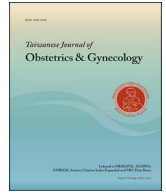




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Case Report

Mosaic trisomy 22 at amniocentesis: Prenatal diagnosis and literature review



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ABSTRACT

Objective: We present prenatal diagnosis of mosaic trisomy 22 at amniocentesis in a pregnancy with facial cleft, oligohydramnios and intrauterine growth restriction (IUGR), and we review the literature.

Case report: A 37-year-old woman underwent amniocentesis at 19 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XX,+22[9]/46,XX[9]. Array comparative genomic hybridization (aCGH) analysis on uncultured amniocytes showed a result of arr(22) × 3 [0.8]. Prenatal ultrasound revealed fetal median facial cleft, oligohydramnios and IUGR. Repeat amniocentesis at 22 weeks of gestation using uncultured amniocytes revealed an aCGH result of arr 22q11.1q13.33 (17,397,498–51,178,264) × 2.8 compatible with 80% mosaicism for trisomy 22, and a fluorescence *in situ* hybridization (FISH) result of mosaic trisomy 22 with trisomy 22 in 54/100 interphase cells. The cultured amniocytes at repeat amniocentesis had a karyotype of 47,XX,+22[12]/46,XX[8]. The parental karyotypes were normal. Polymorphic DNA marker analysis confirmed a maternal origin of the extra chromosome 22. The pregnancy was terminated, and a 256-g female fetus was delivered with facial dysmorphism and median facial cleft. Cytogenetic analysis of the skin fibroblasts revealed a karyotype of 47,XX,+22[33]/46,XX[7].

Conclusion: Fetuses with high level mosaicism for trisomy 22 at amniocentesis may present IUGR, facial cleft and oligohydramnios on prenatal ultrasound.

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Introduction

Mosaic trisomy 22 can be compatible with life. In a review of 21 patients with mosaic trisomy 22, Abdelgadir et al. [1] summarized

the common clinical features as the followings: advanced maternal age (58%), a female preponderance (male: female = 8:13), intra-uterine growth restriction (IUGR) (81%), postnatal growth failure (71%), microcephaly (80%), developmental delay (60%), facial

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dysmorphism (90%) including epicanthic folds, hypertelorism, preauricular pit, low-set ears, flat nasal bridge and abnormal hair-line, congenital heart defects (76%), genitourinary tract abnormalities (38%) including cryptorchidism, hypospadias and streak gonads, gastrointestinal anomalies (19%), anal atresia (10%), hearing loss (38%), hypotonia (19%), body asymmetry (62%), 5th finger clinodactyly (43%), syndactyly (19%), skin pigmentary changes (hypomelanosis of Ito) (33%) and dysplastic nails.

We previously reported a fetus with cleft palate, imperforate anus and IUGR in a pregnancy with trisomy 22 confined placental mosaicism [2]. Here, we present a case of true mosaic trisomy 22 detected by amniocentesis in a pregnancy with fetal median facial cleft, oligohydramnios and IUGR.

Case report

A 37-year-old, primigravid woman underwent amniocentesis at 19 weeks of gestation because of advanced maternal age. The parents were phenotypically normal. Amniocentesis revealed a karyotype of 47,XX,+22[9]/46,XX[9]. Among 18 colonies of cultured amniocytes, nine colonies had a karyotype of 47,XX,+22, whereas the other nine colonies had a karyotype of 46,XX. Simultaneous array comparative genomic hybridization (aCGH) analysis using Affymetrix 750 K Array (Affymetrix, Santa Clara, CA, USA) on uncultured amniocytes showed a result of $\text{arr}(22) \times 3 [0.8]$, with a gene dosage increase in 34.3-Mb 80% 22q11.1q13.33. Prenatal ultrasound at 22 weeks of gestation revealed oligohydramnios, facial cleft (Fig. 1), IUGR and a fetal

