Introduction

Congenital heart disease (CHD) is the most common congenital anomaly. Previous studies have reported a varying prevalence for CHD, as well as significant geographical differences in its occurrence. Asia has the highest CHD birth prevalence, with 9.3 per 1000 live births [1]. Ventricular septal defect (VSD) is a common type of CHD, with a reported prevalence of 4 per 1000 live births, and it accounts for one-third of all heart defects diagnosed during the first year of postnatal life [1,2]. According to a nationwide database in Taiwan, the prevalence of CHD is 13.08 per 1000 live births. Moreover, in Taiwan, the most common subtype of CHD is VSD, with a prevalence of 4.01 per 1000 live births [3]. The outcome of neonates with VSD is related to the defect location, size and whether it is associated with other congenital anomalies. The aim of this review is to discuss the outcome of isolated VSD, which prenatally diagnosed and without any other congenital defect.

Types of VSD

VSD may occur in various locations including the membranous septum, muscular septum, supracristal area, and atrioventricular valve inlet area (Fig. 1). Muscular septum VSD (m-VSD) can be divided into mid-muscular, apical, anterior, and posterior defects. Mid-muscular VSD, the most common type, is approximately 5-fold more prevalent than apical defects [4]. The physiologic effects of VSD depend on the size of the defect. Although no universally accepted definition has been established for VSD sizes, commonly used categorizations in clinical studies are as follows: small <4 mm; moderate 4–6 mm; large >6 mm. Moderate to large VSD can be detected in utero at as early as 16–18 weeks of gestation; however, small to moderate VSD can be missed during fetal echocardiography. Hill et al. reported that the rate of prenatal detection of critical CHDs increased from 44% in 2007 to
69% in 2013 [5]. The causes contributing to increased detection and prevalence are as follows: 1) improved precision of ultrasound equipment, 2) wide use of ultrasound in prenatal diagnosis, 3) well training and education for ultrasound doctors and technicians, 4) delaying childbearing to an older maternal age, causing a higher prevalence of birth defects, and 5) survival of premature infants, increasing total CHD and particularly VSD birth prevalence [4–6].

Fetal echocardiography

By ACOG and most fetal echocardiographic guideline, the current screening strategy in most countries is a standard anomaly scan at 20 weeks of gestation. In Taiwan, a nationwide fetal biometry and structural screening program for unselected pregnant women was introduced in 1995 with the aim of detecting congenital anomalies. Prenatal detection of fetal anomalies improves neonatal outcomes and reduces morbidity and mortality. It enables the planning of deliveries at a tertiary care center, ensuring optimal neonatal and peri-surgical care [7,8]. In Taiwan, the national standard anomaly scan for pregnant women at 20 weeks of gestation includes the four-chamber view of the fetal heart. Fetal echocardiography has been widely applied (self-paid newborn echocardiographic screening) in the past 10 years. A study published in 2010 observed a decreasing trend not only for severe forms of CHD but also for simple forms of CHD in Taiwan [3]. The advanced technique of fetal echocardiography and its widespread application have facilitated the early detection of even minor CHD (e.g., small isolated VSD). In some cases, pregnancy termination may be an option.

Isolated VSD versus trisomy 21

Approximately 50% of individuals with Down syndrome have CHD. In the largest population-based study conducted from 1985 to 2006 in England, cardiovascular abnormalities were identified in 42% of infants born with Down syndrome [9]. Although complete atrio-ventricular septal defect is the most common cardiovascular anomaly in the Down syndrome population, VSD accounts for approximately 31% of CHD in this population. Whether further diagnostic testing is required for a fetus with isolated VSD identified to be at risk for trisomy 21 is still debated. Previous reports of the association between VSD and various types of aneuploidies have not distinguished between isolated VSD and VSD associated with additional cardiac anomalies and major extra-cardiac anomalies. Ori Shen et al. reported 92 cases with isolated VSD, and none of the cases in the study group had trisomy 21 [10]. This finding is consistent with that of two reports, which found no cases of trisomy 21 among 25 [11] and 248 [12] cases of isolated VSD without any additional major anomalies. According to the results of these studies, trisomy 21 is considered uncommon when VSD is the only sonographic abnormality.

Another study determined prevalence rates of 6.2% for trisomy 21 associated with isolated VSD and of 11.1% for isolated VSDs among fetuses with trisomy 21 [13], suggesting that isolated VSD is associated with chromosomal abnormalities, particularly trisomy 21. However, that study included a limited number of cases, that is, only 16 cases of isolated VSD in the study group, and was a single-institution study. These results should be interpreted with caution, because it is clear that a larger series is necessary to provide a more efficient risk assessment for fetal aneuploidy.

Isolated VSD versus DiGeorge syndrome

Sporadic cases of isolated VSD and DiGeorge syndrome have been reported [12,14,15]. DiGeorge syndrome, also known as 22q11.2 deletion syndrome, is caused by the deletion of a small segment of chromosome 22. CHD, particularly conotruncal malformations, was found in 40% of DiGeorge syndrome cases.

