ORIGINAL ARTICLE

Prenatally diagnosed isolated perimembranous ventricular septal defect: Genetic and clinical implications

Lital Gordin Kopylov[1,2] | Nadav Dekel[1,2] | Ron Maymon[1,2] | Noa Feldman[1,2] [iD] |
Ariel Zimmerman[1,2] | Dan Hadas[1,2] | Yaakov Melcer[1,2] [iD] | Ran Svirsky[1,2,3] [iD]

[1]Obstetrical Unit, Shamir Medical Center (formerly Assaf Harofeh Medical Center), Zerifin, Israel

[2]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3]Raphael Recanati Genetic Institute, Rabin Medical Center - Beilinson Hospital, Petach Tikva, Israel

Correspondence
Ran Svirsky, Department of Obstetrics and Gynecology, The Yitzhak Shamir Medical Center (formerly Assaf Harofeh Medical Center), Zerifin, Israel.
Email: rsvirs@gmail.com

Abstract

Objective: To evaluate the incidence of chromosomal aberrations and the clinical outcomes following the prenatal diagnosis of isolated perimembranous ventricular septal defect (pVSD).

Methods: This retrospective study was composed of a cohort of pregnant women whose fetuses were diagnosed with isolated pVSD. Complete examinations of the fetal heart were performed, as well as a postnatal validation echocardiography follow-up at 1 year of age. The collected data included: spontaneous closure of the pVSD, need for intervention, chromosomal aberrations and postnatal outcome.

Results: Fifty-five pregnant women were included in the study. 34/55 (61.8%) of the fetuses underwent prenatal genetic workup which revealed no abnormal results. No dysmorphic features or abnormal neurological findings were detected postnatally in those who declined a prenatal genetic workup during the follow-up period of 2 years. In 25/55 of the cases (45.4%), the ventricular septal defects (VSD) closed spontaneously in utero, whereas in 17 cases of this group (30.9%) the VSD closed during the first year of life. None of the large 3 VSDs cases (>3 mm), closed spontaneously.

Conclusion: Prenatally isolated perimembranous VSD has a favorable clinical outcome when classified as small-to-moderate size, children in our cohort born with such findings had no macroscopic chromosomal abnormalities.

Key points

What's already known about this topic?

- The detection rates of perimembranous ventricular septal defect (PVSD) is improving in recent years.

What does this study add?

- We found no evidence that isolated pVSD is a significant risk factor for chromosomal anomalies.
- Isolated small and medium size (<3 mm) PVSD's have a favorable clinical outcome with resolution either prenatally or within the infant's first year of life.

1 | INTRODUCTION

Congenital heart defects (CHD) are the most common of all major congenital malformations, with an estimated prevalence of about 0.3%–1.2% of all newborns.[1,2] The most prevalent cardiac malformations are ventricular septal defects (VSD). Ventricular septal defects accounts for up to 40% of neonates with cardiac malformations and 10% of fetal heart malformations].[2,3] Isolated VSD is defined as a defect in the interventricular septum (IVS) without other sonographic abnormalities. Isolated VSD can be divided into 4 groups according to its ventricular septal location as muscular, perimembranous, inlet, or subarterial. These defects are found in association with other structural cardiac defects and complex malformations.[4] Therefore, a detailed echocardiographic examination is indicated upon VSD detection as well as a genetic consultation. The latter is recommended given the proven association of chromosomal anomalies in 26%–32% of all prenatally detected VSD in two large studies.[5,6] Prenatal diagnosis of this common defect therefore usually results in an invasive procedure in order to rule out underlying chromosomal aberrations. The outcome of isolated VSD is considered to be favorable. Nevertheless, the prognosis and outcomes differ in terms of the VSD location. More accurately, small muscular VSDs detected prenatally are likely to close spontaneously or be hemodynamically insignificant postnatally. By contrast, prenatally diagnosed pVSD) are considered to be associated with genetic abnormalities and have worse clinical outcomes.[7] Although technological progress in ultrasound resolution has resulted in better prenatal detection of pVSD, little is known about its clinical and genetic outcomes. The rise in pVSD detection underscores the need for clear and coherent patient consultations on the expected prenatal course and postnatal outcomes of VSD to facilitate rational decision-making. Additionally, the changing approaches to screening for aneuploidy with the highly sensitive and specific non-invasive prenatal screen (NIPS) in the first trimester, fundamentally alters the population of fetuses presenting for second trimester survey and contemporaneous studies are needed.

