Original Article

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Pathology Section

Foetal Autopsy: A Cross-sectional Study of 41 Cases at a Tertiary Care Centre in Kuppam, Andhra Pradesh, India

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ABSTRACT

Introduction: Perinatal mortality includes both late foetal deaths and early neonatal deaths. The perinatal mortality rate in India was 23/1000 live births for the year 2016, with congenital anomalies being the major cause of perinatal mortality. Thus, foetal autopsy plays an important role in identifying various types of congenital anomalies, determining the cause of foetal death, and thereby helping in counselling the parents.

Aim: To identify various causes of foetal death and determine the most prevalent cause of foetal death.

Materials and Methods: The present cross-sectional study was conducted in the Department of Pathology, PES Institute of Medical Sciences and Research (rural tertiary care referral Institute), Kuppam, Andhra Pradesh, India, from January 2018 to December 2022. Autopsies were performed according to a standard protocol and categorised using the Cunningham and Hollier classification. The data were entered into Microsoft (MS) Excel 2007 and further analysed using Statistical Package for the Social Sciences (SPSS) software version 26.0.

Results: The maternal age ranged from 19-36 years with a mean±Standard Deviation (SD) of 24.1±3.37 years. Out of the 41 cases, 29 (70.73%) cases were terminated, and 12 (29.26%) cases had intrauterine foetal death. The majority of cases were in the second trimester, with 37 (90.24%) cases, followed by 4 (9.75%) cases in the third trimester. Foetal causes constituted the majority of cases, 23 (56.09%), followed by placental causes, 12 (29.26%) and maternal causes, 6 (14.63%).

Conclusion: The present study concluded that congenital anomalies constituted the most prevalent cause of foetal death, with central nervous system anomalies being the most common. This information helps clinicians in early intervention and counselling parents to avoid similar outcomes in subsequent pregnancies.

Keywords: Autopsies, Causes, Congenital anomalies, Foetus

INTRODUCTION

The foetus is a product of conception irrespective of the duration of pregnancy [1]. Perinatal mortality includes both late foetal death and early neonatal death. More than 3 million perinatal deaths occur every year worldwide. The perinatal mortality rate in India was 23/1000 live births, providing an indication of the extent of pregnancy wastage and the quality of healthcare available to mothers and newborns [2]. Even in the current era with the availability of modern technologies, autopsies play an important and gold standard role in identifying and confirming the cause of foetal death, potentially leading to changes in the healthcare system and enhancing clinical diagnosis [3]. Although the majority of deaths were attributed to be of foetal origin, congenital malformations account for 10-15% of perinatal mortality in India. It is also estimated that 3% of neonates have major congenital malformations, and 0.7% have multiple malformations [4]. Cases with multiple malformations have a recurrence risk of 25% [1].

A single pregnancy loss makes women more apprehensive and reluctant about future pregnancies. Therefore, every effort should be made to establish and identify the correct diagnosis [4]. The present study was conducted in a rural tertiary care centre, serving patients from a tristate region, to determine the causes of foetal death and to enlighten families about foetal death and the need for genetic counseling to prevent future pregnancy loss. The study aimed to identify various causes of foetal death and determine the prevalent cause.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Pathology, PES Institute of Medical Sciences and Research (rural tertiary care referral Institute), Kuppam, Andhra Pradesh, India, from January 2018 to December 2022, over a five-year period. The study approval was granted by the Institutional Ethics Committee (IEC No: PESIMSR/IHEC/C-144/2023).

Inclusion criteria: All cases of foetal autopsies received in the Department of Pathology were included in the study.

Exclusion criteria: Macerated and autolysed foetuses were excluded from the study.

Sample size calculation: All cases of foetal death reported during the study period were considered as samples in the study, excluding macerated and autolysed foetuses.

Study Procedure

Foetal autopsy examination was performed after obtaining informed, written consent from parents, explaining the details of the procedure. The autopsies were conducted by a pathologist. The foetus was examined according to the protocol followed in the Department of Pathology, which included anthropometry followed by external and internal examination. External examination was carried out to identify skin lesions, cyanosis, and developmental anomalies. The internal examination involved the en bloc removal of cervical, thoracic and abdominal organs, followed by dissecting them into organ blocks. The position, size and weight of each organ were observed and measured. Examination of the placenta was also conducted, wherever available.

