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Trisomy 18: Prenatal Diagnosis and Outcome in a Tertiary Care Fetal Medicine Center in South India

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Abstract

Edwards' syndrome (trisomy 18) is the second most common aneuploidy known in humans, with an overall incidence of 1 in 6,000 live births. It occurs due to the presence of complete or part of an extra copy of chromosome 18 in all or a few body cells of the affected fetus, and it causes major anomalies in the organ systems. Despite this, an accurate diagnosis is often not made antenatally due to its very varied phenotype and the subtle nature of some of the common and consistent findings associated with this condition. This leads to lapses or delays in cytogenetic confirmation as well as delays in decision regarding termination of pregnancies with this mostly lethal fetal aneuploidy. We describe the prenatal profile of 45 confirmed cases of trisomy 18 at a tertiary fetal medicine unit. The presence of a combination of ultrasound (US) findings described in these cases will help alert sonologists and clinicians to suspect this condition and offer a confirmative cytogenetic test without delay for prenatal diagnosis. This study describes the prenatal diagnostic profile of cytogenetically confirmed trisomy 18 cases in a tertiary fetal medicine center in India. A retrospective analysis of records of 45 prenatally diagnosed trisomy 18 cases at a single tertiary fetal medicine center over a period of 11 years was done. Data were collected to describe maternal demography, indication for evaluation, major and minor US findings (trimester-wise), type of invasive test, and gestational age at diagnosis. Outcomes in terms of pregnancy termination, miscarriage, stillbirth, or livebirth were documented. Presenting at a mean maternal age and gestation age of 31.7 years and 22 + 5 weeks, respectively, 41/45 (91%) fetuses showed major and 40/45 (89%) showed minor US findings with an overall US sensitivity of 100%. The most common major US finding was a cardiac anomaly in 26 (57.8%) patients, while clenched fist with pointing index finger, observed in 17 (37.8%) cases, was the most common minor US finding. Fetal growth restriction (FGR) was noted in 20 (44.4%) patients. After cytogenetic confirmation, 37.8% underwent termination, 17.8% had a fetal demise, and only 11.1% had live birth with the longest survival noted at 5.5 months postnatally. Gender was documented in 13 fetuses with a male-to-female ratio

Keywords
- fetal trisomy 18
- cytogenetic analysis
- sonographic findings
- invasive test
- prenatal detection

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of 0.6. A meticulously performed US examination can detect a combination of anomalies that could alert the sonologist to the possibility of trisomy 18. While the US profile could vary among fetuses, an understanding of the spectrum of the anomalies commonly seen in these fetuses would enable caregivers to reach an early accurate diagnosis, and offer appropriate genetic counseling and pregnancy decisions in these cases.

Introduction

Edwards' syndrome (trisomy 18) is the second most common autosomal trisomy after Down's syndrome (trisomy 21).[1] It was first described by Edwards et al in 1960.[2] The syndrome comprises recognizable major and minor congenital structural anomalies, increased fetal and neonatal morbidity and mortality,[3,4] and significant psychomotor and cognitive disturbances in postnatal life. It is also a source of confusion and stress to the couple in its prenatal course as well as postnatally, which puts additional psychological and financial burdens on the family. Prompt prenatal diagnosis of this condition continues to remain a challenge except to trained fetal specialists, as the pattern of ultrasound (US) findings is varied and at times subtle. This often leads to missed or delayed cytogenetic confirmation and to the birth of fetuses with this lethal condition.[5] We describe the prenatal profile of 45 confirmed cases of trisomy 18 at a tertiary fetal medicine unit. The presence of a combination of the US findings described in these cases will help alert sonologists and clinicians to suspect this condition and offer a confirmative cytogenetic test without delay for prenatal diagnosis.

Materials and Methods

All genetically confirmed trisomy 18 fetuses over an 11-year period (from January 2011 through January 2022) at the Fetal Medicine Unit in Amrita Institute of Medical Sciences, a tertiary referral center in India, were included. Prenatal diagnostic profile of these cases was then retrospectively obtained from the hospital information system (HIS) and Sonocare, our US reporting database. Maternal demographic data, indications for the US examinations, and US features including all major and minor anomalies including soft markers were noted in detail. All the ultrasonographic studies in the included cases were performed by certified fetal medicine specialists with over 5 years of experience, using a curved linear array transducer and two-dimensional ultrasonography on a Voluson E10 or P8 machine from GE Healthcare, Milwaukee, WI, United States, adhering to the international norms prescribed by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).

The abnormal scan findings were grouped based on the gestational age at detection into first (before 14 weeks), second (beyond 14 weeks till 27 weeks 6 days), and third trimester (28 weeks till term) of pregnancy and categorized into major (obvious anomaly involving major organ systems) and minor findings (include milder US features that may appear as variants in normal populations when seen as isolated finding and do not constitute structural defect as such but may point toward an underlying chromosomal abnormality when associated with other minor or major US findings). Growth abnormality and cystic hygroma were included under the major group, while findings like polyhydramnios, umbilical cord abnormalities, abnormal hand positioning, choroid plexus cysts (CPCs), etc., were grouped under minor findings.

