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DiGeorge Syndrome: Prenatal Diagnosis and Outcome in a Tertiary Care Fetal Medicine Center

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Abstract

Introduction DiGeorge syndrome (DGS), caused by defects during embryonic development, is primarily sporadic and detectable via prenatal ultrasound, which reveals features like cardiovascular abnormalities and thymic hypoplasia. Early diagnosis of deletion 22q11.2 aids in effective prenatal, perinatal, and postnatal care management.

Objectives The aim of this series was to delineate the common and unusual sonographic abnormalities as well as outcomes of prenatally diagnosed DiGeorge fetuses from a single tertiary care center.

Methods This is a single center retrospective study of eight fetuses detected in the mid trimester between 2012 and 2020. They were evaluated extensively for anatomic anomalies on ultrasound and diagnosed deletion 22q11.2 using fluorescence *in situ* hybridization or microarray based comparative genomic hybridization.

Results Congenital heart disease (CHD) was the primary indication for evaluation in six of eight fetuses, while one had a strong family history of DGS. The mean maternal age and gestational age were 33 years 4 months and 19 weeks 3 days, respectively. The majority (5 of 8) had conotruncal heart defects. Three of eight fetuses had extracardiac findings in varying combinations. Hypoplasia of the thymus and small for gestational age were common findings in three of eight fetuses. Lesser known associations like congenital talipes equinovarus (CTEV), choroid plexus (CP) cysts, and clenched fists with pointing index finger were noted in one fetus each, thereby expanding the fetal phenotypic spectrum. Four of eight of the families decided to terminate the pregnancy. Two of eight babies expired and the two surviving infants are doing well with near normal developmental milestones.

Conclusion Though conotruncal CHD is the most consistent finding in DGS prenatally, CTEV, polyhydramnios, clenched fists with pointing index finger, and CP cyst in association with other subtle fetal markers in the absence of CHD should raise a high index of suspicion of DGS prenatally. Early and prompt diagnosis is imperative for counseling families, enabling them in decision making, and to garner knowledge about anticipatory postnatal care.

Keywords
- DiGeorge syndrome
- deletion 22q11.2
- conotruncal defects
- congenital talipes equinovarus
- clenched fists
- choroid plexuses cysts

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Introduction

Named after the Italian American physician and pediatric endocrinologist Dr. Angelo M. DiGeorge (1965), DiGeorge syndrome (DGS) is a combination of signs and symptoms caused by a defect in the pharyngeal pouch structure during human embryo development.[1] Statistically, more than 90% of cases with deletion(del) 22q11.2 are sporadic and only a few are inherited,[2–4] which can easily be diagnosed by fluorescence in situ hybridization (FISH) or microarray based comparative genomic hybridization (aCGH).[5] Prenatal ultrasound (US) is a valuable tool in the detection of sporadic cases of DGS with sonographic features like cardiovascular abnormalities, thymic hypoplasia/aplasia, genitourinary anomalies, central nervous system (CNS) defects, skeletal deformities, fetal growth restriction (FGR), increased nuchal translucency (NT), and abnormal amniotic fluid levels. Among these, conotruncal cardiac defects are a prominent feature and are found in more than 90% of the cases.[6–8] Additionally, the detection of thymic and genitourinary abnormalities, along with other less frequently associated findings on US can enhance the detection rate of 22q11.2(del). Owing to the phenotypic diversity of DGS, a prompt and early prenatal diagnosis of 22q11.2(del) would help obstetricians, surgeons, pediatric cardiologists, neonatologists, and geneticists to plan an optimum management strategy for prenatal, perinatal, and postnatal care. We share our experience in sonographic-based prenatal diagnosis and outcomes of eight patients from a single tertiary center in South India. We also highlight a unique case diagnosed based on a clue from subtle US findings in the absence of congenital heart disease (CHD).