Histopathology: Sections were obtained from the tongue, thymus, heart, lungs, liver, stomach, spleen, pancreas, large and small intestines, bilateral adrenals with kidneys, brain, umbilical cord and placenta. The sections were processed routinely and stained with Haematoxylin and Eosin (H&E) staining. Autopsy findings were correlated with Ultrasonograph (USG) findings and X-ray

findings, whenever required and available. The cases were further categorised according to the Cunningham and Hollier classification [5]. The cases were categorised into foetal, placental and maternal categories as follows:

- Foetal: Chromosomal anomalies, non chromosomal birth defects, non immune hydrops, infections;
- Placental: Abruption, foetalmaternal haemorrhage, cord accident, placental insufficiency, intrapartum asphyxia, placenta previa, chorioamnionitis;
- Maternal: Diabetes, hypertensive disorders, trauma, abnormal labour, sepsis, uterine rupture, post-term pregnancy, drugs, antiphospholipid antibodies, unexplained.

STATISTICAL ANALYSIS

The data was entered into MS Excel 2007 version and further analysed using SPSS software version 26.0. For descriptive analysis, the categorical variables were analysed using percentages, and the continuous variables were analysed by calculating the mean±Standard Deviation (SD).

RESULTS

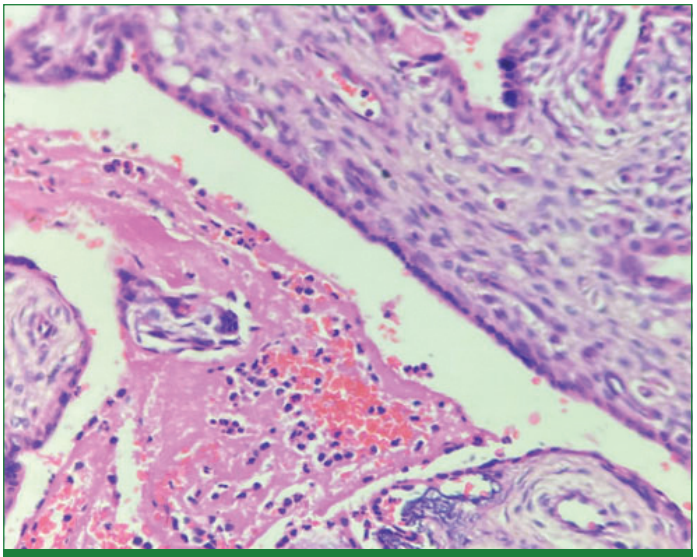
The study included 41 cases over five years period, of which 29 (70.73%) cases were terminated and 12 (29.26%) cases had intrauterine foetal death. The maternal age ranged from 19-36 years (mean of 24.1±3.37 years). The majority of cases were in the second trimester, with 37 (90.24%) cases followed by 4 (9.75%) cases in the third trimester. In 23 (56.09%) cases, the cause of death was foetal, 12 (29.26%) had placental cause of death and 6 (14.63%) had maternal cause of death. [Table/Fig-1] Placental ischaemia was the leading placental cause in 7 (17.07%) cases [Table/Fig-1,2].

Causes	N=41, n (%)
Foetal causes	**23 (56.09)**
1) Congenital anomalies	17 (41.46)
2) Syndromes	4 (9.75)
3) Non immune hydrops	1 (2.43)
4) Foetal infection	1 (2.43)
Placental causes	**12 (29.26)**
1) Placental ischaemia	7 (17.07)
2) Chorioamnionitis	1 (2.43)
3) Abruptio placenta	1 (2.43)
4) Oligohydramnios	1 (2.43)
5) Premature rupture of membranes	1 (2.43)
6) Antepartum haemorrhage	1 (2.43)
Maternal causes	**6 (14.63)**
1) Hypertension	1 (2.43)
2) Eclampsia	1 (2.43)
3) Cervical incompetence	1 (2.43)
4) Unicornuate uterus	1 (2.43)
5) Rh-negative pregnancy	1 (2.43)
6) Cause not identified	1 (2.43)

[Table/Fig-1]: Cause of foetal deaths.

