Original Article

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Congenital Malformations in Perinatal Autopsies – A Study of 100 Cases

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ABSTRACT

Background: Congenital malformations remain a common cause of perinatal deaths and even though ultrasonogram can give fairly accurate diagnosis, perinatal autopsy is essential to confirm the diagnosis and look for associated malformations.

Objectives: To emphasize the importance of perinatal autopsy in diagnosing congenital malformations and to compare the same with the prenatal ultrasound findings.

Methods: The present study comprises 100 consecutive perinatal autopsies conducted after obtaining the approval from the Institutional Ethics Committee. In cases where prenatal ultrasound findings were available they were compared with the autopsy findings.

Results: Out of 100 perinatal autopsies, 44 cases were congenital anomalies with M:F = 1:1.5. Majority of the fetuses with congenital malformations (36.36%) were therapeutically terminated, Cental nervous system malformations being the commonest indication. The most common timing of therapeutic termination being 20 -24weeks. Congenital malformations were common between 35-39 weeks gestational age and birth weight range 350- 1000g. The malformations involving the central nervous system were commonest, seen in 15 cases (34.09%) followed by renal anomalies in 9 cases (20.45%) and multiple malformations in 7cases (15.91%). Autopsy confirmed the prenatal ultrasound findings in 50% of the cases, added to diagnosis in 29.54%, while it completely changed the primary diagnosis in 9.09% of the cases.

Conclusion: This study highlights the importance of perinatal autopsy in confirming the diagnosis of congenital anomalies by prenatal ultrasound findings.

Key Words: Perinatal autopsy, Congenital malformations, Prenatal ultrasound

INTRODUCTION

Congenital malformations remain a common cause of perinatal deaths accounting for 10-15% in developing countries like India. [1] and still remain one of the least focused areas of disease surveillance in India compared with communicable and some chronic disease. Unlike the situations in developed countries, where congenital malformations are leading cause of infant mortality, in India low birth weight, prematurity, sepsis and infections are still the leading causes. Perhaps for this reason not much attention has been paid to the problem of congenital malformations in India [2]. Antenatal sonography developed in recent years, however it continues to lag behind a complete fetal autopsy in accurately diagnosing the cause of fetal death [3]. Only few studies have comparatively examined prenatal ultrasound findings & postnatal autopsy results.

MATERIALS AND METHODS

The present study comprises 100 consecutive perinatal autopsies conducted after obtaining the approval from the of the Institutional Ethics Committee. In the present study all fetuses with gestational age 20 weeks to 7 completed days after delivery and birth weight greater than 350 g were included while all autolysed foetuses, fetus with gestational age less than 20 weeks and more than 7 days of life, birth weight less than 350 g were excluded.

Consent for autopsy was obtained from either of the parent after explaining the need. Each fetus was examined according to predetermined protocol which included ultrasound diagnosis, photograph, external and internal examination. The autopsy protocol included the removal of thoracic, cervical, abdominal and pelvic organs en block and subsequently dissected into organ blocks [4]. The placenta, fetal membranes and umbilical cord were studied in all the cases. Histological sections were taken from lung, liver, kidney, thymus, brain, placenta and umbilical cord.

In cases where the antenatal ultrasonography diagnosis was available, were compared with the postnatal autopsy findings.

RESULTS

Out of 100 perinatal autopsies, 44 cases were congenital anomalies which included 25 females, 17 males, one case of female pseudohermaphroditism (preesently called as 46 XX Disorders of Sex Development) [5] and one case in which sex could not be identified. Among the 44 cases ,16 were therapeutic terminations, 12 were still births, 8 cases of Intrauterine Deaths and 8 were live born. The most common timing of therapeutic termination encountered in this study was 20 – 24 weeks.

Each case was classified on the basis of gestational age and birth weight. Congenital malformations were common between 35-39 wks & birth weight range 350- 1000g [Table/Fig-1 & 2].