Materials and Methods

This was a retrospective study of eight patients who visited the feto maternal unit in a single tertiary care center in Kerala, South India, between 2012 and 2020. We analyzed the hospital database and identified eight prenatally diagnosed DGS fetuses. All patients underwent detailed anomaly scans and fetal echocardiography (ECHO) by dedicated feto maternal specialists and pediatric cardiologists using Voluson P8 and E10 machines. Genetic counseling was offered to all families by an experienced clinical geneticist at our institute concerning prenatal and postnatal care and to devise a treatment strategy. Data regarding maternal age, consanguinity, parity, inheritance, family history, sonographic findings, gestational age, mode of delivery, and postnatal outcomes were analyzed. All patients underwent amniocentesis for confirmation of 22q11.2del either by FISH with a probe specific for the TUPLE I region or microarray.

Results

All of the fetuses were diagnosed in the mid trimester following anatomic scans except one with a strong family history of DGS, who was offered genetic counseling in the early second trimester (►**Table 1**). With a mean gestational age of 19 weeks 3 days (16 weeks 05 days to 26 weeks 06 days), the majority (87.5%, 7 of 8) of the cases were singleton pregnancies excluding one which was a case of dichorionic diamniotic (DCDA) twins wherein one fetus had DGS. The mean maternal age was 33.4 years (25–36 years). Fifty percent (4 of 8) of the patients were primigravida, 25% (2 of 8) were second gravida, and the remaining 25% (2 of 8) were third gravida. Note that 87.5% (7 of 8) were nonconsanguineously married, while 12.5% (1 of 8) were married consanguineously (third degree). The 11 to 14 weeks scan of 5 patients was normal and data of 3 patients was unavailable for evaluation.

In most patients (75%, 6 of 8), CHD was the primary indication for DGS evaluation. Note that 12.5% (1) had a family history of DGS (wherein her husband and previous child were affected), and the remainder 12.5% (1) had an unusual case diagnosed on the basis of subtle US features in the absence of CHD. Most of the fetuses with CHD exhibited conotruncal anomalies (62.5%, 5 of 8), of which 37.5% (3 of 8) had tetralogy of Fallot, and 25% (2 of 8) had double outlet right ventricle (DORV). Echogenic intracardiac foci (EICF) with the right aortic arch was seen in 12.5% (1) and variants in normal cardiac anatomy like persistent left superior vena cava draining into the coronary sinus were seen in 12.5% (1). Among the fetuses with conotruncal anomalies, 25% (2 of 8) had other associated cardiac findings such as aberrant right subclavian artery seen in 12.5% (1) and pulmonary atresia with multiple aortopulmonary collaterals in 12.5% (1) (►**Table 1**). Thymic hypoplasia and small for gestation (SGA) fetuses were each identified in 37.5% (3 of 8) cases. Other extracardiac findings were seen in varying combinations in 37.5% (3 of 8) cases. CNS findings were noted in 37.5% (3 of 8) (dilated cavum septum pellucidum [CSP] in 25% [2 of 8], choroid plexus cyst in 12.5% [1]). Polyhydramnios and skeletal abnormalities were documented in 25% (2 of 8) each. Among the skeletal findings, bilateral congenital talipes equinovarus (CTEV) and clenched fists with pointing index fingers were identified in 12.5% (1) each.

Half (50%, 4 of 8) of the prenatally diagnosed DGS patients decided to terminate their pregnancy after comprehensive counseling by a multidisciplinary team of experts and none of them opted for fetal autopsy. Among the patients who continued their pregnancy, 25% (2 of 8) born at other centers, expired. One of them expired due to failure to thrive on day 14 of life and the other death, at 3 years of age, was attributed to aspiration pneumonia post CHD correction. Among the remaining 25% (2 of 8) alive babies born at our center, one has facial dysmorphism, mild developmental delay, hypoparathyroidism, stridor, and CTEV. This patient is subsequently described as a unique case and is detailed below. The other baby was born with ambiguous genitalia (micropenis and hypoplastic scrotum) along with high anorectal malformation (imperforate anus), who underwent permanent sigmoid colostomy on day 5 of life and was eventually operated on for DORV with a favorable outcome.