growth biometry equivalent to 19 weeks. Repeat amniocentesis was performed at 22 weeks of gestation. aCGH analysis using SurePrint G3 Unrestricted CGH ISCA v2, 8×60 K (Agilent Technologies, Santa Clara, CA, USA) on uncultured amniocytes revealed a result of $\text{arr} 22q11.1q13.33 (17,397,498-51,178,264) \times 2.8$ with a \log_2 ratio of 0.489 compatible with 80% mosaicism for trisomy 22 (Fig. 2). Interphase fluorescence *in situ* hybridization (FISH) analysis using Vysis LSI TUPLE1 (HIRA) Spectrum Orange/LSI ARSA Spectrum Green Probe set (Abbott, Abbott Park, IL, USA) on uncultured amniocytes showed trisomy 22 in 54 of 100 interphase cells compatible with 54% mosaicism for trisomy 22 (Fig. 3). The cultured amniocytes at repeat amniocentesis had a karyotype of 47,XX,+22[12]/46,XX[8]. The parental karyotypes were normal. Polymorphic DNA marker analysis using the DNA extracted from the parental bloods and uncultured amniocytes showed a maternal origin of the extra chromosome 22 (Fig. 4). The pregnancy was subsequently terminated, and a 256-g malformed female fetus was delivered with facial dysmorphism of median facial cleft, hypertelorism and low-set ears (Fig. 5). Postnatal cytogenetic analysis of the skin fibroblasts revealed a karyotype of 47,XX,+22[33]/46,XX[7] (Fig. 6).

Discussion

We have presented prenatal diagnosis of mosaic trisomy 22 by amniocentesis associated with abnormal ultrasound findings in the second trimester. Our case shows that fetuses with high level mosaicism for trisomy 22 at amniocentesis may present IUGR, facial cleft and oligohydramnios on second-trimester ultrasound. Our case is associated with advanced maternal age, a female fetus, IUGR and facial dysmorphism which are consistent with the common features of mosaic trisomy 22 reported by Abdelgadir et al. [1].

Table 1 shows the clinical features of the reported cases with prenatally detected mosaic trisomy 22 at amniocentesis. To date, at least 20 cases of prenatally detected mosaic trisomy 22 by amniocentesis have been reported (Table 1). Among these 20 cases, six cases were normal, and 14 cases were abnormal. The abnormality rate is 70%. The male: female ratio is 5:15, indicating a female preponderance in prenatal diagnosis of mosaic trisomy 22 at amniocentesis. The mosaic trisomy 22 levels of the six normal cases (Stioui et al. [4], Hsu et al. [7] case XVII-3, case XVII-4, case XVII-5 and case XVII-7, and Leclercq et al. [10] case 1) ranged from 5%–28% at initial tapping with the median level ranging from 10% to 16%. The mosaic trisomy 22 levels of the other 14 abnormal cases range from 3.6%–50% with a median level of 20%. The abnormal prenatal ultrasound findings include IUGR, congenital heart defects, nuchal thickening, hydrothorax, hydrocephaly and facial cleft. IUGR is the most common prenatal ultrasound abnormalities, and at least 50% of the reported case had IUGR.

Prenatal diagnosis of mosaic trisomy 22 at amniocentesis has been reported to be associated with normal liveborns. Stioui et al. [4] reported a normal liveborn with 28%–31.7% mosaic trisomy 22 levels at amniocentesis with no structural abnormalities except IUGR. Hsu et al. [7] reported two normal liveborns with mosaic trisomy 22 levels of 5% and 10%, respectively. Leclercq et al. [10]