The type of confirmation testing performed (chorionic villous sampling [CVS]/amniocentesis/cordocentesis) and the outcomes of these cases were also noted. Information not available in HIS was obtained telephonically. Data thus obtained were compiled and tabulated for ease of comparison with similar studies.

This research was conducted in accordance with the Declaration of Helsinki following good clinical practice and has received ethical approval from the ethics committee of the institute. Patient consent was not required as no personal data were published.

Results

Forty-five cases met the inclusion criteria. All the patients belonged to South Asian ethnicity, hailing from different parts of Kerala or from nearby states. The mean maternal age was 31.7 years (range: 21–44 years) and the mean gestational age at presentation was 22 + 5 weeks (range: 11.3–36 weeks). Nineteen patients were primigravida including 2 who conceived with in vitro fertilization (IVF), 15 were second gravida, 6 third, 4 fourth, and 1 fifth gravida with a history of ectopic pregnancy and previous poor pregnancy outcomes.

In 11 of the 45 cases (26.7%), the indication for the US was a high-risk score for trisomy 18/trisomy 13, on aneuploidy screening. Six of these were first trimester combined screens and five were second trimester triple test screens. Six (13.3%) patients were diagnosed during a routine first/second trimester scan, whereas 27 (60%) patients were referrals for second opinion with abnormal scan findings. Seven (15.5%) cases were detected in the first trimester, 25 (55.5%) in the second trimester, and 13 (28.9%) in the third trimester.

►**Table 1** summarizes the maternal age, gestation at presentation, major and minor abnormal sonographic findings, and pregnancy outcome in all 45 cases.

Major sonographic findings commonly seen in these fetuses are described in ►**Table 2**. Out of 7 first trimester

Table 1 Sonographic features of fetuses with trisomy 18 ($n = 45$) grouped according to gestational age into trimesters at the time of examination

Sl. no.	Maternal age (y)	Gestation (wk)	Major US findings (*n*)	Minor US findings (*n*)	Pregnancy outcome
1st trimester (up to 13 wk and 6 d)					
1	25	13.4	–	Increased NT (3.5 mm), DV "a" wave reversal, unossified nasal bone (3)	MTP: physical findings—hypoplastic left thumb, right thumb absent, right radial club hand, left hypoplastic pinna, flat nasal bridge, and short neck
2	23	13	Cystic hygroma; miscarriage (2)	–	MTP: cystic hygroma; no other external findings
3	34	13.1	Cystic hygroma (1)	–	–
4	42	13.3	AVSD (1)	Increased NT (5.4 mm), DV "a" wave reversal, unossified nasal bone (3)	–
5	34	12.1	Cystic hygroma, omphalocele (2)	Unossified nasal bone, DV "a" wave reversal, tricuspid regurgitation, B/L club hand (4)	MTP
6	29	11.3	–	Increased NT (3.5 mm), DV "a" wave reversal, unossified nasal bone (3)	MTP
7	42	12.6	–	Increased NT (8.9 mm), DV "a" wave reversal, unossified nasal bone (3)	MTP
2nd trimester (14 wk to 27 wk and 6 d)					
8	23	23	Lumbosacral open spina bifida: meningo-myelocele, hypoplastic left heart (2)	Fixed flexion postures of the hand, SUA (2)	MTP
9	24	16	Cystic hygroma (1)	–	MTP
10	32	17.3	Early onset FGR (1)	B/L CP cyst, occipital flattening (2)	MTP: female, retrognathia, low-set posteriorly placed pinna
11	37	20	?DORV, left talipes, FGR (3)	–	MTP
12	37	23	Bilateral talipes, CHD (large conoventricular VSD; 2)	Echogenic kidney, micrognathia, polyhydramnios, SUA (4)	–
13	43	17.5	FGR, CHD (? DORV with VSD), umbilical hernia measuring 11 × 11 mm, right foot talipes (4)	B/L CP cyst, occipital flattening, unossified NB, both hands kept in flexed posture throughout the examination (4)	MTP
14	30	21.3	Omphalocele, VSD, right aortic arch with left ductus; ?anomalous systemic venous drainage (2)	Strawberry-shaped skull with brachycephaly, bilateral clenched fists with pointing index fingers, polyhydramnios (3)	MTP, female/270 g Externally: flat nasal bridge, long philtrum, thin upper lip, medial deviation of fingers, herniation above umbilical cord with intestinal loops herniating

