



Prenatal screening of DiGeorge (22q11.2 deletion) syndrome by abnormalities of the great arteries among Thai pregnant women

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Objective

22q11.2DS (deletion syndrome) is one of the common serious anomalies resulting in high perinatal morbidity and mortality rate. Nevertheless, prenatal diagnosis of 22q11.2DS in Southeast Asia has never been described and its prevalence in prenatal series has never been explored. The objective of this study was to describe the experience of prenatal diagnosis of 22q11.2DS in the Thai population and to determine its prevalence among fetuses prenatally diagnosed with abnormalities of the great arteries.

Methods

A prospective study was conducted on pregnant Thai women prenatally diagnosed with abnormalities of the great arteries in the second trimester. The recruited cases were investigated for fetal 22q11.2 deletion by in situ hybridization with a probe specific to the DiGeorge/VCFS TUPLE 1 region located on chromosome 22 for the locus D22S75, and 22qter for a telomere specific sequence clone as the control region.

Results

Five out of the 42 (11.9%) fetuses with abnormalities of the great arteries meeting the inclusion criteria were proven to have 22q11.2DS. The most common abnormalities were the tetralogy of Fallot (or variants) and right-sided aortic arch, followed by a thymic hypoplasia.

Conclusion

As observed in the western countries, we have documented that, among pregnant Thai women, 22q11.2DS is highly prevalent in fetuses with abnormalities of the great arteries (approximately 12%). This information is important when counselling couples to undergo prenatal testing for 22q11.2DS, since this information is vital in the patients' decision of termination or continuation of pregnancy and in a well-prepared management of the affected child.

Keywords: 22q11.2 deletion syndrome; Congenital heart defect; DiGeorge syndrome; Right aortic arch; Thymus

Introduction

22q11.2 deletion syndrome (22q11.2DS) is one of the most common deletion syndromes in humans with a prevalence of 1 in 2,000 to 6,000 live births [1]. It is caused by a developmental defect of the third and the fourth pharyngeal pouches and the fourth aortic arch. This leads to several presentations, including craniofacial anomalies such as cleft palate, micrognathia, eye anomalies, congenital heart defect, absent or a small thymus, and the parathyroid gland leading to hypocalcemia and immunodeficiency, musculoskeletal

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anomalies, developmental delay, seizure, and behavioral or psychiatric complications. Most cases (83.3–95%) that are diagnosed prenatally are noticed by an abnormal fetal cardiac structure [2-4]. Other prenatal findings that are rarely reported, include renal anomalies, cerebral anomalies, and neural tube defects [3,5]. At Maharaj Nakorn Chiang Mai Hospital, the prevalence of the disease is unknown because FISH analysis for this disease is not a standard practice. In cases at this hospital, after evaluation of the fetuses by a maternal-fetal specialist, prognosis, and genetic counselling, most parents choose termination of pregnancy without further investigation (karyotyping, FISH, or microarray) due to economic limitations.

Though prenatal diagnosis of 22q11.2DS has been reported several times, most cases have been reported by western countries and are rarely from other parts of the world. Little is known about the extent of this problem in our country or in Southeast Asia. Only a few reports of 22q11.2DS among the Thai population have been studied [6-9]. Noteworthy, Wichajam and Kampan [6] reported that there was a difference in clinical phenotypes and immunological features of 22q11.2DS in north-eastern Thai children compared to those in the western countries. Moreover, to the best of our knowledge, prenatal diagnosis of 22q11.2DS has rarely been described among the Asian population. However, one retrospective study of the Korean population was reported by Lee et al. [10], who demonstrated a strong association between a variety of prenatally-diagnosed conotruncal cardiac defects and 22q11.2DS. Accordingly, prenatal diagnosis of 22q11.2DS in other parts of the world including our country remains to be explored. Thus, we conducted this prospective study with an aim to describe the experience of prenatal diagnosis of 22q11.2DS in the Thai population and to determine its prevalence among fetuses prenatally diagnosed with abnormalities of the great arteries.