The current study aims were to contribute to decision-making by clarifying the clinical and genetic outcomes of prenatally diagnosed isolated pVSD.

2 | METHODS

2.1 | Patient selection

Fetal echocardiographic examinations for pregnant women referred to our obstetrical ultrasound unit at the Shamir Medical Center were collected retrospectively for the period ranging from 1st January 2015 to 31 May 2021. Inclusion criteria were women with a singleton pregnancy where the pVSD was the only abnormal fetal finding. All women were subjected to at least two fetal echocardiograms, and the newborn were followed postnatal within the first month of life with at least one echocardiogram. Postnatal echocardiography within the first month of life as follow-up. All these women were offered genetic counseling and evaluation. Patient demographics and clinical information were retrieved from patient medical records and computerized patient management software. Postnatal clinical outcomes were obtained as part of the routine patient follow-up using telephone interviews. The parents were asked about the cognitive development of their child, his/her general physical health, and specifically whether there was a need for surgical intervention due to the pVSD.

2.2 | Echocardiographic parameters

The fetal echocardiography was performed by a single senior certified pediatric cardiologist of our team specialist in Fetal & Pediatric cardiology (L.G.K), who also reviewed all the prenatal echo exams for this study. Ultrasound scans were performed trans-abdominally with an E10 system (GE healthcare, Milwaukee, WI). Perimembranous ventricular septal defect were demonstrated by greyscale and color Doppler using standard views (at least 2) but mainly the long axis view, and measured in greyscale if possible (Figure 1). The ultrasound beam was situated as perpendicularly as possible with reduction of the color velocity to a low limit. The pVSD was characterized as small solely by qualitative estimation and as medium or large by both qualitative and quantitative estimation. A pVSD was defined as small if only color was detected passing through the septum with no visible gap/defect in greyscale.[8] Medium was defined as a pVSD that was visible both on greyscale and color and the pVSD measurement on the greyscale was up to 3 mm. Large pVSD was defined as a pVSD measured in greyscale >3 mm.

2.3 | Data collection

The following parameters were collected and anonymized:

Prenatal data: maternal age, gravity, parity, abortions, indications for fetal echocardiography, history of congenital heart disease (CHD), gestational age (GA) during first exam and follow up, pVSD patent or not at follow-up, estimated size of the VSD, other cardiac malformation, intrauterine or postnatal closure, genetic analysis including results for NIPS, chromosomal microarray (CMA) and additional case specific investigation if performed.

Postnatal data: collected by neonatal record review and parents' phone questionnaire, GA at birth, birth weight, mode of delivery, postnatal echocardiography – age when acquired and results for each echo conducted during first year of life (Figure 2), postnatal treatment if required as well as, postnatal relevant morbidity.