Congenital anomalies were observed in 17 (41.46%) cases. Anomalies of the central nervous system were more common (n=9), followed by anomalies of the cardiovascular system (n=3). Two cases of diaphragmatic hernia and one case each of cystic hygroma with situs ambiguous, increased nuchal thickness, and musculoskeletal system anomalies were observed [Table/Fig-3,4,5].

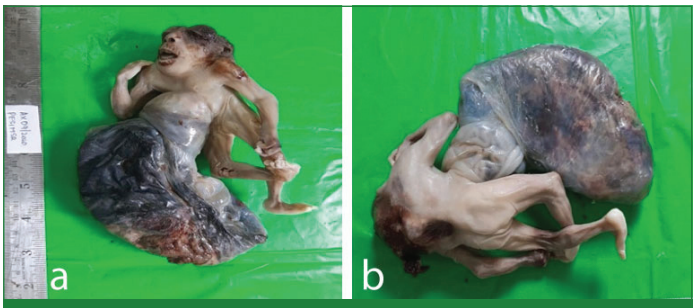
Among the 41 cases, syndromes were observed in 4 (9.75%) cases. [Table/Fig-6] one case each of Pentalogy of Fallot [Table/Fig-7], Twin Reversed Arterial Perfusion (TRAP) [Table/Fig-8a,b], Potter syndrome [Table/Fig-9a,b,c] and Meckler-Gruber syndrome [Table/Fig-10a-e] was observed.



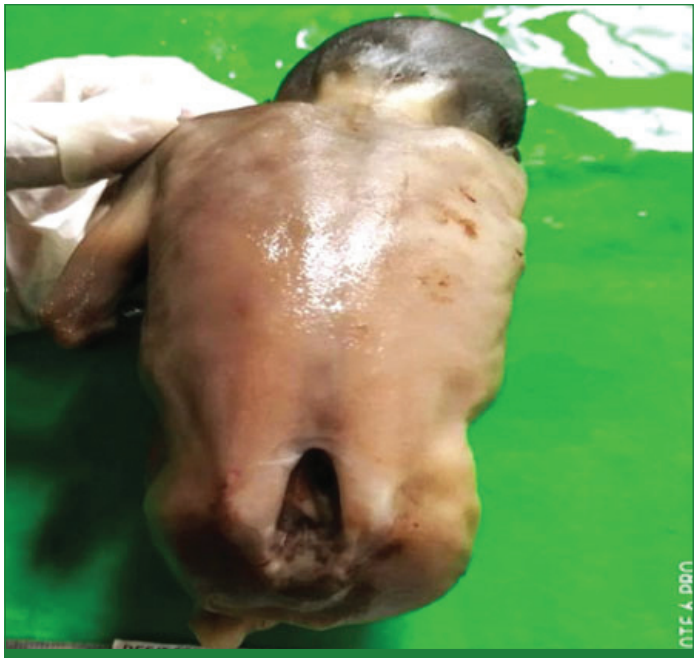
[Table/Fig-2]: Placental ischaemia (H&E, 40x).

Type of anomaly	Associated anomaly	n
Central nervous system (n=9)		
a) Anencephaly		1
b) Cerebellar hypoplasia, hydrocephalus, posterior cranial fossa abnormality		1
c) Bilateral choroid plexus cysts	Hypoplastic nasal bone	1
d Anterior encephalocele	Bilateral club foot and bilateral clenched fists	1
e) Semilobar holoprosencephaly	Short long bones, partial agenesis of corpus callosum and single umbilical artery	1
f) Acrania [Table/Fig-4a]	Omphalocele, club foot and spinal dysraphism [Table/Fig-4b]	1
g) Lumbosacral bifida with Arnold-chiari malformation [Table/Fig-5]		1
h) Sacrococcygeal myeloschisis		1
i) Occipital encephalocele	Cystic hygroma, Arnold-chiari malformation and low-set ears	1
Cardiovascular system (n=3)		
a) Tricuspid valve stenosis with hypoplastic right ventricle, severe mitral regurgitation, pulmonary artery stenosis.	Lemon-shaped skull	1
b) Left axis deviation, pericardial effusion, rhythm abnormality.		1
c) Bilateral ventriculomegaly		1
Musculoskeletal system (n=1)		
Ulnar hemimelia, 13 pairs of ribs and short right humerus.	Umbilical cord single artery and hypercoiled cord	1
Diaphragmatic hernia		2
Nuchal thickness increased		1
Cystic hygroma and situs ambigous		1

[Table/Fig-3]: Foetal anomalies.