Materials and methods

A prospective descriptive study was conducted at the Maharaj Nakorn Chiang Mai Hospital between July 2015 and April 2018, with an ethical approval by the Institute Review Boards (Study code: OBG-2560-04711). The pregnant women meeting the inclusion criteria were invited to participate in the study with a written informed consent. The inclusion criteria

were as follows: 1) women with fetuses prenatally diagnosed with abnormalities of the great arteries including conotruncal heart defects (TOF, tetralogy of Fallot; DORV, double-outlet of the right ventricle; TGA, transposition of the great arteries, the truncus arteriosus), aortic or pulmonary stenosis, coarctation or interrupted aortic arch, and right-sided aortic arch. 2) women undergoing fetal echocardiography in the second trimester, in which extra-cardiac anomalies and fetal thymus were included. The recruited cases were investigated for 22q11.2 deletion by in situ hybridization with a probe specific to the DiGeorge/VCFS TUPLE 1 region located on chromosome 22 for the locus D22S75 and 22qter for a telomere specific sequence clone as the control region using amniocentesis, cordocentesis, or postnatal peripheral blood. Demographic data of the pregnancies, prenatal ultrasound characteristics, and pregnancy outcomes were described and recorded in the study record form. All the recruited cases were followed until delivery for the final outcomes of pregnancy. In statistical analysis, descriptive statistics were used to express mean, standard deviation, and percentage, using SPSS version 21.0 (IBM Corp.; IBM SPSS Statistics for Windows, Armonk, NY, USA).

Table 1. Main indications for 22q11.2DS testing

Main indications	Frequency
Right-sided or double aortic arch	8 (19.0)
Aortic stenosis or hypoplasia	5 (11.9)
TOF (simple)	5 (11.9)
TOF (complex) ^{a)}	5 (11.9)
Pulmonary stenosis or atresia	4 (9.5)
Coarctation or interrupted aortic arch	4 (9.5)
Double-outlet right ventricle	4 (9.5)
Transposition of great arteries	3 (7.1)
Complex conotruncal defects ^{b)}	2 (4.8)
Truncus arteriosus	1 (2.4)
Thymus hypoplasia and overriding aorta	1 (2.4)
Total	42 (100)

Data are presented as number of frequency (%).

TOF, tetralogy of Fallot.

^{a)}TOF with pulmonary atresia or absent pulmonary valve or right-sided aortic arch or associated extracardiac anomalies or thymus hypoplasia. ^{b)}Double-outlet right ventricle with atrioventricular canal, coarctation and aortic stenosis (1 case) and a case of aortic stenosis with atrioventricular canal and aberrant right subclavian artery (1 case).

Results

During the study period from July 2015 to April 2018, 240 cases of the conotruncal cardiac anomalies were prenatally diagnosed in our institute. A total of 45 cases was tested for 22q11.2DS during the study period, with 21 cases by cordocentesis (22.1±3.5 weeks of gestation), 8 cases by amniocentesis (16.5±1.8 weeks of gestation), and 16 by a postnatal work-up. However, 3 cases failed to report due to a laboratory technical error. Although a large number of fetuses with cardiac abnormalities underwent fetal echocardiography at our institution, only 45 cases were tested for 22q11.2DS, because in most couples, women with fetuses with cardiac defects opted for a termination of the pregnancy after a detailed anatomical scan without further investigation. Thus, the remaining 42, including 11 cases (26.2%) with associated anomalies and 31 cases (73.8%) of isolated cardiac defects were available for analysis. The mean (±standard deviation [SD]) maternal age was 29.4±7.1 (17–43) years. The mean

(±SD) gestational age at the time of first fetal echocardiography was 21.7±4.0 (14–28) weeks. Various indications for 22q11.2DS testing have been presented in Table 1. Of them, either the TOF with isolated cardiac defects or the TOF with associated anomalies; i.e., pulmonary atresia, absent pulmonary valve, right-sided aortic arch, and so on, was the most common indication, accounting for approximately 24%, whereas a right-sided aortic arch was the most common indication as an isolated abnormality (19%). The prevalence of 22q11.2DS in this series was relatively high, 11.9% (5 out of 42) among fetuses with prenatally diagnosed conotruncal heart defects. The remaining 37 cases were negative for 22q11.2 deletion. In our study, termination of pregnancy because of severe fetal anomalies, mainly associated with cardiac defects, was performed in 33.3% (14 out of 42) of the cases. Five of our 22q11.2DS cases had prenatal features and pregnancy outcomes as presented in Table 2. The main prenatal features were conotruncal defect, mainly TOF, DORV, and right-sided aortic arch. Notably, Case 1 exhibited isolated