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Maternal age (y)	Gestation (wk)	Major US findings (*n*)	Minor US findings (*n*)	Pregnancy outcome
15	31	21	Symmetric IUGR. DORV, hypoplastic LV and mitral valve, bilateral absent radius with short, bowed ulna resulting in mesomelic limb shortening of both upper limbs, spinal deformity at the level of lumbar vertebra with kyphoscoliosis (4)	B/L CP cyst, SUA (2)	MTP: male/470 g
16	39	21.4	Complex CHD (DORV, mitral atresia, hypoplastic LV, hypoplastic aortic arch), microcephaly, FGR (3)	SUA (1)	–
17	37	21.1	Complex CHD (single ventricle of RV type, hypoplastic LV and mitral valve), early onset FGR, hypoplastic cerebellum (3)	SUA, clenched fist with pointing index finger, micrognathia, polyhydramnios, absent stomach bubble, CP cyst left side, strawberry-shaped skull (7)	–
18	27	25	Cleft lip and palate, B/L radial ray defect, B/L talipes (3)	–	IUD: details not available
19	37	27	HLHS, FGR, B/L CTEV (3)	SUA (1)	IUD: details not available
20	25	27.5	Generalized anasarca, FGR, cerebellar hypoplasia, interhemispheric cyst, left CDH, complete agenesis of the portal venous system, horseshoe kidney (6)	Clenched fists, SUA (2)	IUD at 28 wk, male/300 g Autopsy confirmed the findings
21	34	23	Inlet VSD, pericardial effusion, mild ascites (2)	SUA, increased NT, pointing index finger, B/L CP cyst (4)	PPROM, abortion
22	38	14.4	? omphalocele	Increased NT, absent NB	MTP
23	28	23	FGR, dysgenesis of corpus callosum, AVSD, small omphalocele (4)	Strawberry skull, clenched fists with overriding fingers, unossified NB (3)	Miscarriage
24	40	16	–	Bilateral CP cysts, bilateral prominent renal pelvis measuring 3.5 mm (2)	Miscarriage at 23 wk and 6 d, female/475 g Externally: right-sided cleft palate, clinodactyly, B/L rocker bottom feet, low-set ears
25	39	14	Hydrops fetalis (1)	Increased NT, DV a wave reversal (2)	MTP

Table 1 (*Continued*)

Sl. no.	Maternal age (y)	Gestation (wk)	Major US findings (*n*)	Minor US findings (*n*)	Pregnancy outcome
26	25	14	NIH (B/L pleural effusion, ascites), AVSD (2)	B/L unossified nasal bone, increased NT (8.5 mm), tricuspid regurgitation, SUA (4)	MTP
27	21	21.6	Hypoplastic cerebellum and prominent cisterna magna, prominent CSP, cardiomegaly and AVSD (2)	B/L clenched fist with pointing index finger (1)	PPROM and abortion at 23 wk and 1 d, male/ 440 g; the rest of details not available
28	23	22.5	FGR, ventriculomegaly, TOF with pulmonary atresia (3)	Clenched fist, rocker bottom foot, brachy-cephaly, wide CSP, unilateral CP cysts, prominent GB (2)	Aborted at 23 wk and 3 d, male/430 g Autopsy: male fetus with dysmorphic features; brachyceph-aly, low-set ears, web-bing of neck, clenched fists with pointing index fingers, right flat foot, TOF with pulmonary stenosis, Meckel's diverticulum, CP cysts
29	37	23.5	HLHS, VSD (1)	Clenched fist, CP cysts, wide CSP, flat foot (4)	–
30	44	16.1	FGR, DORV with pulmonary stenosis	Micrognathia, overlap-ping digits with pointing index finger	MTP
31	34	18	B/L ventriculomegaly, posterior fossa obliterated, frontal bossing seen Meningomyelocele at the sacral area, B/L talipes, poor muscle mass (3)	Thick umbilical cord with small cyst (2)	MTP
32	40	20.6	FGR, membranous VSD Persistent LSVC draining into coronary sinus, ventricular disproportion: LV $<$ RV (2)	Brachycephalic skull Wide CSP, U/L CP cyst, SUA, B/L rocker bottom foot Bilateral overlapping digits (6)	Opted to continue with the pregnancy, had miscarriage at 24 wk
3rd trimester (28 wk to term)					
33	27	33	B/L hydronephrosis, ? bladder outlet obstruc-tion, short forearm with fixed flexion deformity on right upper limb, FGR (3)	Micrognathia, prominent cisterna magna (10.2 mm), clenched fist in the left hand, polyhydram-nios (4)	IUD at term, female fetus
34	27	30	FGR, B/L pelviectasis, CHD (hypoplastic LV? single ventricle physiol-ogy, mitral atresia and transposed outflows; 3)	Flat foot (1)	CS at term (PPROM, fetal distress): female/ 1.3 kg—NND

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Maternal age (y)	Gestation (wk)	Major US findings (*n*)	Minor US findings (*n*)	Pregnancy outcome
35	28	36	FGR, HLHS, right renal agenesis, mega cisterna magna (11 mm), cerebellar hypoplasia (4)	SUA (1)	FTVD, female/1.8 kg, externally: facial dysmorphic features, right renal agenesis, echo: right aortic arch, multiple VSDs, PDA, PAH, and hypertonia. Parents opted no active management: NND (cardiorespiratory arrest)
36	40	28	Large VSD (1)	B/L CP cyst, abnormal posturing of both hands, SUA (3)	–
37	22	33.6	ACC, prominent cisterna magna, vermian hypoplasia, large perimembranous VSD (2)	Polyhydramnios (1)	FTVD, male/2 kg, did not cry at birth, intubated, dysmorphic facies: microcephaly, low-set malformed ears, micrognathia, short sternum, ocular hypertelorism, clenched fists, and overlapping fingers ECHO: large VSD, PDA Growth at lower centiles Poor developmental milestones. Died at 5 mo and 15 d due to cardiorespiratory arrest
38	27	30.4	FGR, minimal ascites, DV agenesis (3)	Brachycephaly, strawberry shaped skull with flat occiput, mildly echogenic bowel, overriding digits with pointing index finger (4)	IUD: details not available
39	25	29.1	Symmetrical FGR, complex congenital heart disease (DORV with pulmonary atresia, right aortic arch; 2)	SUA, wide CSP (2)	–
40	25	33.5	FGR, pericardial effusion, prominent cisterna magna, arachnoid cyst, DORV, VSD with pulmonary stenosis (3)	SUA (1)	IUD, details not available
41	32	29.6	Mega cisterna magna, corpus callosum hypoplasia, FGR (2)	SUA (1)	–
42	30	31.4	Severe FGR, mega cisterna magna, cerebellar hypoplasia, ventricular disproportion, LV < RV, perimembranous VSD, hypoplastic transverse arch (3)	Brachycephaly, rocker bottom feet, clenched fist (3)	IUD at 32 wk and 3 d, female/810 g; the rest of the details are not available