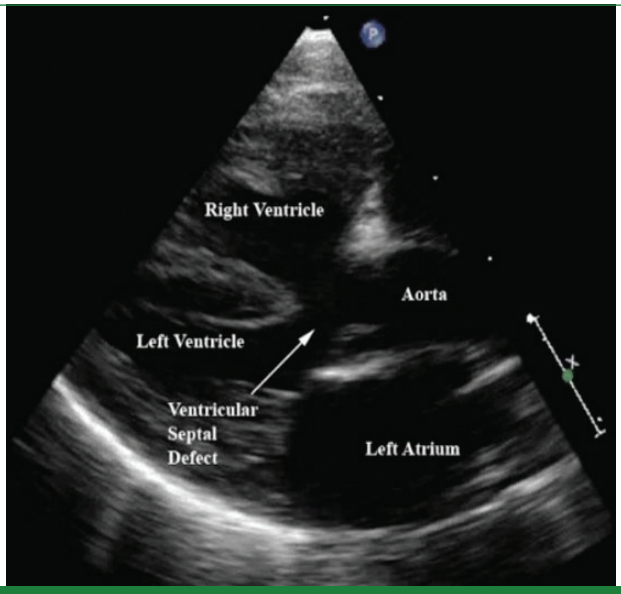
[Table/Fig-4]: a) Acrania. b) Omphalocele, club foot and spinal dysraphism.



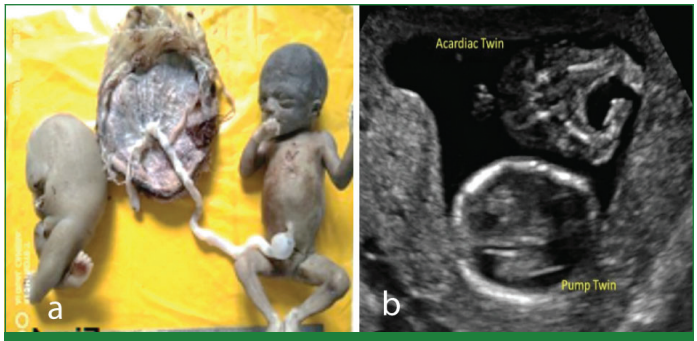
[Table/Fig-5]: Lumbosacral bifida.

Syndromes	Gross features of the foetus on autopsy	USG findings
Pentalogy of fallot	USG features were confirmed on gross	Patent ductus arteriosus, atrial septal defect, ventricular septal defect, right ventricular hypertrophy and overriding aorta [Table/Fig-7]
Twin Reversed Arterial Perfusion (TRAP)	Gross: Donor twin-cardiomegaly and hypertrophy of the donor twin with a single umbilical artery. Acardiac twin-fleshy mass with bits of intestinal loops, absent heart, and well-developed lower limbs [Table/Fig-8a]	In diamniotic monochorionic pregnancy, the anterior amniotic sac shows a single live foetus with a single umbilical artery and the posterior amniotic sac shows echogenic mass with no distinct head and cardia [Table/Fig-8b]
Potter syndrome	Gross: Only tibia identified and no foot in left lower limb [Table/Fig-9a]. Microscopy-polycystic kidney in right and renal agenesis in left kidney [Table/Fig-9c]	Anhydramnios [Table/Fig-9b], bradycardia
Meckler-Gruber syndrome	Gross: Encephalocele [Table/Fig-10a], bilateral polycystic kidneys [Table/Fig-10b], post-axial polydactyly, low set ears. Microscopy: polycystic disease bilateral [Table/Fig-10e]	Loss of temporal bone, encephalocele [Table/Fig-10c], Arnold-chiari malformation [Table/Fig-10d]

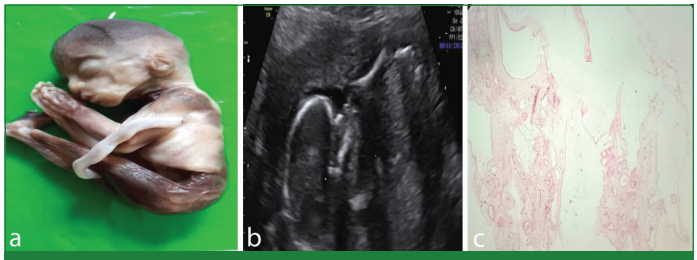
[Table/Fig-6]: Syndromes.