The most common congenital anomalies included Central Nervous System defects, anencephaly being commonest among them. followed by renal anomalies. Multiple congenital anomalies were observed in 7 cases. One case each of Prune Belly syndrome. Meckel Gruber syndrome, Thanatophoric Dysplasia Type 1,

Gestational age	Number of cases	Percentage (%)
20- 24 wks	11	25
25-29 wks	11	25
30-34 wks	07	15.90
35-39wks	13	29.54
1-7 days	02	4.54
Total	**44**	**100**

[Table/Fig-1]: Gestational age distribution of congenital anomalies

Birth weight (g)	Total cases	Percentage (%)
350-1000	19	43.18
1001-2000	12	27.27
2001-3000	10	22.72
3001-4000	03	6.81
Total	**44**	**100**

[Table/Fig-2]: Birth weight distribution of congenital anomalies

Sirenomelia and OEIS (Omphalocele- Exstrophy-Imperforate anus-Spinal defects) complex was seen. 3 cases of diaphragmatic hernia & 2 cases of congenital Atrial Septal Defect were noted. Also encountered were 2 cases of congenital cystic adenomatoid malformation of lungs and 1 case of infantile hemangioendothelioma liver [Table/Fig-3].

One case of Arnold Chiari malformation was encountered in which lower medulla, vermis and cerebellum were herniating through foramen magnum into the upper cervical canal with congenital hydrocephalus. This was of type 2 Chiari malformation which is the commonest of all four types [6].

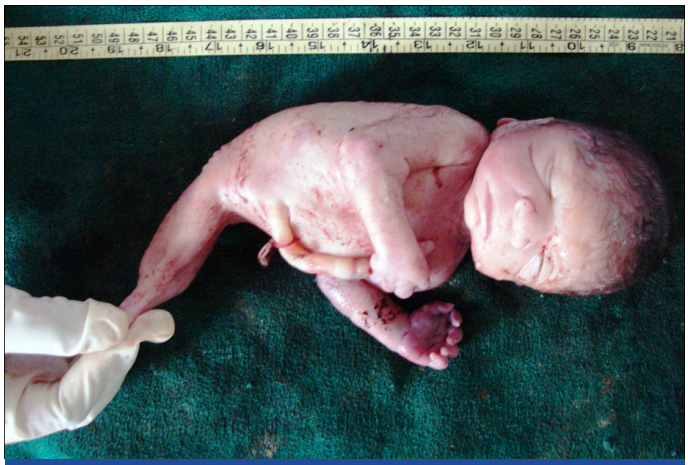
The Prune Belly syndrome comprised of wrinkled abdomen, absent anterior abdominal wall muscles, empty scrotal sac, rudimentary penis and imperforate anus. Left kidney showed multiple cysts, and microscopy revealed multicystic renal dysplasia. Section from cystic mass at the inferior aspect of bladder showed features of primitive uterine endometrium, also seen were clusters of cells with vacuolated cytoplasm, large vesicular nucleus, prominent nucleoli suggestive of primordial ovarian follicles, favouring the diagnosis of female pseudohermaphrodatism (presently called as 46 XX DSD that is Disorders of Sexual Development as recommended by Consensus Statement in 2006) [5]. In Meckel Gruber syndrome, the classical triad was present which included posterior encephalocele , also diagnosed on ultrasonography, upper limb polydactyly and diffuse cystic dysplasia along with pulmonary hypoplasia, ductal plate malformation liver and penile agenesis. Thanatophoric Dysplasia type 1, fetus had large head with frontal bossing, narrow thorax, depressed nasal bridge, generalized edema, rhizhomalic shortening of lower limbs [Table/Fig-4] and section from femur growth plate reveals marked retardation of growth zone, fibrous band noted at the periphery of the physeal growth plate, with disordered and hypertrophic chondrocytes. The case of Mermaid syndrome demonstrated imperforate anus, single umbilical artery and bilateral renal agenesis [Table/Fig-5] with X ray showing single lower limb with only 2 bones. OEIS complex was diagnosed on the findings of omphalocele, exstrophy of the cloaca, imperforate anus, and spinal defects which included meningomyelocele [Table/Fig-6].