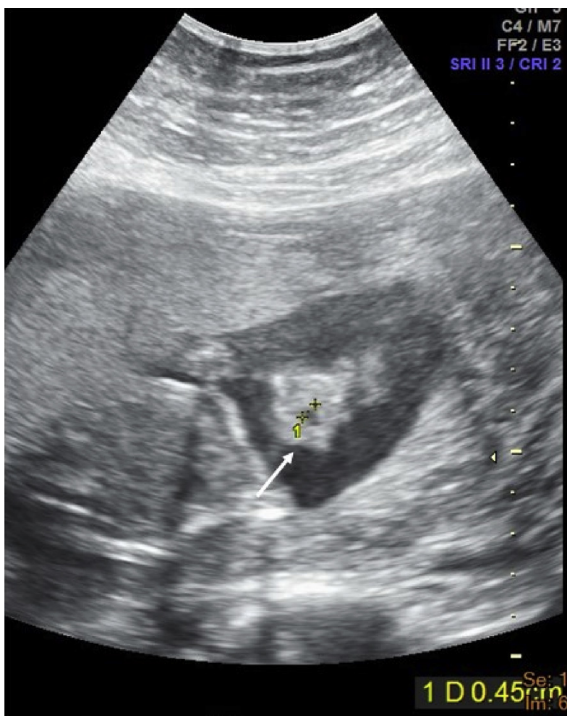


Fig. 1. Prenatal ultrasound at 22 weeks of gestation shows median facial cleft (arrow).