Table 2. Prenatal ultrasound findings and pregnancy outcomes of the cases with 22q11.2DS

Case No.	GA at diagnosis (wk)	Cardiac abnormality	Other structural abnormality	Karyotype	Outcomes
1	20	Right-sided aortic arch and ductal arch	Polyhydramnios at 31 weeks (AFI 32cm.), normal size thymus	46,XX	Cesarean delivery at 38.2 wk; Surviving baby 3,075 g. Apgar scores 10 at 5 min, right-sided aortic arch, low-set ears, small palpebral fissure both eyes, symptomatic hypocalcemia, hypothyroid, vitamin D deficiency
2	20.2	TOF with absent pulmonary valve and subaortic VSD	Thymus hypoplasia (<5th percentile), bilateral paramedian cleft lip and palate, single umbilical artery, minimal ascites	46,XY	TOP; Hypertelorism, bilateral paramedian cleft lip, low-set ears, cardiomegaly with right ventricular hypertrophy, VSD perimembranous type, absent pulmonary valve, absent ductus arteriosus, absence thymus, mild dilation of both ureters
3	19.5	DORV, pulmonary stenosis, ARSA, perimembranous VSD	Absent thymus, bilateral ventriculomegaly, abnormal posture of all extremities, FGR, oligohydramnios	No result	TOP; DORV, severe PS, subaortic VSD, absent ductus arteriosus, ARSA, partial syndactyly at proximal 3rd-4th digit of left hand, brachydactyly right hand, rocker bottom feet
4	23.1	DORV (TOF-like) with pulmonary stenosis, VSD	Single umbilical artery, postaxial polydactyly	46,XY	Normal delivery at 38 wk, surviving baby 2,940 g. Apgar scores 8 at 5 min, normal thymus, mild hypocalcemia, postaxial polydactyly, DORV with staged surgical correction with fair outcome
5	18.1	TOF with right-sided aortic arch & ductal arch	Duodenal atresia, thymus hypoplasia (<5th percentile), polyhydramnios	46,XX	Cesarean delivery, at 30 wk, surviving baby 1,850 g. Apgar scores 9 at 5 min, TOF with right-sided arches, thymus hypoplasia, duodenal atresia, fair outcome after surgical correction, failure to thrive, neonatal death at 1 mon

GA, gestational age; AFI, amniotic fluid index; TOF, tetralogy of Fallot; VSD, interventricular septal defect; TOP, termination of pregnancy; DORV, double-outlet right ventricle; ARSA, aberrant right subclavian artery; FGR, fetal growth restriction; PS, pulmonary stenosis.

right-sided arches only without any other conotruncal or cardiac anomalies, whereas 2 cases underwent a termination of pregnancy and one experienced preterm birth with death of the neonate. Two cases survived with a prolonged NICU admission. Fig. 1 demonstrates examples of prenatal ultrasound findings and pathological findings post the termination of pregnancy in cases of 22q11.2DS. Additionally, fetal karyotyping was performed in 26 cases, resulting in 46,XX (11 cases); 46,XY (10 cases); 47,XX,+18 (1 case); 47,XY,+13 (1 case); 47,XY,+21 (1 case); 46XX,r(13) (1 case) and 69,XXY (1 case).

Discussion

Insights gained from this study demonstrate that among the Thai or probably the Asian population, the prevalence of 22q11.2DS is as high as nearly 12% of the fetuses prenatally diagnosed with abnormalities of the great arteries. It may be concluded that the prevalence is similar to that reported in western countries. Our evidence strongly suggests that pregnancies with a prenatal detection of abnormal great arteries should be encouraged to test for fetal 22q11.2DS. Owing to the fact that prenatal screening of 22q11.2DS has never been practiced in our country, our finding can probably lead to a change in our practice in Thailand and Southeast Asia, although analysis of its cost-effectiveness remains to be explored.