Table 1

| The incidence of spontaneous VSD closure rate. | Remained patent during first year of life by Paladini D. (Ref. 19) |
| Size of the defect | VSD <3 mm | 15.8% |
| Spontaneous close rate by Miyake T. (Ref. 23) | VSD >3 mm | 71.4% |
| Site of the defect | Midv-ventricular muscular trabecular VSD | 89% |
| Spontaneous close rate by Meberg A. (Ref. 24) | Apical muscular trabecular VSD | 84% |
| Type of the defect | Anterior muscular trabecular VSD | 83% |
| Spontaneous close rate by Axt-Fliedner R. (Ref. 20) | Follow-up duration | In uterus | 32.7% |
| Spontaneous close rate by Gómez O. (Ref. 12) | Within 1 year | 44.3% |
| In uterus | 5% |
| Within 1 year | 76% |
syndrome cases, and VSD was found in 14% of DiGeorge syndrome cases [16]. Pathogenetically, each type of VSD is thought to have different embryological origins, as follows: conal–septal VSD (also called supracristal VSD) results from conotruncal anomalies; perimembranous VSD results from multiple factors including abnormal blood flow; and muscular VSD results from excessive cellular death. Because it is categorised as a conotruncal anomaly, it has been proposed that supracristal VSD is associated with del.22q11. To elucidate whether conal–septal VSD or other types of VSDs are associated with del.22q11, Yamagishi et al. prospectively analyzed the chromosomes of consecutive Japanese patients with conal–septal VSD. They also retrospectively evaluated the types of VSDs observed in patients with del.22q11. They identified that all VSDs observed in three patients with del.22q11 were perimembranous VSDs, suggesting that del.22q11 is not a common cause of conal–septal VSD [17].

A large retrospective single-center cohort demonstrates the utility of array comparative genomic hybridisation (aCGH) in 1252 CHD patients, and the copy number variants are no significant statistical significance between patients with CHD (28.9%) and patients without CHD (26.3%) [18]. However, of the patients with CHD, those with left-sided heart disease had the highest proportion (45.13%) of abnormal aCGH results, followed by those with conotruncal heart disease (34.48%), endocardial cushion defects (26%). On the other hand, only 3 of 22 patients described as isolated CHD had an abnormality detected by aCGH, and they suggest that aCGH may have a higher diagnostic yield in patients with left-sided CHD, and perhaps of little benefit in isolated CHD patients. Microarray testing has become more common in recent years; thus, more information on the prevalence of microdeletions and microduplications in fetuses with CHD will become available.

**Isolated VSD versus other aneuploidies**

The rate of chromosomal anomalies associated with fetal isolated VSD is controversial. According to two large studies, the presence of VSD increases the risk of aneuploidy and extracardiac anomalies in an affected fetus [19,20]. However, the evolution and outcome of prenatally diagnosed isolated VSD have not been definitely established. Gómez et al. evaluated the risk of associated chromosomal anomalies in a large cohort of prenatally diagnosed isolated VSD cases [12]. During the 6-year study period, 248 isolated VSD cases were diagnosed among 995 CHD cases (24.9%). Amniocentesis for genetic diagnosis was performed in 119 pregnancies, and the karyotypes of the remaining 129 cases were clinically assessed postnatally. The prevalence of chromosomal anomalies was 1.2% (3/248 cases). In another 5-year study, 534 CHD cases were detected among 23,500 pregnancies referred for fetal echocardiographic examination. Moreover, 76 isolated m-VSD cases were found, but no chromosomal anomalies were identified, suggesting that isolated m-VSD is a benign finding during pregnancy [4].

During Asia population, Liu et al. investigated 214 fetuses with VSD in China, and 46 (21.5%) isolated VSD cases were diagnosed [21]. Of these 46 cases with isolated VSD, karyotypes were obtained for 29 cases, and chromosomal abnormalities were diagnosed in only one case. The chromosomal abnormalities prevalence of isolated VSD was 3.4% in that study, which is much higher than that reported by Gómez et al. Estimates of the chromosomal anomalies prevalence in isolated VSD cases vary depending upon demographics, race, year of data collection, and regional differences in prenatal screening. Additional studies should be conducted to determine the possible association between prenatally diagnosed isolated VSD and chromosomal abnormalities. Although the proportion of cases with chromosomal abnormalities and isolated VSD is relatively low, fetal karyotyping should be discussed with, and offered to, all pregnant patients until the prevalence of chromosomal abnormalities in fetuses with isolated VSD is definitely established in future studies.

**Spontaneous closure of isolated VSD**

It has long been recognized that VSD can close spontaneously, but the incidence and mechanism remain unclear. The reported incidence of spontaneous VSD closure ranges from 5% to 84%, depending on the size, site, and type of the defect, and the follow-up duration [22]. Several studies have demonstrated that spontaneous VSD closure occurs more frequently for small defects than for large ones. It was reported that defects, particularly m-VSD, with a diameter of ≤3 mm were more likely to close spontaneously in up to 83.8% cases during gestation or the first year of life [4]. One study observed that only 15.8% of VSD <3 mm remained patent in comparison with 71.4% of VSD >3 mm during first year of life [19].

