributed to fetal causes in the Winsconsin Stillbirth Service Program had a major structural malformation identified at autopsy [7]. Faye Petersen and colleagues [5] found that one-third of fetal deaths were caused by structural anomalies of which neural tube defects, hydrops and congenital heart disease were the most common. Neural tube defects have recurrence risk of 5% [9] as were seen in two of our cases. Birth defects are currently the leading cause of infant mortality accounting for 20% of all infant deaths [10]. Placenta, membranes and cord abnormalities known to cause fetal deaths constitute about 25-35% of the causes of fetal deaths [11] [Table/Fig-3].

Irregularly matured villi are frequent in placentas associated with a variety of chromosomal abnormalities. The trisomy D [12-15] chromosomal anomaly exhibits variable Placental maturation, reduced villous vasculature and giant cytophoblast in 50% or more of villi [Table/Fig-4]. Tetrasomy 12 is a well-recognised chromosomal error with usually lethal anomalies, severely malformed fetus with normal birth weight and essentially normal placenta [13]. Shepard et al.,[14] undertook 20 y analysis of aborted specimen and found that 19% of fetus had a localized defect. Neural tube defects existed in 3.6% cases and recognizable abnormal phenotypes due to chromosomal errors were present in 2.7%. Other abnormalities like renal agenesis, facial cleft and amnionic bands were also seen.

Davies and Arroyo [15] were able to ascertain the cause of perinatal death by autopsy alone in 47.6%. For the purpose of ascribing a cause of death, a placental study was necessary in an additional 34%. Salafia and Vintzilcos [16] were equally emphatic about the need to examine all placentas. If the cause of perinatal mortality is strongly corroborated by placental findings, the same is likely to be true of possible perinatal fetal or neonatal damage, making the examination of this organ all the more mandatory. Abnormal placental findings were also seen in premature and anomalies infants [12]. Bonetti et al., were able to find reasonable cause of death in 79.8% cases of fetal autopsy in their study. They found that the major relevant conditions associated to stillbirth were feto-placental infection in early gestational age (GA) and placental insufficiency both in early and late GA, mainly associated with intrauterine growth retardation [17].

Placental findings in cases of vascular insufficiency and infection correlated well in those reported by other authors. Placental anomalies were mainly represented by avascular villi with stromal fibrosis associated with thrombosis of major and minor vessels in placental insufficiency cases [17] [Table/Fig-5,6]. Soma and colleagues [18] found placental infarction in 54.7% cases of toxemia which was the most common lesion found in pregnancy induced Hypertension (PIH)/ pre-eclamptic toxemia (PET). Wentworth [19] examined 679 consecutive placentas of which 12 were from severe and 77 from mild PIH patients. Infarction was present in 67% cases with severe PIH and in 11.7% cases with mild PIH. Naeye [20] deduced that placental infarction caused 2.26 of 1000 perinatal deaths.

Increased syncytial knotting is also referred to as Tenny-Parker change [21] who emphasized that increased budding of placental syncytium is characteristic of preeclapsia [Table/Fig-6]. When > 30% of tertiary villi possess syncytial buds especially in premature placenta it is diagnostic of a perfusional compromise. Increased incidence of syncytial knotting points to abnormal villous shape and are usually found under hypoxic conditions typically as in Hypertensive disorder [22].

Patients with severe toxemia even had higher values of calcification when they delivered prematurely but not at term [23]. Fox [24] stated that calcification is in no way related to degenerative changes but that fetal distress and neonatal asphyxia were more common with calcified placenta [Table/Fig-8].

Infection are not only much more common in premature deliveries, they are indeed probably a main reason for most premature births before 30 weeks of gestation [25]. Bengston et al., [26], ascertained charioamnionitis in 45.8% of 59 patients with premature rupture of membranes before 26 wk of gestation, of which 49.1% had perinatal mortality signifying chorioamnionitis as significant cause of IUD. The most important feature of ascending infection is the type of infectious agent and perhaps the time of onset but not the degree or type of inflammatory response [12]. It is well known that attempted abortion with non-sterile instruments is frequently followed by sepsis and chorioamnionitis [27] as was the history given in both of our cases of chorioamnionitis. The predominant opinion now is that amnionic sac infection is a primary cause of premature rupture of membranes and preterm labour at least in those pregnancies that terminate spontaneously before 30 wk of gestation [12]. There is also evidence that these infections have an important role in the causation of stillbirth and neonatal deaths [28]. The histological hallmark of CMV infection is a chronic lymphoplasmacytic infiltrate [12] and this is one of the major causes of chronic villitis. The fetal and neonatal disease in this case has many manifestations including stillbirth, as 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 placenta or fetus.

Although maternal causes appear to make only 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 [7,11]. Causes like trauma, infection, cord accident are preventable causes, which if taken care of, would lead to a favourable outcome in future pregnancies. Even congenital abnormalities due to exposure to a known teratogen or poor glycaemic control are preventable. Though a higher degree of recurrence is associated with maternal medical disorders like hypertension, diabetes but appropriate clinical intervention either preconceptionally or early pregnancy may improve the outcome in subsequent pregnancies.

CONCLUSION

Thus, determining the cause of fetal death facilitates the psychological adaptation to a significant loss and helps to assuage the guilt that is a part of grieving. It also makes counseling regarding recurrence more accurate and may prompt therapy or intervention to prevent a similar outcome in the subsequent pregnancy.