Here, we highlight an unusual case of a 28 year old primigravida with DCDA twins at 20 weeks 4 days, who reported to us for a second opinion for bilateral CTEV in one fetus. She was nonconsanguineously married for 2.5 years

Table 1 Overview of indications, obstetric history, prenatal scan findings, and outcomes of prenatal diagnosed 22q11.2DS

Patient no.	Indication	Obstetric history and consanguinity	Gestation	Scan findings	Microarray/FISH result	Outcome
P1	CHD	G1, NCM	Singleton, 20W4D	EICF, right aortic arch	Deletion of 22q11.2	TOP
P2	CHD	G3P2L2, NCM	Singleton, 25W2D	DORV with severe PS, PLSVC, clenched fists and pointing index finger, polyhydramnios, SGA	Deletion of 22q11.2	FTND, male/2.6 kg, micropenis with hypoplastic scrotum and imperforate anus, karyotype: 46 XY, permanent colostomy. Staged correction of CHD done with fair outcome, mild developmental delay. Alive
P3	CHD	G1, 3rd degree consanguinity	Singleton, 22W5D	DORV-TGA like, severe pulmonary stenosis, ARSA	Deletion of 22q11.2	Preterm 32 weeks (PPROM) cesarean, female/1.5 kg, CHD corrected with fair outcome. Expired at 3 years of age due to aspiration pneumonia
P4	CHD	G3P1L1A1, NCM	Singleton, 26W6D	TOF, SGA	Deletion of 22 q 11.2	Preterm delivery at 32 weeks. Expired on day 14 due to failure to thrive
P5	CTEV	G1, NCM	DCDA, 20W	Polyhydramnios, dilated CSP, cavum vergae, thymic hypoplasia, bilateral CTEV, SGA	Deletion of 22q11.2	Preterm 36 weeks cesarean delivery at, male/1.95 kg, low set ears, squared nasal tip, micrognathia. Laryngomalacia, CTEV, hypoparathyroidism, status post tendo-Achilles tenotomy. Mild developmental delay. Alive
P6	CHD	G1, NCM	Singleton, 21W6D	TOF with pulmonary atresia, CP cysts	Deletion of 22q11.2	TOP
P7	Family history (husband and previous child with DGS)	G2P1L1, NCM	Singleton, 20W5D	PLSVC draining into CS, dilated CSP, thymic hypoplasia	Deletion of 22q11.2	TOP
P8	CHD	G2P1L1, NCM	Singleton, 20W5D	TOF with pulmonary atresia, MAPCAs, tortuous DA, thymic hypoplasia	Deletion of 22q11.2	TOP

Abbreviations: A, abortion; ARSA, aberrant right subclavian artery; CHD, congenital heart disease; CP, choroid plexuses; CS, coronary sinus; CSP, cavum septum pellucidum; CTEV, congenital talipes equinovarus; DA, ductus arteriosus; DCDA, dichorionic diamniotic; DGS, DiGeorge syndrome; DORV, double outlet right ventricle; EICF, echogenic intracardiac foci; FISH, fluorescence in situ hybridization; FTND, full-term normal delivery; G, gravida; L, living; MAPCAs, multiple aortopulmonary collaterals; NCM, nonconsanguineous; P, para; PLSVC, persistent left superior vena cava; PPROM, preterm premature rupture of membranes; PS, pulmonary stenosis; SGA, small for gestational age; TGA, transposition of great arteries; TOF, tetralogy of Fallot; TOP, termination of pregnancy.