The incidence of spontaneous VSD closure varies depending on the site of the defect. Miyake et al. observed that the mid-ventricular muscular trabecular VSD tended to spontaneously close earlier and more frequently than the anterior or apical muscular trabecular VSD, with closure rates of 83%, 84%, and 89% for the anterior, apical, and mid-ventricular septum defects, respectively [23]. However, another study reported that spontaneous closure occurred more frequently for apical defects; however, no significant difference was observed for spontaneous closure between the mid-muscular and apical defects [4]. Erol et al. also observed that 9.3% of mid-muscular defects closed spontaneously in utero, and 71.8% closed within the first year of life. However, none of the apical defects closed in utero, and 83.3% closed within the first year of life. Therefore, the incidence of spontaneous VSD closure varies depending on the population studied, methods employed, and follow-up duration.

The incidence of spontaneous VSD closure also depends on the type of the defect. Muscular VSD is more likely to close spontaneously than membranous VSD or perimembranous VSD. Meberg et al. showed that 74% (119 of 161) of m-VSD and 22.2% (8 of 36) of membranous VSD closed spontaneously [24]. However, another study observed that prenatal closure occurred mainly for small perimembranous VSDs, whereas postnatal closure occurred mainly for m-VSDs [12].

The incidence of spontaneous VSD closure is also related to the follow-up duration; 32.7% (37/113) of defects closed
spontaneously in utero, 44.3% (50/113) closed spontaneously within 1 year, and 23% (26/113) remained patent [20]. By contrast, Gómez et al. found that 5% of defects closed prenatally and 76% closed before the age of 1 year; in 16% of postnatally closed defects, the defect closed in the peripartum or early neonatal period [12]. Although the percentage of spontaneous closure differed across different periods, the final spontaneous closure incidence was similar (up to 77%–81%) if the follow-up duration reached postnatal year 1.

A similar result was observed in the Asian population [25,26]. Li et al. reported a spontaneous closure rate of 45.2% (81/179) for isolated VSD [25]. In that study, approximately 27.4% (49/179) of defects spontaneously closed in utero, 17.9% (32/179) closed after birth, and 75% (24/32) closed in the first year of life. This study also revealed that the spontaneous closure rate was 59% for the \( \leq 2.0 \) mm group, 36% for the 2.1–5.0 mm group, and no spontaneous closure for the >5.0 mm group. According to the type of VSD, the spontaneous closure rate was 45.4% in the perimembranous group and 44% in the muscular group. No significant difference was observed between these two groups. A neonatal study in Taiwan revealed that the spontaneous closure rate was 81.8% for isolated m-VSD at 12-month follow-up. Moreover, 89.2% of mid-muscular VSD, spontaneous closure rate was 81.8% for isolated m-VSD at 12-month follow-up. Moreover, 89.2% of mid-muscular VSD, spontaneous closure for the perimembranous group and 44% in the muscular group. No significant difference was observed between these two groups. A neonatal study in Taiwan revealed that the spontaneous closure rate was 81.8% for isolated m-VSD at 12-month follow-up. Moreover, 89.2% of mid-muscular VSD, spontaneous closure for the perimembranous group and 44% in the muscular group. No significant difference was observed between these two groups.

Consulting for perinatal diagnosed isolated VSD

Approximately 0.2 million live births per year occur in Taiwan; according to the nationwide database, VSD occurs in approximately 4.01 per 1000 live births, and nearly 800 children are born with VSD every year. In recent years, the widespread application of prenatal ultrasound has improved the prenatal diagnosis of CHD. However, a decreasing trend was observed not only for severe forms of CHD but also for simple forms of CHD in Taiwan [3], which may be related to pregnancy termination in some cases. More small m-VSDs have been diagnosed owing to high-resolution ultrasound equipment; thus, counseling patients having fetuses with isolated VSD is clinically important. The accuracy of prenatal diagnosis, existence of associated anomalies, available treatment options, and prognosis are factors considered in the decision-making process for the termination of CHD cases.

Conclusion

In this review, we discussed the risk of aneuploidy and the outcome of isolated VSD. First, the proportion of cases with chromosomal abnormalities and isolated VSD is relatively low, and trisomy 21 is considered uncommon when VSD is the only sonographic abnormality. Second, although sporadic cases of isolated VSD and DiGeorge syndrome have been reported, additional studies should aim to determine the prevalence of microdeletions and microduplications in fetuses with CHD. Finally, the incidence of spontaneous VSD closure depends on the size, site, and type of the defect (Table 1). The spontaneous closure incidence of isolated VSD is higher for small VSD (diameter \( \leq 3 \) mm) and m-VSD is more likely to close spontaneously than the membranous or perimembranous type. Isolated VSD may spontaneously close in utero or postnatally, and the vast majority of m-VSDs spontaneously close before the age of 1 year. Therefore, the diagnosis of isolated m-VSD without other anomalies can be considered a benign finding. However, more information is needed to establish the risk of chromosomal anomalies in fetuses with other types of VSD and whether VSD occurs with other abnormal soft marker findings.

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