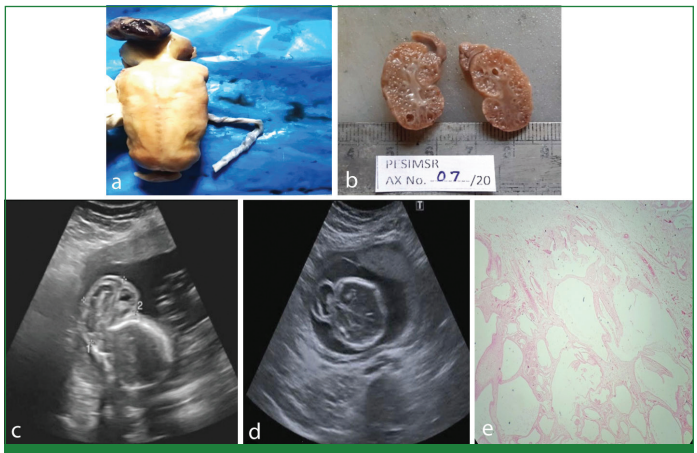
[Table/Fig-7]: Pentalogy of Fallot.



[Table/Fig-8]: a) Twin Reversed Arterial Perfusion (TRAP); b) Acardiac twin and pump twin.



[Table/Fig-9]: a) Tibia identified and no foot in left lower limb; b) Anhydramnios; c) Polycystic right kidney.



[Table/Fig-10]: a) Encephalocele; b) Bilateral polycystic kidneys; c) Encephalocele; d) Arnold-chiari malformation; e) Polycystic kidney disease.

DISCUSSION

Foetal autopsy plays an important role in the diagnosis of intrauterine foetal death, and congenital anomalies are major contributors to perinatal death [6]. Of the 41 cases studied, termination of pregnancy was observed in 70.73% of cases, and 29.26% had intrauterine death. The majority of cases were in the second trimester, which was higher (90.24%) compared to the study conducted by Venkataswamy C et al., (75.8%) [7].

The majority of deaths were attributed to be of foetal origin (56.09%), which was higher compared to the study carried out by Fatima U et al., where foetal causes contributed 35.72% [1]. Among the foetal causes, congenital anomalies were the major (41.46%) causes of foetal death. A comparison of congenital anomalies with other studies has been presented in [Table/Fig-11] [3,7-9]. The most

Authors name	Place of study	No. of subjects, N	Congenital anomalies (%)
Venkataswamy C et al., [7]	Tamil Nadu, India	66	40.09
Choukimath SM et al., [3]	Karnataka, India	105	29.5
Saini SK et al., [8]	Karnataka, India	217	23.50
Silesh M et al., [9]	Ethiopia	3346	5.95
Present study	Andhra Pradesh, India	41	41.46

[Table/Fig-11]: Comparison of congenital anomalies with other studies [3,7-9].

common anomaly observed involved the central nervous system, followed by the cardiovascular system. This is in concordance with the study conducted by Venkataswamy C et al., in which the central nervous system was most commonly involved, followed by the genitourinary system [7].

Neural tube defects affect approximately one in every 1000 pregnancies globally. The congenital anomalies of the central nervous system that arise during embryonic development due to incomplete neural tube closure are grouped as neural tube defects. Neural tube defects include anencephaly (0.66-5.56%), spina bifida (4.38-17.31%) and encephaloceles (2.08-12.29%) [10]. Neural tube defects are polygenic and multifactorial, where many genes, nutritional factors, and environmental factors either individually or in combination play a role [11]. In the present study, six cases of neural tube defects were observed, including two cases of encephalocele, one case each of anencephaly, sacrococcygeal myeloschisis, lumbosacral bifida and acrania. A single case of cerebellar hypoplasia associated with hydrocephalus was identified. Cerebellar hypoplasia is a disorder of cerebellar formation in which the cerebellum is not completely developed or is smaller than it should be. Cerebellar hypoplasia can occur in isolation or can be associated with several metabolic and neurodegenerative disorders. In a study conducted by Howley MM et al., out of 87 cases of cerebellar hypoplasia, nine cases were associated with hydrocephalus [12].