Table 1 (*Continued*)

Sl. no.	Maternal age (y)	Gestation (wk)	Major US findings (*n*)	Minor US findings (*n*)	Pregnancy outcome
43	39	35.2	FGR, left CDH, crossed fused ectopic kidney (3)	CP cyst, brachycephalic skull, overlapping fingers, pointing index, polyhydramnios, enlarged cisterna magna (5)	IUD at term; details not available
44	24	34	ACC, omphalocele	Clenched fist with overlapping fingers, SUA	PPROM, preterm delivery, female/ 1.56 kg, early neonatal death
45	26	27	AC: 2SD, right CDH (2)	Prominent cisterna magna, polyhydramnios (2)	PPROM, preterm delivery at 31 wk and 2 d, male/1.06 kg, baby was dysmorphic at birth, right ear anotia, left ear normal, small jaw with high arched palate, scaphoid abdomen, large hematomas over the right and left lateral thigh present; had early neonatal death

Abbreviations: ACC, agenesis of corpus callosum; AVSD, atrioventricular septal defect; CHD, congenital heart disease; CP, choroid plexus; CSP, cavum septum pellucidum; CTEV, congenital talipes equinovarus; DORV, double outlet right ventricle; DV, ductus venosus; FGR, fetal growth restriction; FHR, fetal heart rate; FTVD, full-term vaginal delivery; GB, gallbladder; HLHS, hypoplastic left heart syndrome; LV, left ventricle; NB, nasal bone; NT, nuchal translucency; RV, right ventricle ; SUA, single umbilical artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 2 Trisomy 18: common major structural malformations[23,28]

Frequency	Organ/system	Prevalent malformation
Common (> 75%)	Heart	Septal defects, patent ductus arteriosus, and polyvalvular disease
Frequent (25–75%)	Genitourinary	Horseshoe kidney
Less frequent (5–25%)	Gastrointestinal	Omphalocele, esophageal atresia with tracheoesophageal fistula, pyloric stenosis, and Meckel's diverticulum
	Central nervous system spina bifida	Cerebellar hypoplasia, agenesis of corpus callosum, and polymicrogyria
	Craniofacial	Orofacial clefts
	Eye	Microphthalmia, coloboma, cataract, and corneal opacities
	Limb	Radial aplasia/hypoplasia

cases, 5 had major findings, whereas all 25 cases (100%) presenting in the second trimester manifested major anomalies. Cardiac anomalies (18 cases/72%) were the most common, followed by skeletal in 11 (44%), fetal growth restriction (FGR) in 10 (40%), central nervous system (CNS) in 8 (32%), gastrointestinal (GI) in 4 (16%), and 1 (4%) case each of genitourinary (horseshoe kidney), thorax (left congenital diaphragmatic hernia [CDH]), and cystic hygroma. Other findings were the following: six (24%) in this group included three fetuses with hydrops and one case each of umbilical cord cyst, mild ascites, and portal venous system agenesis. All 13 cases diagnosed in the third trimester also showed major anomalies, FGR (10 [76.9%]) being the most common presentation followed by 9 (69.2%) CNS findings, 7 (53.8%) cardiovascular system (CVS), 4 (30.8%) genitourinary findings, 2 (15.4%) thoracic anomalies, 1 (7.7%) each of GI (omphalocele), and skeletal finding (unilateral upper limb mesomelia). Three (23%) other findings noted in the third trimester were one each of mild ascites, echogenic kidneys, and ductus venosus agenesis.