Prenatal ultrasound finding were available in 39 cases. Autopsy diagnosis confirmed the prenatal ultrasound diagnosis in 35 cases

Congenital anomalies	Associated anomalies	Number of cases (n=44)
1) CNS Defects		**15 (34.09%)**
a) Meningocele	Rachischisis	2
b) Anencephaly		7
c) Anencephaly with meningocele		1
d) Meningomyelocele		1
e) Microcephaly and encephalocele		1
f) Arnold chiari malformation	Congenital Hydrocephalus	1
g) Absent corpus callosum		1
h) Congenital Hydrocephalus	Spina bifida	1
2) Renal Defects		**9(20.45%)**
a) Renal agenesis		
- Unilateral	Imperforate anus	1
- Bilateral	Imperforate anus, ambiguous genitilia, SUA*	1
b) Polycystic kidney disease		
- Unilateral	Imperforate anus, polydactyly, CTEV †, SUA*	1
- Bilateral	Liver plate malformation, polydactyly	2
c) Wilms tumor	DORV ‡	1
d) Obstructive uropathy (PUV)	-ASD §(secundum), CTEV† -Hydronephrosis, hydroureter	2
e) Horse shoe kidney	Hydrops fetalis	1
3) Multiple Congenital Anomalies	**1)** Cleft lip, depressed nasal bridge, low set ears, polydactyly, syndactyly, MS†† **2)** Anencephaly with multicystic renal dysplasia **3)** Anencephaly, diaphragmatic hernia & facial deformities **4)** Low set ears & polydactyly **5)** Hydrocephalus with low set ears & cleft lip **6)** Sacrococcygeal teratoma with SUA* **7)** HMD ¶ with SUA * & thoracolumbar scoliosis	**7(15.91%)**
4) Syndromes		**5 (11.36)**
a) Prune Belly syndrome		1
b) Meckel Gruber syndrome		1
c) Sirenomelia/ Mermaid syndrome		1
d) Thanatophoric dysplasia Type 1		1
e) OEIS**		1
5) Diaphragmatic Hernia	Shortened cervical spine(C1-5 fusion)	**3 (6.82%)**
6) Cardiac Defects		**2 (4.54%)**
a) ASD (Secondum)	Choanal atresia	1
b) ASD With MS††	Hypoplastic left heart syndrome	1
7) Respiratory Causes	Cystic adenomatoid malformation of lung	**2 (4.54%)**
8) Infantile Hemangioendothelioma		**1(2.27%)**

[Table/Fig-3]: System wise distribution of congenital anomalies.
* Single umbilical artery, † Congenital Talipes Equino Varus, ‡ Double Outlet Right Ventricle, § Atrial Septal Defect, ¶ Hyaline Membrane Disease, * Omphalocele- Exstrophy-Imperforate anus-Spinal defects, †† Mitral Stenosis

[Table/Fig-4]: Thanatophoric Dysplasia Type 1- large head with frontal bossing, narrow thorax, depressed nasal bridge, generalized edema, shortening of lower limbs



[Table/Fig-5]: Mermaid syndrome – Fetus showing flexed single lower extremity, shield chest and lack of external genitilia

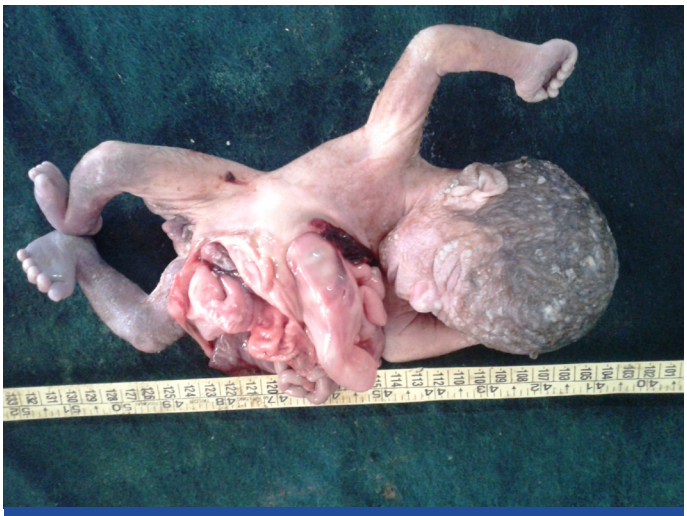
and in 13 cases additional findings were observed. In 4 cases there was discordance with prenatal ultrasound diagnosis. [Table/Fig-7].