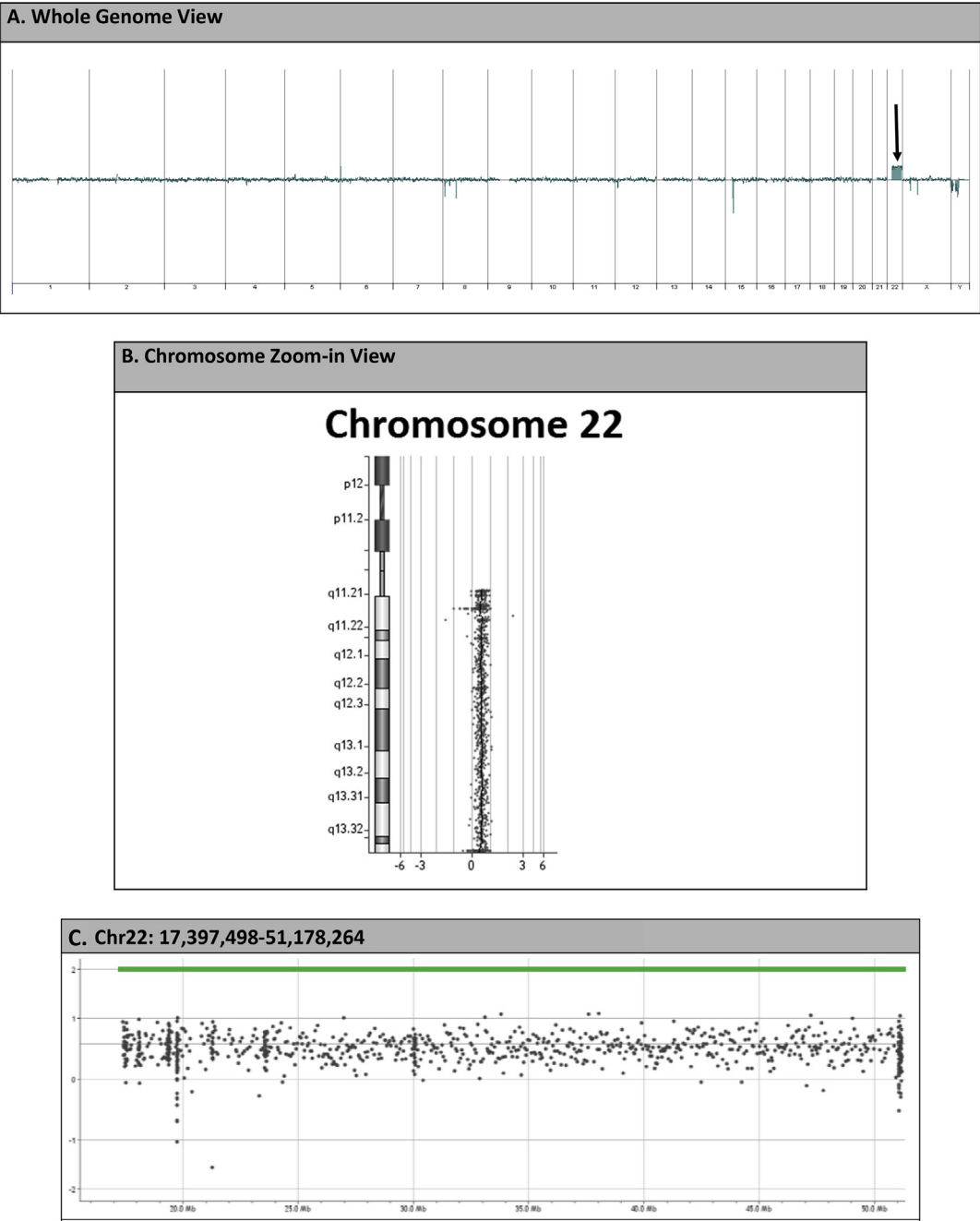


Fig. 2. Array comparative genomic hybridization analysis shows the result of 22q11.1q13.33 (17,397,498–51,178,264) \times 2.8 with a \log_2 ratio of 0.489 compatible with 80% mosaicism for trisomy 22. (A) The whole genome view, and (B) and (C) chromosome 22 zoom-in view.

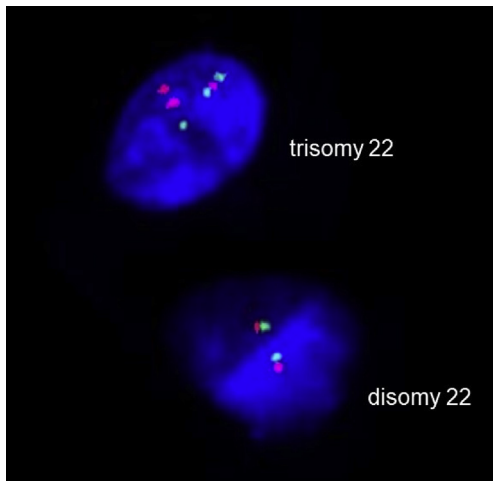


Fig. 3. Interphase fluorescence *in situ* hybridization analysis on uncultured amniocytes using Vysis LSI TUPLE1 (HIRA) Spectrum Orange/LSI ARSA Spectrum Green Probe set (Abbott) shows a trisomy 22 cell (upper cell) and a normal disomy 22 cell (lower cell).

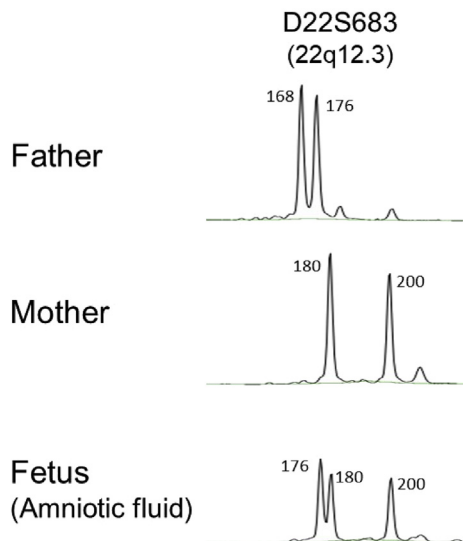


Fig. 4. The polymorphic DNA marker analysis using the informative marker D22S683 (22q12.3) shows a maternal origin of the extra chromosome 22. The fetus inherits two alleles of 180 bp and 200 bp from the mother and one allele of 176 bp from the father.

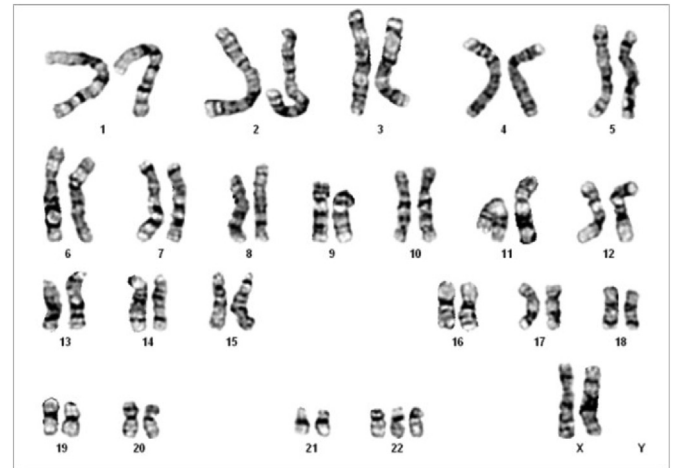


Fig. 6. The karyotype of 47,XX,+22.

reported a normal case with 16% mosaicism for trisomy 22 at amniocentesis. In that case, postnatal cytogenetic analysis revealed 6% mosaicism in the skin and normal karyotype in the blood. The neonate was normal at age four years.