Overall, the most common organ system affected by major anomalies (►**Table 3**) was CVS (57.8%), with double outlet right ventricle (DORV) being the most common finding in 7 cases, followed by hypoplastic left heart syndrome (HLHS) in

Table 3 Detection of major sonographic findings ($n = 45$)

Sl. no.	Affected organ system	First trimester ($n = 7$)	Second trimester ($n = 25$)	Third trimester ($n = 13$)	Total ($n = 45$)
1	CNS	–	8 (32%)	9 (69.2%)	17 (37.8)
	Cerebellar hypoplasia		2	2	4 (23.5%)
	Corpus callosum abnormality		1 (hypoplastic)	3 (1 hypoplastic and 2 ACC)	4 (23.5%)
	Ventriculomegaly		2	1	3
	Vermian hypoplasia		–	1	1
	NTD		2 (1 open) + 1 closed	1	3
	Microcephaly		1	–	1
	Arachnoid cyst		–	1	1
2	CVS	1 (14.3%)	18 (72%)	7 (53.8%)	26 (57.8%)
	AVSD	1	2	–	3
	DORV	–	5	2	7 (26.9%)
	HLHS	–	4 (1 hypoplastic arch) out of 4, 1 had hypoplastic arch	2 (1 hypoplastic left arch)	6 (23%)
	VSD	–	4	1	5 (19.2%)
	LV with MV hypoplasia	–	1	–	1
	Small LV, mitral atresia with TGA	–	–	1	1
	TOF with PA (PA VSD)	–	1	–	1
	Ventricular disproportion	–	1 (LV > RV)	1 (LV < RV)	2
3	Thorax/pulmonary	–	1 (4%)	2 (15.4%)	3 (6.7)
	Left CDH	–	1	1	2
	Right CDH	–	–	1	1
4	GI	1 (14.3%)	4 (16%)	1 (7.7%)	6 (13.3)
	Omphalocele	1	3	1	5
	Umbilical hernia	–	1	–	1
5	GU	–	1(4%)	4 (30.8%)	5 (11.1)
	Horseshoe kidney	–	1	1	2
	Unilateral renal agenesis	–	–	1	1
	Cross-fused ectopic kidneys	–	–	1	1
	B/L hydroureteronephrosis (?BOO)	–	–	1	1
	B/L pelviectasis	–	–	1	1
6	Skeletal	–	11 (44%)	1 (7.7%)	12 (26.7)
	Talipes	–	6 (2 unilateral), 4 bilateral	–	6 (50%)
	Kyphoscoliosis	–	1	–	1
	Upper limb mesomelia	–	2 (1 unilateral), 1 bilateral	1 (unilateral)	3
	B/L radial ray defect	–	1	–	1
	B/L cleft lip and palate	–	1	–	1
7	Cystic hygroma	3 (42.8%)	1 (4%)	–	4 (8.9%)
8	FGR	–	10 (40%)	10 (76.9%)	20 (44.4)
9	Others	–	6 (24%; 3 hydrops, 1 umbilical cord cyst, 1 ascites, 1 portal venous system agenesis)	3 (23%; 1 ascites, 1 echogenic kidneys, 1 DV agenesis)	9 (20%)

Abbreviations: ACC, agenesis of corpus callosum; AVSD, atrioventricular septal defect; BOO, bladder outlet obstruction; CDH, congenital diaphragmatic hernia; CNS, central nervous system; CVS, cardiovascular system; DORV, double outlet right ventricle; FGR, fetal growth restriction; GI, gastrointestinal; GU, genitourinary; HLHS, hypoplastic left heart syndrome; NTD, neural tube defect; PA, pulmonary atresia; TOF, tetralogy of Fallot; UL, upper limb; VSD, ventricular septal defect; TGA, Transposition of the great arteries.

Table 4 Detection of minor sonographic findings ($n = 45$)

Sl. no.	Sonographic finding	First trimester ($n = 7$)	Second trimester ($n = 25$)	Third trimester ($n = 13$)	Total ($n = 45$)
1	Increased NT	4 (57.1%)	4 (16%)	–	8 (17.8%)
2	Absent NB	5 (71.4%)	4 (16%)	–	9 (20%)
3	DV "a" wave reversal	5 (71.4%)	1 (4%)	–	6 (13.3%)
4	TR	1 (14.3%)	1 (4%)	–	2 (4.4%)
5	SUA		9 (36%)	6 (46.1%)	14 (31.1%)
6	Prominent cisterna magna (isolated CNS finding)	–	–	3 (23.1%)	3 (6.7%)
7	Wide CSP (isolated CNS finding)	–	3 (12%)	1 (7.7%)	4 (8.9%)
8	CP cysts	–	9 (36%)	2 (15.4%)	11 (24.4%)
9	Brachycephaly/strawberry-shaped skull	–	6 (24%)	3 (23.1%)	9 (20%)
10	Clenched fist with pointing index finger	–	11 (44%)	6 (46.1%)	17 (37.8%)
11	Rocker bottom feet/flat feet	–	3 (12%)	2 (15.4%)	5 (11%)
12	Polyhydramnios	–	3 (12%)	4 (30.8)	7 (15.5%)
13	Micrognathia	–	3 (12%)	1 (7.7%)	4 (8.9%)
14	Others	–	2 (1 mild-pelviectasis, 1 and prominent GB)	1 (EB)	3 (6.7%)

Abbreviations: CNS, central nervous system; CP cyst, choroid plexus cyst; CSP, cavum septum pellucidum; GB, gallbladder; NB, nasal bone; NT, nuchal translucency; SUA, single umbilical artery; TR, tricuspid regurgitation; DV, ductus venosus.