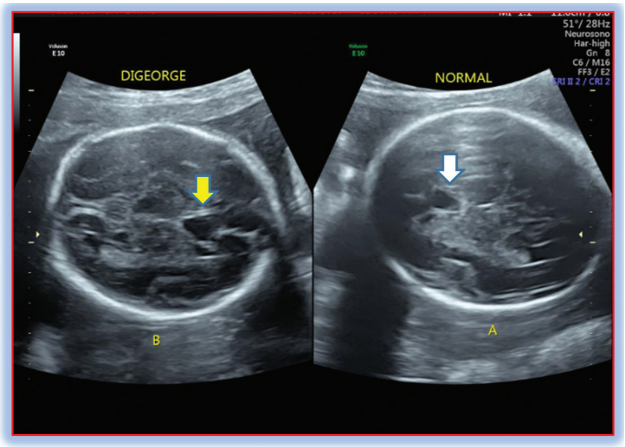

Fig. 1 Dilated cavum septum pellucidum (yellow arrow) in a fetus (twin b) with 22q11.2 deletion syndrome and normal cavum septum pellucidum (white arrow) in a normal fetus (twin a) in axial view.

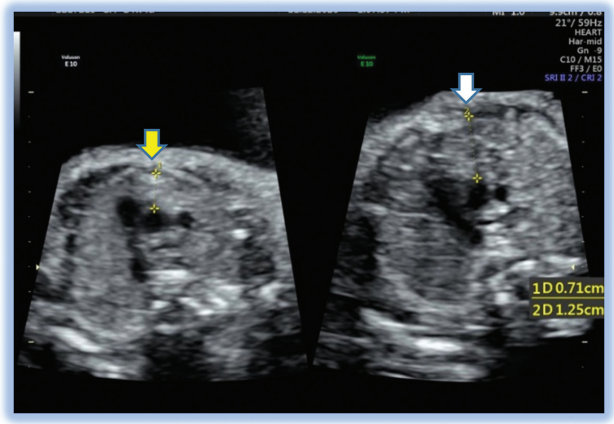

Fig. 3 Three vessel cardiac view showing hypoplastic thymus (yellow arrow) in twin b and normal thymus (white arrow) in twin a.

and conceived this pregnancy following intrauterine insemination. Her NT scan was normal, but the anomaly scan done elsewhere revealed bilateral CTEV in one fetus.

Detailed anatomic scan done at our center showed twin A with EICF in the left ventricle and twin B had dilated CSP (►**Figs. 1** and **2**) with prominent cavum vergae, bilateral CTEV (►**Fig. 4**), and hypoplastic thymus (►**Fig. 3**). With a provisional diagnosis of 22q11.21(del) in twin B, amniocentesis for aCGH confirmed our diagnosis. Subsequent scans at 24 and 29 weeks additionally revealed polyhydramnios and at 36 weeks 2 days the estimated fetal weight for twin B was < 10th centile (SGA).

She underwent an emergency cesarean for breech presentation and delivered a normal female baby weighing 2.76 kg and a DGS affected male baby weighing 1.95 kg. The affected baby had phenotypic features of DGS, viz., hypertelorism, bilateral dysplastic pinna, squared nasal tip, long fingers, micrognathia, and bilateral CTEV. Biochemical investigations revealed normal serum calcium, phosphorus, thyroid, and parathyroid levels. US abdomen, neurosonogram, and ECHO were all normal. Both neonates were discharged after an uneventful stay in the neonatal intensive care unit.

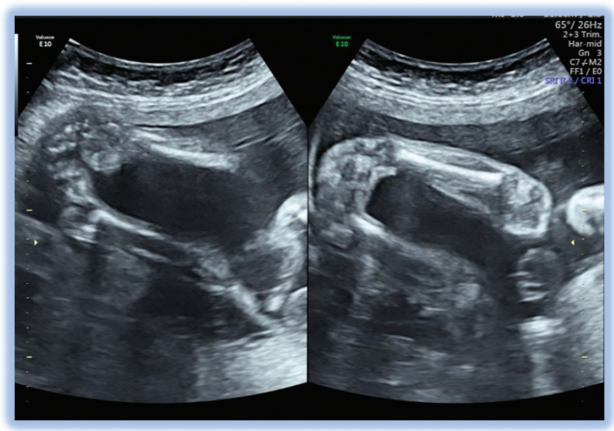

Fig. 4 Bilateral lower limbs show congenital talipes equinovarus in a fetus with DiGeorge syndrome (twin b).