DISCUSSION

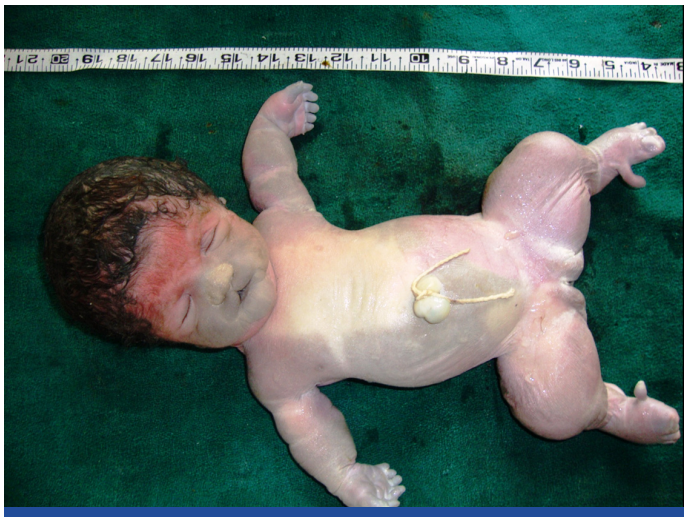
Fetal autopsy significantly contributes to the diagnosis of Intrauterine fetal death and congenital anomalies are a major cause of perinatal death [3]. In the present study of 100 perinatal autopsies, 44 cases of congenital anomalies were encountered with M:F ratio of 1:1.5. The most common mode of death was therapeutic termination of pregnancy (36.36%) and CNS malformations were most common indication for the same. The gestational age of most of the fetuses with congenital anomalies ranged from 35-39 wks & birth weight range 350-1000g. The most common defects were of Central Nervous System, seen in 15 cases (34.09) which correlates with the study of Kaiser et al., [7] and Tomatir et al., [9] [Table/Fig-8]. The most common defect was Anencephaly with 11 cases (25%), which was accurately diagnosed with Ultrasonography.

The next common anomalies were of Renal system accounting for 9 cases (20.45%) which included renal agenesis, polycystic kidney disease, Wilms tumor, obstructive uropathy and horseshoe kidney which was incidently observed in a case of Hydrops Fetalis. The finding is also supported by study conducted by Sankar & Phadke where urinary tract malformations constituted the second most common group of anomalies [1].

There were 7 cases(15.91%) of multiple malformations [Table/Fig-9] not fitting into any specific diagnosis, 5 cases (11.36%) of



[Table/Fig-6]: Fetus with omphalocele and club foot in a case of OEIS complex



[Table/Fig-9]: A case of multiple malformations including cleft lip, depressed nasal bridge, low set ears, polydactyly and syndactyly

syndromes diagnosed as Prune Belly syndrome, Meckel Gruber syndrome, Thanatophoric Dysplasia Type 1, Mermaid syndrome or Sirenomelia and OEIS complex, 3 cases (6.82%) of diaphragmatic hernia, 2 cases (4.54%) of congenital heart defects and 2 cases (4.54%) of congenital cystic adenomatoid malformations lung. A case of Infantile hemangioendothelioma liver [Table/Fig-10] was encountered.

The Prune Belly syndrome encountered in this study was associated with female pseudohermaphrodatism (46 XX DSD) [5] which is extremely rare with only 4 reported cases so far [10]. Meckel Gruber syndrome, a lethal rare autosomal recessive disorder, characterized by an occipital encephalocele, cystic dysplastic kidneys and polydactyly (constituting classical triad). Associated features that can be present are ductal plate malformation liver, ambiguous genitilia and hypoplastic lungs which were all seen in this case. Over 200 cases has been reported so far [11].

Thanatophoric dysplasia is one of the most common and severe form of dwarfism. It is always lethal; most of them die within a few hours after birth [12]. The case seen in the present study was diagnosed to be of type 1.