Prenatal diagnosis of mosaic trisomy 22 should raise a suspicion of uniparental disomy (UPD) 22. De Pater et al. [6] reported prenatal diagnosis of mosaic trisomy 22 at amniocentesis with 20% mosaic trisomy 22 level in a pregnancy with IUGR and fetal ventricular septal defect on ultrasound. Postnatal analysis showed 22% mosaic trisomy 22 in skin and maternal UPD 22. Tissue-specificity has been noted in trisomy 22 mosaicism, and there is cytogenetic discrepancy in blood and amniotic fluid and other tissues of the patients with mosaic trisomy 22 [12]. Table 1 shows that only two out of 11 cases with blood cytogenetic analysis revealed mosaic trisomy 22 while the rest nine cases had normal karyotypes, indicating fetal blood sampling for confirmation of mosaic trisomy 22 can be misleading and should be cautious.

In summary, we present prenatal diagnosis of mosaic trisomy 22 at amniocentesis and a literature review. Fetuses with high level mosaicism for trisomy 22 at amniocentesis can be associated with structural abnormalities, and IUGR is frequently noted in mosaic trisomy 22 at amniocentesis. aCGH and FISH analyses on uncultured amniocytes are useful for rapid confirmation of mosaic trisomy 22 at repeat amniocentesis.



Fig. 5. The craniofacial dysmorphism of the fetus at birth.

Table 1
Prenatal diagnosis of mosaic trisomy 22 at amniocentesis.