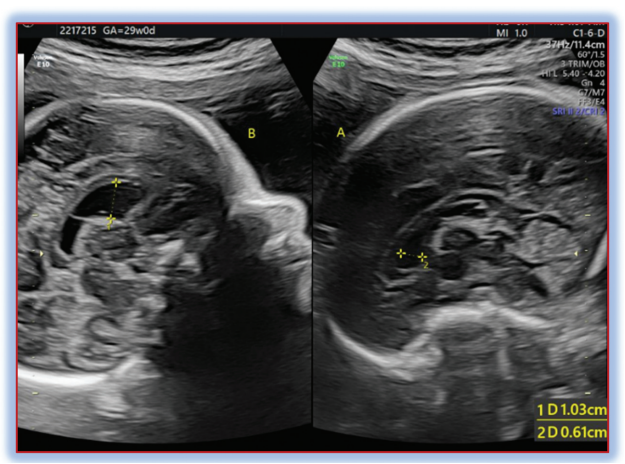

Fig. 2 Dilated cavum septum pellucidum (yellow arrow) in a fetus (twin b) with 22q11.2 deletion syndrome and normal cavum septum pellucidum (white arrow) in a normal fetus (twin a) in sagittal view.

After 2 weeks, the affected baby boy was brought back to the neonatal unit with feeding difficulty and stridor. He was detected to have hypoparathyroidism and was initiated on medications. An ear, nose, and throat specialist opined the possibility of laryngomalacia as the cause for stridor and he is under follow up for the same. At 2 months of age, he underwent bilateral tendo Achilles tenotomy for CTEV. During his last visit at the age of 22 months, he was fully immunized for his age and is doing well with near normal developmental milestones.

Discussion

DGS occurs in 1 in 4,000 to 6,000 live births and is one of the most common survivable deletion syndromes in humans.[1,8] With other syndromes like velocardiofacial syndrome, Cayler cardio facial syndrome, Shprintzen-Goldberg syndrome, Sedlackova syndrome, and conotruncal anomaly face syndrome, DGS is historically grouped under a broad genetic diagnosis of 22q11.2 deletion syndrome. The names of these

syndromes can be used interchangeably as they denote a common underlying genetic etiology.[5] The variety of phenotypic expressions has supported the use of different nomenclatures for the same entity.[9]

Etiologically, DGS is a result of 1.5-3 megabase deletion on the long arm(q) of chromosome 22 at 11.2 locus; hence, labeled as 22q11.2(del) which causes defective development of the third and fourth pharyngeal pouches and the fourth aortic arch which are embryologic precursors for development of the middle and external ear, maxilla, mandible, palatine tonsils, thymus, thyroid, parathyroids, aortic arches, and cardiac outflow tracts. This leads to abnormal facies, cleft palate, speech abnormalities, recurrent infections due to immunodeficiency secondary to thymic aplasia/hypoplasia, hypocalcemia due to small/absent parathyroid glands, developmental delay, seizures, and most frequently, cardiac anomalies.[5]

Predominantly, DGS occurs de novo and less than 10% are inherited as autosomal dominant.[2–4] Astonishingly, Besseau-Ayasse et al reported a higher incidence of inheritance in a 2014 study, wherein 27% of the cases were inherited from either one of the parents.[7] The recurrence risk for unaffected parents to have another affected child is low; nevertheless, prenatal testing should be offered to such families due to the possibility of germline mosaicism. Out of > 90 genes encoded in 22q11.2, T box transcription factor 1 (*TBX-1*) gene abnormality correlates with several prominent phenotypes of DGS, as confirmed by researchers in mouse and zebrafish knockout models.[10,11]

Although DGS affects 1:1,000 of fetuses, the actual prenatal and postnatal prevalence may be higher,[1,10] possibly due to underestimation of lethal phenotypes remaining undiagnosed and due to the postnatal phenotypic variability, children with subtle anomalies may be underdiagnosed.[12] Third, unavailability of genetic expertise in most centers could also lead to underrepresentation of these cases.