6 cases, ventricular septal defect (VSD) in 5 cases, and atrioventricular septal defect (AVSD) in 3 cases. FGR was the second most common finding, noted in 44.4% of fetuses, followed by CNS findings in 37.8% fetuses (cerebellar hypoplasia and corpus callosum abnormality in 4 fetuses each and ventriculomegaly and NTDs in 3 fetuses each being commonly noted). Skeletal findings were noted in 26.7% (with talipes being the most common finding), GI findings in 13.3% (omphalocele being the most frequent finding), thoracic in 6.7% (2 left and 1 right CDH), urinary system findings in 11.1% fetuses, cystic hygroma in 8.9%, and other findings in 20% as described in the table.

Minor sonographic findings with trimester-wise distribution are shown in ►**Table 4**. A clenched fist with a pointing index finger seen in 17 (37.8%) cases was the most common finding, followed by a single umbilical artery in 14 (31.1%) fetuses. CPCs were seen in 11 (24.4%) cases, unossified nasal bone in 9 (20%) cases, increased nuchal translucency in 8 (17.8%) cases, ductus venosus "a" wave reversal in 6 (13.3%) cases, polyhydramnios in 7 (15.5%) cases, rocker bottom feet in 5 (11%) cases, wide cavum septum pellucidum (CSP) and micrognathia in 4 (8.9%) cases each, prominent cisterna magna in 3 (6.7%) cases, and tricuspid regurgitation in 2 (4.4%) cases. Other findings like mild pelviectasis, prominent gallbladder, and echogenic bowel were noted in three (6.7%) fetuses.

Direct fetal testing was done in all the cases to reach the diagnosis of trisomy 18. CVS was done in 9 (20%) cases, amniocentesis in 34 (75.5%) cases, and cord blood sampling in 2 (4.4%) cases (►**Table 5**).

►**Table 6** shows details about the outcome of our study. Five (11.1%) of our patients had a spontaneous miscarriage, and 17 (37.77%) underwent medical termination after

Table 5 Type of invasive test employed for cytogenetic analysis ($n = 45$)

Sl. no.	Invasive test ($n = 45$)	n	%
1	Chorionic villous sampling	9	20
2	Amniocentesis	34	75.5
3	Cordocentesis	2	4.4

Table 6 Outcome of prenatally diagnosed trisomy 18 cases ($n = 45$)

Outcome, $n = 45$	n (%)
Spontaneous miscarriage	5 (11.1)
TOP/MTP	17 (37.77)
IUD	8 (17.8)
Live birth	5 (11.1)
Lost to follow-up	10 (22.2)

Abbreviations: IUD, intrauterine death; MTP, medical termination of pregnancy; TOP, termination of pregnancy.

confirming the cytogenetic result. Ten (22.2%) patients did not follow up further with us and hence the outcome could not be traced in these cases. Eight (17.8%) patients had intrauterine fetal demise and five (11.1) were live born. Postnatal details were available in 13 cases with more females (8) than males (5), with a male-to-female ratio of 0.62. External examination of these available cases showed that most of the abortuses/stillborn/newborn babies with trisomy 18 showed characteristic facial dysmorphic features including ear anomalies. All live born babies died postnatally due to cardiorespiratory arrest and the longest survival noted was till 5.5 months of age in one case (male baby). The rest succumbed to complications of the syndrome in the early neonatal period. These details are recorded in ►**Table 1** alongside the prenatal sonographic findings.

Discussion

With an overall prevalence of 1 in 6,000 live births,[1] Edwards' syndrome is more common in females than in males, likely due to higher male fetal losses than female fetal losses.[3,4] Furthermore, live born females show better survival than live born males.[6]

Trisomy 18 can be complete, mosaic, or a partial trisomy.[1,6–9] In complete trisomy, the most common form (~94% of cases), every cell of the fetus contains three entire copies of chromosome 18. The extra chromosome is most often of maternal origin and it occurs due to nondisjunction (error of segregation) during meiosis or postzygotic mitosis. Although the cause of nondisjunction is unknown, its frequency increases with advanced maternal age.[10] In mosaic trisomy 18 (< 5% cases), both normal trisomy and complete trisomy coexist in different cell lines and the phenotype is extremely variable, ranging from apparently normal phenotype to complete trisomy 18 phenotypic expression.[11] The partial trisomy form accounts for 2% and shows the presence of a segment of the chromosome 18 long arm in triplicate, often resulting from a balanced translocation or inversion carried by one parent. The extra genetic material disrupts the normal course of development, causing the characteristic features of trisomy 18 affecting various organ systems. Trisomy 18 is usually considered a fatal condition as most of these cases succumb to the major defects.