22q11.2DS has been documented far more in newborns than those in fetuses. The clue to a prenatal diagnosis is the presence of a congenital heart disease. The large prenatal series found that conotruncal heart defects were the most common fetal phenotype (92%) followed by a thymic hy-

poplasia (86%) and a urinary tract abnormality (34%) [3]. Conotruncal malformations refer to the abnormality involving either the aortic or the pulmonary outflow tract, and is more relevant than the non-conotruncal malformations [2,11]. The most prevalent cardiac defect in literature is the TOF, accounting for 20–45%, followed by pulmonary atresia with VSD; 10–25% [12]. In our study, 4 out of the 5 cases were categorized as cases with a conotruncal defect and one case exhibited only a right-sided aortic arch. The specific cardiac defect is the main cause of neonatal death, at an average age of 3–4 months [13]. Also in adults, sudden cardiac death and heart failure are the most common causes of death, even in patients without a congenital heart disease [14].

Notably, in this study, the isolated right-sided aortic arch without other structural anomalies was found in 1 of the 5 cases with 22q11.2DS, consistent with the findings reported in western countries [15]. However, an abnormal laterality associated with 22q11.2DS may include a right-sided aortic arch, double aortic arch, cervical aortic arch, and an abnormal origin of the subclavian arteries [13]. A recent meta-analysis showed that the proportion of 22q11.2 deletion was 5.1 (95% CI, 2.4–8.6) in fetuses with a right-sided aortic arch and in the absence of other intra-cardiac or extra-cardiac abnormalities [15]. However, 5% of these had extra-cardiac abnormalities detected after birth such as a unilateral renal agenesis and a gastrointestinal malformation [15]. Thus, in cases of isolated abnormalities of the aortic arch, a follow-up study and an immediate postnatal echocardiography and an electrolyte study to detect other associated anomalies that may be overlooked in the first scan are highly recommended [1,16]. Early detection and management can improve fetal and neonatal outcomes.

When Case 1 was diagnosed with 22q11.2DS at 20 weeks

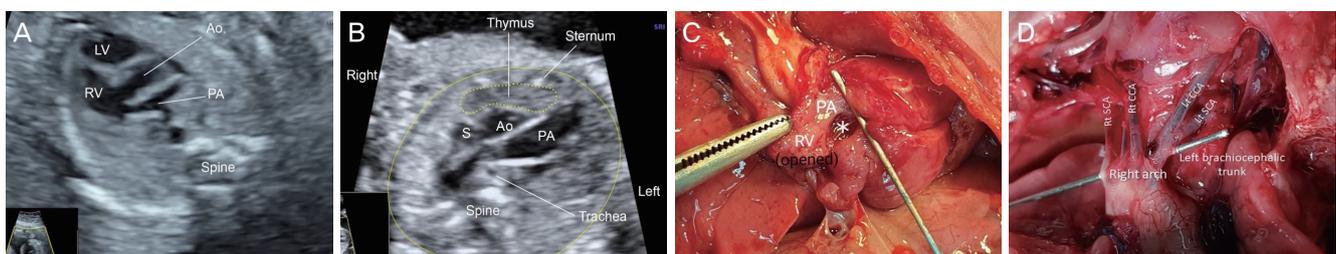


Fig. 1. Examples of the findings of fetuses with 22q11.2DS: prenatal ultrasound findings of double-outlet right ventricle (A: Case 4), and right-sided aortic arch with relatively small thymus (B: Case 5); and pathological findings of absent pulmonary valve (C: Case 3) and right-sided aortic arch (D: Case 5). Asterisk (*) presented pulmonary annulus. LV, left ventricle; RV, right ventricle; Ao, aorta; PA, pulmonary artery; S, superior vena cava; SCA, subclavian artery; CCA, common carotid.

of gestation, the couple decided to continue pregnancy after comprehensive counselling. During prenatal follow-up, polyhydramnios developed at 31 weeks of gestation (amniotic fluid index [AFI], 32 cm) and amnioreduction was performed 1 week later due to maternal discomfort (AFI, 39 cm). The cause of polyhydramnios was unclear. Hypothetically, it was due to an airway compression by the right-sided aortic arch. However, it may be also caused by an airway abnormality [17,18], but the cause of the polyhydramnios in our case was not proved postnatally. Sacca et al. [19] reported that about 70% of the patients with a 22q11.2 deletion syndrome were identified to have airway anomalies including tracheomalacia (36%), subglottic stenosis (28%), and laryngomalacia (26%). Thus, the evaluation of airway structure and function should be considered and included in a systemic assessment among these patients since it can sometimes lead to a neonatal death.