Currently, indications for prenatal evaluation for DGS are abnormal sonographic findings and positive family history. The primary indication for evaluation in our series was CHD (75%). This is in accordance with prior studies, which reported 76 to 100% of fetuses with CHD (►**Table 2**). It is well established that the frequently associated CHD in DGS is conotruncal defects.[8] We documented the majority (62.5%) to have conotruncal anomalies in the current series, in similarity to other cohorts.[8] DGS is commonly seen in CHD patients with aortic arch malformation. Interrupted aortic arch is seen in 50 to 80% of cases and common arterial trunk in 35% of cases.[2,13] However, in the current study, we prenatally diagnosed a fetus with DGS who had right aortic arch without any CHD or other fetal markers. Surprisingly, hypoplastic left heart syndrome has also been reported to be associated with 22q11.2(del) in a study by Noël et al.[6]

A large prenatal series reported conotruncal heart defects to be the most common finding (92%), followed by thymic hypoplasia (86%) and urinary tract anomalies (34%).[6] Other extracardiac anomalies include CNS anomalies (15.4–38%), polyhydramnios (9.2–30%), facial dysmorphism (5.9–21%), skeletal defects (16.9–19%), genitourinary disorders (10–33.8%), gastrointestinal (GI) anomalies (14%), and pulmonary disorders (7%).[6–8]

Interestingly, 90% of the fetuses were identified to have extracardiac manifestations in a 2018 study.[6] Cleft lip/palate are considered to be markers for DGS when associated with other defects.[8] However, it is an uncommon finding as cleft palate is seen in < 10% of children and merely 1 to 2% present with cleft lip.[1,6,14] No fetus in our series had cleft lip/palate, restating the rarity of this finding, though it is an important marker for DGS. Hypoplastic thymus was noted in 25% (2/8) of fetuses in our cohort, which is kindred to a study by Schindewolf et al, whereas various other studies reported a lower prevalence of 2.7 to 4%[6–8] (►**Table 2**). Increased NT and

Table 2 Literature review of prenatally diagnosed 22q11.2 deletion syndrome

Case series Prenatal US finding	Current study ($N = 8$)	Schindewolf et al.[8] ($N = 42$)	Besseau-Ayasse et al.[7] ($N = 228$)	Noël et al.[6] ($N = 74$)	Bretelle et al.[21] ($N = 8$)
Cardiac	6 (75%)	40 (95%)	228 (83%)	56 (76%)	8 (100%)
CNS	2 (25%)	16 (38%)	n/a	4 (5%)	n/a
Skeletal	2 (25%)	8 (19%)	n/a	2 (2.7%)	2 (25%)
GI	n/a	4 (9.5%)	n/a	2 (2.7%)	n/a
Pulmonary	n/a	3 (7%)	n/a	n/a	n/a
GU	n/a	7 (17%)	25 (11%)	14 (19%)	
Facial	n/a	9 (21%)	16 (7%)	3 (4%)	n/a
Thymic hypoplasia	2 (25%)	11 (26%)	10 (4%)	2 (2.7%)	n/a
Polyhydramnios	2 (25%)	13 (31%)	25 (9.2%)	11 (15%	n/a
FGR/SGA	3 (37.5%)	0%	n/a	6 (8%)	n/a
Other findings	n/a	SUA 1 (3%)	Increased NT 20 (8.7%)	Increased NT 11 (15%)	n/a
Live birth	4 (50%)	42 (100%)	67 (25%)	1 (1.35%)	0

Abbreviations: CNS, central nervous system; FGR/SGA, fetal growth restriction/small for gestational age; GI, gastrointestinal; GU, genitourinary; n/a, not applicable; NT, nuchal translucency; SUA, single umbilical artery; US, ultrasound.