The routinely used first trimester aneuploidy screening based on maternal age, serum markers with assessment of nuchal fold, and nasal bone identifies 66.7% cases of trisomy 18, and the detection rate increases to 83.3% by including evaluation of the abnormal ductus venosus "a" wave and tricuspid valve regurgitation.[12] Some structural anomalies like omphalocele (21%), abnormal hand posturing (6%), megacystis (4%), and abnormal four-chamber view (4%) can also be detected in the first trimester US.[13] From the second trimester onward, prenatal sonographic findings of trisomy 18 consist of growth retardation, polyhydramnios, brachycephaly (strawberry skull), abnormal posturing of hand fingers (overlapping second and fifth fingers on the third and fourth fingers, respectively, giving the appearance of pointing index finger), CPC, cardiac defects, omphalocele, and single umbilical artery.[14–16] Growth restriction and polyhydramnios become more prevalent in the third trimester. More than 30% of cases show abnormal hand posturing as described earlier, 33% of cases show a single umbilical artery, and CPCs are found in 50% of cases.[14,16] CPC, in most cases (80–90%), is associated with other US findings and isolated in only approximately 5% of cases.[17] The Edwards syndrome fetuses have a high risk of miscarriage or stillbirth. This rate is high for cases detected by abnormal US findings.[14]

Abnormal finger positioning may lead to misdiagnosis of distal arthrogryposis type I and Pena–Shokeir syndrome type I (also shows polyhydramnios). Major malformations may overlap with features of coloboma, heart defects, atresia choanal, growth retardation genital abnormality, ear anomaly (CHARGE) syndrome. Fetal akinesia sequence may be termed as pseudo-trisomy 18 syndrome.

Suspicion of Edwards' syndrome on prenatal US should be followed by explaining to the couple the importance and methods of confirmation by direct fetal testing in the form of CVS/amniocentesis. Molecular diagnosis is important to categorize the syndrome into its subtype as the recurrence risk in families with partial trisomy 18 could be higher compared with complete trisomy 18 (which shows < 1% recurrence risk) depending on genomic rearrangements in one of the parents in the form of translocation or inversion. Sending them for genetic counseling would help them better understand the genetic abnormality. Once the diagnosis is confirmed, the couple should be explained the severity and possible progress of fetal anomalies so as to help them make an informed choice regarding termination or continuation of the pregnancy. In case they opt for continuation, they should be made aware of the adverse outcomes. A predelivery consultation with a neonatologist would help them to make practical decisions concerning newborn management such as resuscitation, life support, and surgical intervention.

Prenatally, trisomy 18 fetuses, particularly those with major structural malformations, have high risk of miscarriages and stillbirth.[14] Approximately 50% of babies with trisomy 18 live longer than 1 week, but only 5 to 10% of children survive beyond the first year. The major causes of death are sudden death due to central apnea, cardiac failure due to cardiac malformations, and respiratory insufficiency due to hypoventilation, aspiration, upper airway obstruction, or, likely, the combination of these and other factors.[18–22] Those who survive through infancy will invariably have growth lag and feeding difficulties,[23] respiratory problems like laryngomalacia or tracheobronchomalacia, and obstructive sleep apnea,[6,7] vision and hearing problems, increased risk of neoplasia like Wilms' tumor and hepatoblastoma.[7,24–26] Significant developmental delay is always present with a profound degree of psychomotor and intellectual disability. Mobility may be restricted with distal limb deformities and contractures (talipes equinovarus and calcaneovalgus) in 50% of trisomy children, and 5 to 10% of cases show major limb malformations like radial aplasia and preaxial limb defects.[27] ►**Table 2** summarizes the most common major malformations seen in cases of trisomy 18.[23,28]

Through this retrospective descriptive study performed at a single tertiary fetal medicine center in south India, we have

Table 7 Summary of trisomy 18 cases detected on prenatal sonography in the literature

Sl. no.	Study	No. of cases (*n*)	Mean maternal age, y (range)	Mean fetal gestation, wk (range)	Most common ultrasound (US) finding (%)	Sensitivity in detecting trisomy 18 (%)
1	Shields et al[31]	35	34 ± 8 (16–47)	17.3 ± 2.0	Abnormal position of fingers (89)	86
2	Brumfield et al[32]	30	32	14–22	Choroid plexus (CP) cyst (43)	70
3	Yeo et al[30]	38	37 (21–42)	20.1 (14.6–36.3)	Shortened ear length <10th percentile (96)	100
4	Bronsteen et al[29]	49	–	15–27	Anomalies of the brain (82)	86 at first US scan, 100 at follow-up
5	Viora et al[15]	71	35.4 (20–45)	11–25	Abnormalities of extremities (40.8)	91.5
6	Dézsi et al[33]	10	33.2 (23–46)	11 (8.2–17.2)	Increased nuchal translucency (NT), > 3 mm (70)	100
7	This study	45	31.7 (21–44)	22.5 (11.3–36)	Cardiovascular anomaly (57.8)	100

tried to bring out the characteristic profile of prenatally diagnosed 45 cases of trisomy 18 in terms of their presentation, evaluation, and outcome.