Authors	Maternal age (y)	Indication and abnormal ultrasound	Amniocentesis	Postnatal confirmation	Outcome
Schinzel [3]	—	IUGR	47,XX+22[50]/46,XX[50] Mosaic T22 = 20%	Cord blood: 47,XX+22[1]/46,XX[26] Mosaic T22 = 4% Blood: 47,XX+22[18]/46,XX[2] Mosaic T22 = 90%	Neonatal death, abnormalities of face, gastrointestinal, genitalia, hands and heart
Stioui et al. [4]	47	AMA, IUGR	47,XX+22/46,XX Mosaic T22 = 28% (50 cells) Retap: Mosaic T22 = 31.7% (41 cells)	Cord blood: 46,XX (360 cells) Amnion: 46,XX (17 cells) Blood: 46,XX (200 cells) Fibroblasts: 46,XX (200 cells) CVS: 47,XX,+22	Normal liveborn
Welborn and Lewis [5]	—	—	47,XX+22/46,XX Mosaic T22 = 20% (10 cells)		Fetal demise at 15 weeks
De Pater et al. [6]	34	AMA, IUGR,VSD	47,XX+22[2]/46,XX[8] Mosaic T22 = 20%	CVS: 47,XX,+22[12] Blood: 46,XX[50] Skin: 47,XX+22[7]/46,XX[25] Mosaic T22 = 22% Maternal UPD 22	Delivery at 39 weeks, multiple anomalies, VSD, facial dysmorphism, finger anomaly
Hsu et al. [7]					
Case XVII-1	—	CHD, abnormal ears	47,XX+22/46,XX Mosaic T22 = 18.2% (11 colonies)	Skin: 47,XX+22[9]/46,XX[1] Mosaic T22 = 90%	Abnormal liveborn
Case XVII-2	—	IUGR, hydrocephaly	47,XX+22/46,XX Mosaic T22 = 28% (60 cells)	Fibroblasts: 47,XX+22[18]/46,XX[2] Mosaic T22 = 90%	Neonatal death
Case XVII-3	39	AMA	47,XY+22/46,XY Mosaic T22 = 20% (15 colonies)	—	Normal abortus
Case XVII-4	37	AMA	47,XY+22/46,XY Mosaic T22 = 5% (40 cells) Retap: Mosaic T22 = 0% (40 cells)	—	Normal liveborn
Case XVII-5	—	—	47,XX+22/46,XX Mosaic T22 = 7.5% (53 cells)	Kidneys, blood, lungs, skin, placenta: 46,XX	Normal abortus
Case XVII-6	—	—	47,XY+22/46,XY Mosaic T22 = 14% (100 cells)	Skin: 47,XY+22/46,XY Placenta: 47,XY+22	Abnormal abortus, facial dysmorphism
Case XVII-7	—	Previous child with NTD	47,XX+22/46,XX Mosaic T22 = 10% (20 colonies)	Cord blood: 46,XX (100 cells) Placenta: 46,XX (100 cells)	Normal liveborn
Case XVII-9	34	AMA	47,XX+22/46,XX Mosaic T22 = 3.6% (56 cells)	Amnion: 46,XX (48 cells)	Abnormal abortus, facial dysmorphism, joint deformity
Case XVII-10	44	AMA	47,XX+22/46,XX Mosaic T22 = 16.7% (12 colonies)	Blood: 46,XX (30 cells) Placenta: 47,XX,+22[2]/46,XX[18]	Abnormal liveborn, facial dysmorphism, TOF, microcephaly, developmental delay at 7.8 months
Berghellar et al. [8]	35	AMA, choroid plexus cyst	47,XY+22[4]/46,XY[15] Mosaic T22 = 21%	Blood: 46,XY (101 cells) Fetal skin: 47,XY+22[7]/46,XY[8] Mosaic T22 = 47% Lung: 47,XY+22[1]/46,XY[14] Mosaic T22 = 3%	Termination, facial dysmorphism
Wang et al. [9]	34	AMA, CHD, IUGR, ASD, PDA, hydrothorax, pericardial effusion, tricuspid regurgitation, LVNC	47,XX+22[6]/46,XX[11] Mosaic T22 = 35%	Blood: 46,XX Skin: 47,XX+22[16]/46,XX[5] Mosaic T22 = 76%	Delivery with dysmorphic features, growth restriction, CHD, LVNC, hemiatrophy at age 4 years
Leclercq et al. [10]					
Case 1	39	AMA	47,XX+22[16]/46,XX[84] FISH mosaic T22 = 16%	Skin: 47,XX+22[6]/46,XX[94] Mosaic T22 = 6% Blood: 46,XX (100 cells) Placenta: 46,XX (100 cells)	Delivery at 41 weeks, normal at age 4 years
Case 2	26	IUGR, abnormal ears	47,XX+22[7]/46,XX[43] FISH mosaic T22 = 14%		IUFD at 34 weeks, dysmorphic features
Case 3	44	AMA, nuchal thickening, hydrothorax, increased NT	47,XX+22[17]/46,XX[49] Mosaic T22 = 26%	Fetal Blood: 47,XX+22[5]/46,XX[109] Mosaic T22 = 4%	Termination, growth restriction
Mazza et al. [11]	41	AMA	47,XY+22[3]/46,XY[6] Mosaic T22 = 33%	Cord blood: 46,XY (100 cells) Cultured placental cells Mosaic T22 = 95% (100 cells) Skin: 47,XY+22[5]/46,XY[145] FISH: mosaic T22 = 4% (100 cells) No UPD 22	Abnormal liveborn, growth deficit, mental retardation
Present case	37	AMA, IUGR, facial cleft, oligohydramnios	47,XX+22[9]/46,XX[9] Mosaic T22 = 50% Retap: 47,XX+22[12]/46,XX[8] Mosaic T22 = 60% FISH: mosaic T22 = 54% (100 cells)	Skin: 47,XY+22[33]/46,XY[17] Mosaic T22 = 82%	Termination, abnormal fetus, growth restriction, facial dysmorphism

—: no information, IUGR: intrauterine growth restriction, T22: trisomy 22, y: year, AMA: advanced maternal age, CVS: chorionic villus sampling, VSD: ventricular septal defect, UPD: uniparental disomy, CHD: congenital heart defect, LVNC: left ventricular non-compaction cardiomyopathy, NTD: neural tube defect, TOF: tetralogy of Fallot, FISH: fluorescence *in situ* hybridization, IUFD: intrauterine fetal death, ASD: atrial septal defect, PDA: patent ductus arteriosus, NT: nuchal translucency.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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