FGR can also be inconsistently associated with DGS.[6,7] The NT scan was essentially normal in our series, though 37.5% of fetuses were SGA. Polyhydramnios is a nonspecific finding and can be present in various conditions. DGS is thought to be associated with GI tract anomaly or weak laryngopharyngeal musculature, causing defective swallowing in the fetus, eventually leading to polyhydramnios.[12] Hence, the occurrence of polyhydramnios with other fetal markers should point toward the diagnosis of DGS.

Over 67% of fetuses with DGS were reported to have dilated CSP in a previous study.[8] Neural tube defects and asymmetric ventriculomegaly, which are atypical findings of DGS, have also been reported.[6,8] In the current series, we identified 25% with skeletal findings. Of these, one had clenched fists with pointing index fingers, which, to our knowledge, is by far the first such case to be reported in DGS. Furthermore, the unique case we encountered had bilateral CTEV, which prompted us to look for other associated anomalies, such as hypoplastic thymus and dilated CSP. CTEV is an uncommon finding and is seen in only 3.3% of 22q11.2(del) affected children, highlighting the rarity of this finding.[15] As these findings are strongly linked to DGS, we confirmed our diagnosis by direct testing. From this, we can infer the importance of identifying additional fetal markers in the absence of CHD which can help us in the diagnosis and management.

22q11.2(del) can be detected either by FISH, multiplex ligation dependent probe amplification, or aCGH but cannot be identified by karyotype. However, the availability and cost effectiveness of these tests may limit their implementation in resource poor countries.[5] DGS manifests in childhood with developmental delay, learning disability, recurrent infections, and psychiatric disorders like schizophrenia.[1,16] Twenty five percent of fetuses in our cohort succumbed due to DGS. Among the surviving infants (25%), one child has a permanent sigmoid colostomy and surgical corrected CHD, and the other has hypoparathyroidism with craniofacial features of DGS, which were not identified antenatally, as it is difficult to ascertain facial dysmorphism in a fetus. Both infants are thriving well with mild developmental delay. One of them had stridor due to laryngomalacia, which is a well known association of DGS.

Management of DGS involves a multidisciplinary team consisting of pediatric cardiologist, otolaryngologist, geneticist, pediatric surgeon, endocrinologist, and psychiatrists formulated to ensure optimal postnatal outcome.[17–20] There are various DGS support groups around the globe to support families affected with this condition, to provide useful advice on various aspects pertaining to this disorder.

Conclusion

This prenatal series of DGS reiterates the importance of evaluating fetuses with conotruncal anomalies. Additionally, prenatal findings like poor growth velocity, CTEV, polyhydramnios, clenched fists with pointing index finger, and wide CSP in the absence of CHD should raise a high index of suspicion of DGS, warranting genetic analysis, preferably microarray, when a combination of multisystem involvement is detected for early diagnosis and optimum management. From our experience, we highly recommend to meticulously evaluate a fetus for subtle sonographic findings, even in the absence of CHD, which would warrant for invasive testing. Timely diagnosis avoids unwanted surprises to the parents and enables them to seek knowledge, anticipate the outcome, make reproductive decisions, and find out ways of coping with the challenges in the management of these children.

Ethical 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.

Authors' Contributions

R.M. prepared the manuscript and did detailed literature search. R.E. helped in manuscript preparation. V.K. had conceived the idea of drafting this paper and has done the final drafting and will act as the guarantor of the manuscript.

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Conflict of Interest

None declared.

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