Our series also supported that absent or hypoplastic thymus (in 3 out of 5 cases), is an indication for determination of 22q11.2DS. Chaoui et al. [20] suggested that the thymus-thoracic ratio of less than 0.25 was highly correlated with 22q11.2DS. Thymus size can be evaluated by measurement of the thymus diameter or thymus-thoracic ratio and comparison with reference ranges. We encourage the use of thymus diameter because our previous study showed that thymus diameter was more reproducible and simpler than the thymus-thoracic ratio [21].

Extracardiac abnormalities associated with 22q11.2DS include CNS anomalies (15.4–38%) [3,4], polyhydramnios (9.2–30%) [2,4], facial dysmorphism (5.9–21%) [2,4], skeletal defects (16.9–19%) [3,4], genitourinary disorders (10–33.8%) [3,4,22], gastrointestinal anomalies (14%) [4], and pulmonary disorders (7%) [4]. More than 90% of these anomalies were not isolated [2]. In our series, only 1 case exhibited an isolated cardiac defect, whereas the others had associated anomalies. Association between FGR and 22q11.2DS has been inconsistently reported, from no association [4], to strong association [2]. Furthermore, 7.4–15% of the fetuses show increased nuchal translucency in the first trimester [2,3].

In the general population, due to multiple and non-specific prenatal presentations, it may be difficult to set the guideline for 22q11.2 analysis. Prompt investigation for 22q11.2DS when congenital heart disease is diagnosed by fetal echocardiography is widely accepted especially defects with a very

high risk such as an interrupted aortic arch, type B (50–80% risk), truncus arteriosus (30–50%), pulmonary atresia with VSD with MAPCAs (30–45%) [23-26]. Based on emerging knowledge, prenatal 22q11.2 analysis is also recommended when ultrasounds show other congenital heart defects combined with other structural abnormalities (as mentioned above), and increased NT in the first trimester [2,4]. This study suggested that, among the Thai and probably the Asian populations, when abnormalities of the great arteries and/or thymus hypoplasia are detected on fetal echocardiography, 22q11.2DS should be taken into account for differential diagnoses and should be selectively tested. Though such a work-up is expensive in our country, the prevalence of the disease is relatively high in cases of the great artery abnormalities and testing in such cases may be worthwhile. The strengths of this study were: 1) A prospective nature of the study enabled us to determine the prevalence of 22q11.2DS among fetuses with conotruncal anomalies. 2) Pediatric echocardiography or fetal autopsy was performed to confirm prenatal ultrasound findings. The weaknesses of this study that could limit its generalizability were: 1) The sample size was too small to allow us to make conclusions with high confidence. 2) Only Thai pregnancies were recruited. Therefore, the study population could not perfectly represent other populations even in Asia.

In conclusion, in an era of a high resolution of ultrasonography, many regions have standard guidelines for prenatal anatomical screening, leading to an increasing number of prenatal diagnoses of 22q11.2DS. The main finding of the disease is the presence of abnormal great arteries and thymus hypoplasia, but it can also be associated with a variety of other anomalies. Similar to the reports in the western countries, we have documented that among Thai pregnant women, 22q11.2DS is highly prevalent in fetuses with abnormalities of the great arteries (approximately 12%). This information is important when counseling couples to undergo a prenatal test for 22q11.2DS, since this information is helpful in patients' decisions of termination or continuation of pregnancy, or in a well-prepared management of the affected child.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

Ethics approval for this study was granted by the Institute Review Boards, Faculty of Medicine, Chiang Mai University, Thailand (Study code: OBG-2560-04711).

Patient consent

The patients provided written informed consent for the publication and the use of their images.

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