Sirenomelia represents a severe form of caudal regression and is comprised of Potter's facies, single umbilical artery, bilateral renal agenesis, absent bladder and fused lower limb [13] and generallty classified as Simpus Apus, Simpus Unipus and Simpus Dipus

USG Findings	No. of Cases = 39	(%)
Confirmed No Change in Diagnosis Added to Diagnosis	35 22 13	79.54 50 29.54
Change In Diagnosis **USG Diagnosis** **Autopsy Diagnosis** 1. Cystic Hygroma Thanatophoric Dysplasia type 1 2. Fetal microcephaly with hydronephrosis B/L PCKD with microcepaly and occipital meningocele 3. Polyhydroamnios (AFI 15*) Diaphragmatic hernia posterolateral type 4. Hydrops fetalis Hypoplastic lung with Meningocele	04	9.09

[Table/Fig-7]: Comparison of USG findings with Autopsy Diagnosis

S No.	Authors	Year	Number/Total	Percentage (%)
1.	Kaiser et al [7]	2000	45/121	37
2.	Sankar and Phadke [1]	2006	60/81	74.2
3.	Grover N et al [8]	2007	72/180	40
4.	Tomatir et al [9]	2009	57/183	31.1
5.	Present study	2012	15/44	34.09

[Table/Fig-8]: Comparitive Analysis of Central Nervous Anomalies

(mermaid). The present case was of Simpus Apus type. Over 300 cases have been reported so far of which 8 cases are reported from India [14].

OEIS complex, involving omphalocele, exstrophy of the bladder, imperforate anus, and spinal abnormalities/ myelomeningocele, is a rare association with incidence of 1 in 200 000 to 1 in 250 000 births. The present case had ambiguous genitilia and club foot which are described as associated features [15].

In the present study, autopsy diagnosis confirmed Ultrasound findings in 35 cases (79.54%), among these in 13 cases(29.54%) it provided additional information while primary diagnosis was changed in 4 cases(9.09%). The findings in this study were similar to those of Sankar and Phadke [1] & Yeo et al., [17] [Table/Fig-11].

CONCLUSION

Even though the prenatal ultrasonogram reasonably predicts the malformations, fetal autopsy is essential to look for additional malformations [1]. In this study fetal autopsy helped in confirming the diagnosis of congenital malformations by antenatal ultrasound findings and identified additional findings in approximately one third of the cases.

This study confirms the utility of fetal autopsy in identifying the cause of fetal loss which will help in genetic counselling of the couple.

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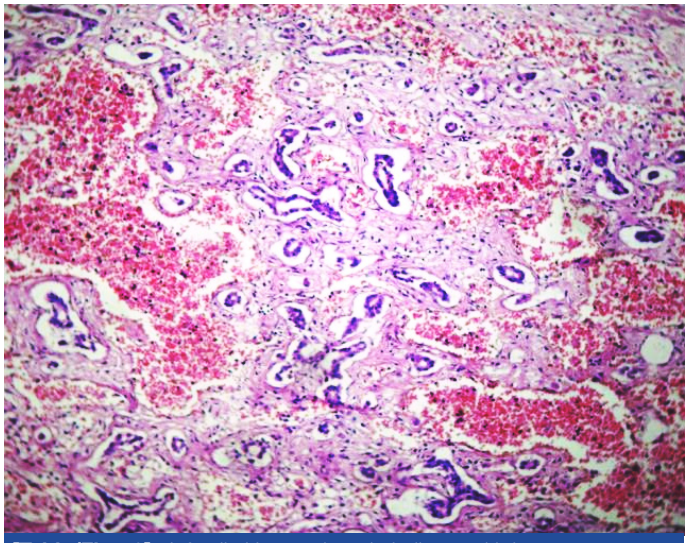

[Table/Fig-10]: Infantile Hemangioendothelioma with immature cord of hepatic cells divided vascular interconnecting channels, cavernous at places lined by plump endothelial cells. (H & E , 400 X)

S No.	Authors	Year	Confirmed USG findings		Changed primary diagnosis
			No change in diagnosis	Added to diagnosis	
1.	Pahi, Phadke et al., [16]	1998	30/61 (49.18%)	10/61 (16.39%)	21/61 (34.4%)
2.	Yeo et al., [17]	2002	27/88 (30.68%)	30/88 (34.09%)	31/88 (35.22%))
3.	Sankar & Phadke [1]	2006	55/134 (41.04%)	77/134 (57.46%)	2/134 (1.49%)
4.	Present study	2012	22/35 (50%)	13/35 (29.54%)	4/35 (9.09%)

[Table/Fig-11]: Comparitive study of Fetal Autopsy and Ultrasonography

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