Several studies (►**Table 7**) have described the types and frequencies of US anomalies associated with trisomy 18. Our study had a comparable outcome with an overall 100% sensitivity of prenatal sonographic findings as an indication for evaluation for fetal aneuploidy. Major findings were noted in 41 (91%) cases and minor findings were noted in 40 (90%) cases, with each case showing one or more minor or major findings. Major findings ranged from zero to six in number, while minor findings ranged from zero to seven. It must be noted that all scans were performed by a skilled sonographer and the most common indication for referral (►**Table 8**) to our center was abnormal sonographic finding (60%), followed by abnormal aneuploidy screen in 11 of 12 (91.6%); 1 case showed a false-negative triple test and 6 (13.3%) cases were detected on routinely scheduled scans. At presentation in our study, the mean maternal age was 31.7 years (range: 21–44) and the mean gestation was 22.5 weeks (range: 11.3–36 weeks), which was comparable to other similar studies. The overall 100% sensitivity of US detection was actually better than other similar studies where the sensitivity ranged from 70 to 100%.[15,29–32]

Table 8 Indications for referral to the sonography unit (45 fetuses with trisomy 18)

Indication for sonography	*n* (%)
Routine scheduled first/second trimester scan	6 (13.33)
Abnormal aneuploidy screen results	11/12[a] (91.66)
Second opinion for abnormal ultrasound findings	27 (60)

[a]Aneuploidy screening was recorded in 12 cases.

The most common major sonographic finding and overall the most common finding in our study were cardiovascular anomaly noted in 26 (57.8%) cases as compared with other studies where it was increased nuchal translucency (NT) greater than 3 mm in 70%,[33] abnormalities of extremities in 40.8%,[15] anomalies of the brain (82%),[29] shortened ear length less than 10th percentile (96%),[30] CPC (43%),[32] and abnormal position of fingers (89%).[31] The most common cardiac finding in our study was DORV (26.9%) followed by HLHS (23%) and VSD (19.2%). Yeo et al[30] had AVSD as the most common cardiac finding (40.6%), while Bronsteen et al[29] noted VSD as the most frequent cardiac anomaly in 82% of their cases.

FGR was seen in 20 (44.4%) of our cases, while Viora et al[15] noted it in 35.2% and Yeo et al[30] in 63% of their cases. The FGR rates in our case might be lower as seven of the cases were detected in the first trimester by which FGR does not usually set in and most of our second trimester cases opted for MTP immediately after diagnosis, few of which would otherwise progress to FGR in their late second and third trimester.

CNS anomalies were noted in 17 (37.8) cases in our study where cerebellar hypoplasia and corpus callosum abnormality were the most common findings noted in four (23.5%) cases each. Bronsteen et al[29] documented brain anomalies in 82% of cases, with CPC being the most common brain finding (51%) followed by cerebellar hypoplasia (45%).

Fifty percent of our 12 (26.7%) skeletal anomalies were talipes (4 bilateral and 2 unilateral) as compared with Viora et al[15] who reported abnormalities of extremities (clenched or closed hands, abnormal position or appearance of toes, overlapping digits) in 40.8% of cases. The lower prevalence of this finding in our study is because we reported abnormal structural defects under this heading, whereas Viora et al[15] reported abnormal hand posturing under this heading. The

actual prevalence of abnormal skeletal findings in their study was 14.1%. Other findings in our study were omphalocele, accounting for 83.3% of 6 GI anomalies, 3 (6.7%) cases of CDH, and 5 (11.1%) cases of renal anomalies. Other findings like mild ascites, umbilical cord cyst, DV agenesis, portal venous system agenesis, and echogenic kidneys and bowel accounted for 9 (20%) of the total findings. These findings were comparable to results noted by Yeo et al[30] and Viora et al.[15]

Among minor sonographic findings, we found that clenched fists with pointing index finger were the most common finding noted in 17 (37.8%) fetuses. This was followed by a single umbilical artery in 14 (31.1%), CPC in 11 (24.4%), absent nasal bone and strawberry-shaped skull in 9 (20%), increased NT in 8 (17.8%), polyhydramnios in 7 (15.5%), and DV "a" wave reversal in 6 (13.3%) cases. These findings were comparable to similar previous studies listed in ►**Table 7**.

When pregnancy outcomes were compared, this study showed a higher rate of medical termination in 17 (37.77%) cases postdiagnosis, 8 (17.8%) cases had IUD, and only in 5 (11.1) cases resulted in live born babies, most of which succumbed in the early neonatal period except 1 baby who died at 5.5 months of life due to cardiorespiratory failure. The male-to-female ratio of 0.6 in our study was similar to other previous studies.

An attempt was made in this retrospective descriptive study to analyze the various prenatal presentations including scan findings. It is important to mention here that this study had its own limitations pertinent to its nature, and a prospective study in the subject matter would definitely throw more light on the parameters that show variation in presentation in various other studies compared here (►**Table 7**).

Conclusion

With advanced US equipment, prenatal US has become a valuable tool to detect a variety of congenital structural malformations throughout gestation. Awareness of the different organ system involvement and the usual gestation at presentation in trisomy 18 cases as depicted in this study should improve prenatal detection of these fetuses. This information is particularly useful in evaluating patients considered to be at increased risk of trisomy 18 on the basis of age, aneuploidy screen result, and other common sonographic findings (like CHDs, FGR) and markers such as abnormal hand posturing, skull shape, and CPCs. Early sonographic identification of the major structural defects and confirming the cytogenetic diagnosis of trisomy 18 should lead to appropriate genetic counseling and allow for more reasonable management of affected pregnancies.

Ethics Approval

Ethical approval for this study was granted by the Ethics (Medical Research) Committee Office, Amrita Institute of Medical Sciences & Research Center, Cochin, Kerala, India.

Conflict of Interest

None declared.

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