REFERENCES

[1] Singh M. Care of the newborn. 5th edn. *Sagar Publications.* 2000.
[2] Park K. Preventive and social medicine. 21st edn. *M/S Banarsidas Bhanot*. 2010.
[3] Brodie M, Laing IA, Keeling JW, Meckenzie KJ. Ten years of neonatal autopsies in tertiary referral centre: retrospective study. *BMJ*. 2002;324(7340): 761-63.
[4] Cunninnham FG, Hollier LM. Fetal Death. Williams Obstetrics. 20th edn (suppl 4) Norwalk Ct. *Appleteon & Lange.* 1997.
[5] Faye-Petersen OM, Guinn DA, Wenstrom KD. The value of perinatal Autopsy. *Obstel Gynecol.* 1999;94(6):915-20.
[6] Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of featal death-1961-1988. *Obstet Gynecol.* 1992;79(1):35-39.
[7] Pauli RM, Reiser CA. Winsconsin Stillbirth service programme II. Analysis of diagnosis and diagnostic categories in first 1000 referrels. *Am J Med Genet.*1994;50(2):135-53.

[8] Pasztor N, Kereszturi A, Kozinzky Z, Pal A. Identification of causes of stillbirth through autopsy and placental examination reports. *Fetal & Paediatric Pathology*. 2014;33(1):49-54.
[9] Shankar VH, Phadke SR. Clinical utility of fetal autopsy and comparison with prenatal ultrasound findings. *Journal of Perinatology*.2006;26:224-29.
[10] Leizel AE. Primary prevention of birth defects by preconceptional care including multivitamin supplementation (review). *Bacillieres Chin Obstel Gynecol.*1995;9:417-21.
[11] Allessandri LM, Stanley FJ, Garner JB, Newham J, Wlaters BNJ. A case-control study of unexplained antepartum stillbirths. *Br J Obstet Gynecol.* 1992;99(9):711-18.
[12] Benirschke K, Kaufman P. Pathology of the Human Placenta. 4th Edn, Springer-verlag,2000.
[13] Shivshankar L, Whitney E, Colmorgen G, et al. Prenatal diagnosis of tetrasomy 47, XY,+i(12p) confirmed by insitu hybridization. *Prenatal diagn*. 1988;8:85-91.
[14] Shepard TH, Fantel AG, Fitzsimmons J. Congenital defect rates among spontaneous abortuses: twenty years of monitoring. *Teratology*. 1989;39:325-31.
[15] Davies BR, Arroyo P. The importance of primary diagnosis in perinatal death. *Am J Obstet Gynecol.* 1985;152:17-23.
[16] Salafia CM. and Vintzileos AM. Why all placentas should be examined by a pathologist in 1990. *Am J Obstet Gynecol*. 1990;163:1282-93.
[17] Bonetti LR, Ferrari P, Trani N, Maccio L, Laura S, Giuliana S, et al. The role of fetal autopsy and placental examination in the causes of fetal death:a retrospective study of 132 cases of stillbirths. *Arch Gynecol Obstet*. 2011;283(2):231-41.
[18] Soma H, Yoshida K, Mukaida T, Tabuchi Y. Morphologic changes in the hypertensive placenta. *Contrib. Gynecol. Obstet*. 1982;9:58-75.
[19] Wentworth P. Placental infarction and Toxemia of pregnancy. *Am J Obstet Gynecol.* 1967;99:318-26.
[20] Naeye RL. Placental infarction leading to fetal or neonatal deaths. A prospective study. *Obstet Gynecol*. 1977;50:583-88.
[21] Tenney B, Parker F. The placental in Toxemia of pregnancy. *Am J Obstet Gynecol*. 1940;39:1000-05.
[22] Alvarez H, Morel RL, Benedetti WL, et al. Trophoblast hyperplasia and maternal arterial pressure at term. *Am J. Obstet Gynecol*. 1969;105:1015-21.
[23] Jeacock MK, Scott J, Plesten JA. Calcium content of the human placenta. *AM J Obstet Gynecol.* 1963;87:34-90.
[24] Fox H. Calcification of the placenta. *J Obstet Gynecol Br Commonwealth.* 1964;71:759-65.
[25] Ornoy A, Tenebaum A. Pregnancy outcome following infections by coxsackie, echo, measles, mumps, hepatitis, polio and encephalitis viruses. *Reprod toxicol.* 2006;21(4):446-57.
[26] Bengtson J.M., Van marter LJ, Barss VA, et al. Pregnancy outcome after premature rupture of membranes at or before 26 weeks gestation. *Obstet Gynaecol*.1989;73: 921-27.
[27] Studdiford WE, Douglas GW. Placental bacteremia: A significant finding in septic abortion accompanied by vascular collapse. *AJOG*. 1956;71:842-58.
[28] Quinn PA, Butany J, Chipman M, et al. A prospective study of microbial infection in stillbirths and neonatal death. *AJOG*. 1985;151:238-49.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Pathology, DMWayanad Institute of Medical Sciences, Naseera Nagar, Mepaddi, Wayanad, Kerala, India.
2. Professor, Department of Pathology, Jawahar Lal Nehru Medical College, AMU, Aligarh, Uttar Pradesh, India.
3. Professor, Department of Obstetrics and Gynaecology, Jawahar Lal Nehru Medical College, AMU, Aligarh, Uttar Pradesh, India.
4. Assistant Professor, Department of Pathology, Jawahar Lal Nehru Medical College, AMU, Aligarh, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Uoos Fatima,
Associate Professor, Department of Pathology, Central Pathology Lab,
DMWIMS, Naseera Nagar, Mepaddi, Wayanad, Kerala, India.
Phone : 8111881125, E-mail : fatimauroos@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 10, 2014**
Date of Peer Review: **Jul 14, 2014**
Date of Acceptance: **Jul 30, 2014**
Date of Publishing: **Oct 20, 2014**