In the current study, a case of bilateral choroid plexus cyst with hypoplastic nasal bone was detected on ultrasound in the second trimester. Foetal choroid plexus cysts are more frequent and transient benign findings. They are identified in approximately 1-2% of foetuses in the second trimester. Isolated choroid plexus cysts detected in the prenatal period with a thorough anomaly scan are considered normal variants, and 90% of them usually disappear by the third trimester. In those with associated anomalies, aneuploidies are likely to be detected in 2.1% of cases. In a study conducted by Shah N, out of 1024 cases, the incidence of choroid plexus cysts was 10/1024 (1%) cases, and associated anomalies were found in 2/1024 (20%) cases [13].

In the present study, a case of semilobar holoprosencephaly associated with short long bones, a single umbilical artery, and partial agenesis of the corpus callosum was identified. Holoprosencephalies are a group of disorders characterised by the failure of differentiation and midline cleavage of the prosencephalon into the right and left cerebral hemispheres. The disorder is estimated to occur in 1 in 16,000 live births and 1 in 250 conceptuses, and is categorised as alobar, semilobar, and lobar. It is usually caused by genetic factors, environmental factors and teratogens [14].

Three (7.1%) cases of cardiovascular anomalies were observed, which was in concordance with a study conducted by Babu RS and Pasula S, constituting 8.10% [15]. Musculoskeletal anomalies were identified in 1 (2.4%) case, which was also in concordance with a study by Dasari P and Aggrawal P, where musculoskeletal anomalies constituted 2.45% [16]. Two cases (4.8%) of diaphragmatic hernia were identified. In a study by Dasari P and Aggrawal P, diaphragmatic hernia constituted 3.27% [16].

In the current study, syndromes were observed in four cases. A case of Pentalogy of Fallot diagnosed on ultrasound in the second trimester was identified. Pentalogy of Fallot is a rare cyanotic congenital heart disease with features of Tetralogy of Fallot (TOF) and an associated atrial septal defect, with an incidence of three in 10,000 live births [17].

A case of Twin Reversed Arterial Perfusion (TRAP) was identified and categorised as Acardiac Acephalus. TRAP affects monochorionic multiple pregnancies. In twin pregnancies, it is characterised by one acardiac twin and the other with normal development. The incidence may be as high as one in 9500-11,000 pregnancies (approximately 2.6%) of monochorionic multiple pregnancies [18]. Based on the morphology of the acardiac foetus, four types are categorised. Acardiac Acephalus is the most common type, with 60-75% of cases characterised by good development of the pelvis and legs and the absence of the cephalic pole, thoracic organs and upper extremities [19].

A case of Potter syndrome presented with skeletal and renal abnormalities. Potter's sequence is a rare congenital malformation with an incidence of one in every 2,000 to 5,000 foetuses and is associated with a recurrence risk of 3-6%. It is characterised by pulmonary hypoplasia, skeletal malformation and kidney abnormalities. Oligohydramnios is a very common cause of Potter's deformity [20].

Meckler-Gruber syndrome is a rare lethal malformation with a high incidence recorded in Gujarati Indians (1 affected birth/1304 with a carrier rate of 1 in 18). It is an autosomal recessive disorder characterised by two of three classic manifestations of renal cystic dysplasia, occipital encephalocele, or any other central nervous system anomaly and postaxial polydactyly [21].

Placental causes constituted 29.26% of cases in the current study. In a study conducted by Fatima U et al., placental causes constituted 43.6%. Maternal causes constituted 14.63% in the current study, which is lower compared to a study done by Fatima U et al., (21.4%) [1]. Although maternal causes appear to make a small contribution to foetal deaths in the current study, appropriate clinical intervention and regular antenatal care may improve the outcome.

Limitation(s)

The number of cases was relatively less in comparison to other studies. Secondly, in many of the cases, evaluation of the placenta was not done; hence, complete assessment was not possible.

CONCLUSION(S)

Foetal autopsy plays an important role in identifying the cause of foetal death. Autopsy, along with other radiological investigations, plays a crucial role in identifying various causes. Congenital anomalies were observed as the major cause of foetal death. Thus, the present study, along with other studies, helps clinicians come up with early intervention and counseling of parents to avoid similar outcomes in subsequent pregnancies.

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