2.4 | Statistical analysis

Descriptive statistics was used to extract frequencies and percent for categorical variables and medians and standard deviation for
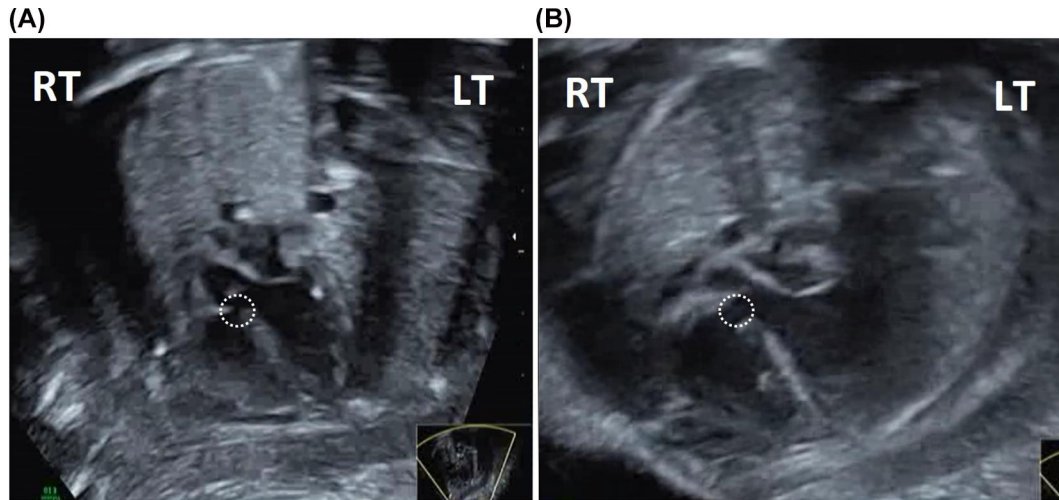
FIGURE 1 A + B –Prenatal ultrasound image of perimembranous ventricular septal defects (VSD) demonstrated in grey scale [Colour figure can be viewed at wileyonlinelibrary.com]
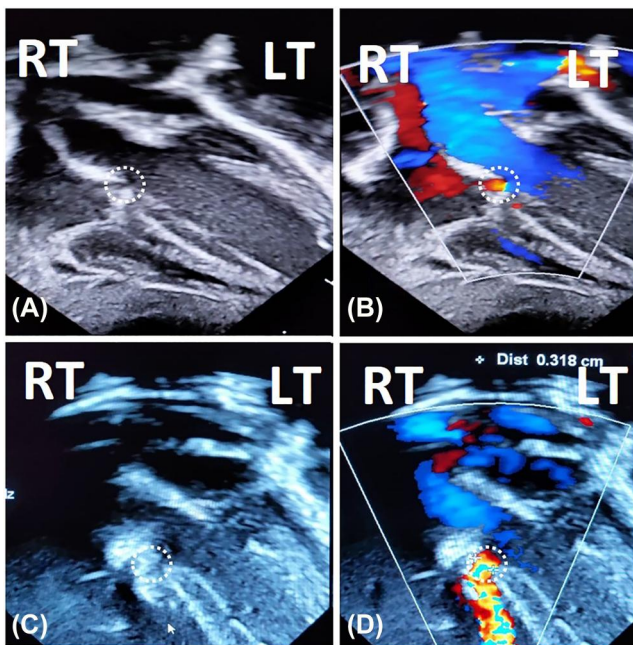

FIGURE 2 A + C -Postnatal ultrasound image of perimembranous ventricular septal defects (VSD) demonstrated in grey scale. B + D – Postnatal ultrasound image of perimembranous VSD demonstrated in grey scale and color doppler [Colour figure can be viewed at wileyonlinelibrary.com]

continuous variables. Aneuploidy rates (like trisomy 21 in the second trimester) and aneuploidy for other isolated cardiac or other structural anomalies and CMA in general fetal population without,[9] and with anomalies[10] were compared to aneuploidy rates in fetuses with isolated VSD, as was previously described.

Data analysis was performed using SPSS software version 27 (IBM Inc., Armonk, NY). Continuous variables were assessed using Student t-test or Mann–Whitney test as appropriate. Nominal variables were compared using the chi-square test or Fisher's exact test,

as appropriate. A two-tailed p-value of <0.05 was considered statistically significant. The study protocol was approved by the local IRB (023-18-ASF).

3 | RESULTS

3.1 | Patient characteristics

During the study period a total of 356 fetuses were diagnosed with VSD. There were 55 cases of isolated pVSD who met our inclusion criteria and formed the study cohort and all the others were excluded (Figure 3). Of these, 27/55 (49.1%) were diagnosed in the late second trimester (18–25 weeks of gestation), and the remaining 28/55 (50.9%) during the third trimester.

The baseline maternal and pregnancy details are depicted in Table 1. The median GA at diagnosis was 25.1 (22.6–29.3 weeks of gestation) and the leading indication was soft markers for aneuploidy noted on ultrasound scan (32.7%) followed by a family history of CHD (21.8%).

3.2 | Genetic outcome

All pregnant women were at low risk for trisomy 21 based on history, serum PAPP-A and Beta human chorionic gonadotropin markers, and normal nuchal translucency. After the detection of pVSD, all were referred to genetic evaluation. Of the 55 patients in this group, 34 (61.8%) had genetic counseling, and from this group NIPS test was taken by 4 (7.3%), and 30 (54.5%) went through invasive amniocentesis and CMA. Of these 34 fetuses with a prenatal diagnosis of isolated pVSD, none had pathogenic or likely pathogenic copy number variants, or high-risk NIPS results. In those women who declined invasive testing, none of the
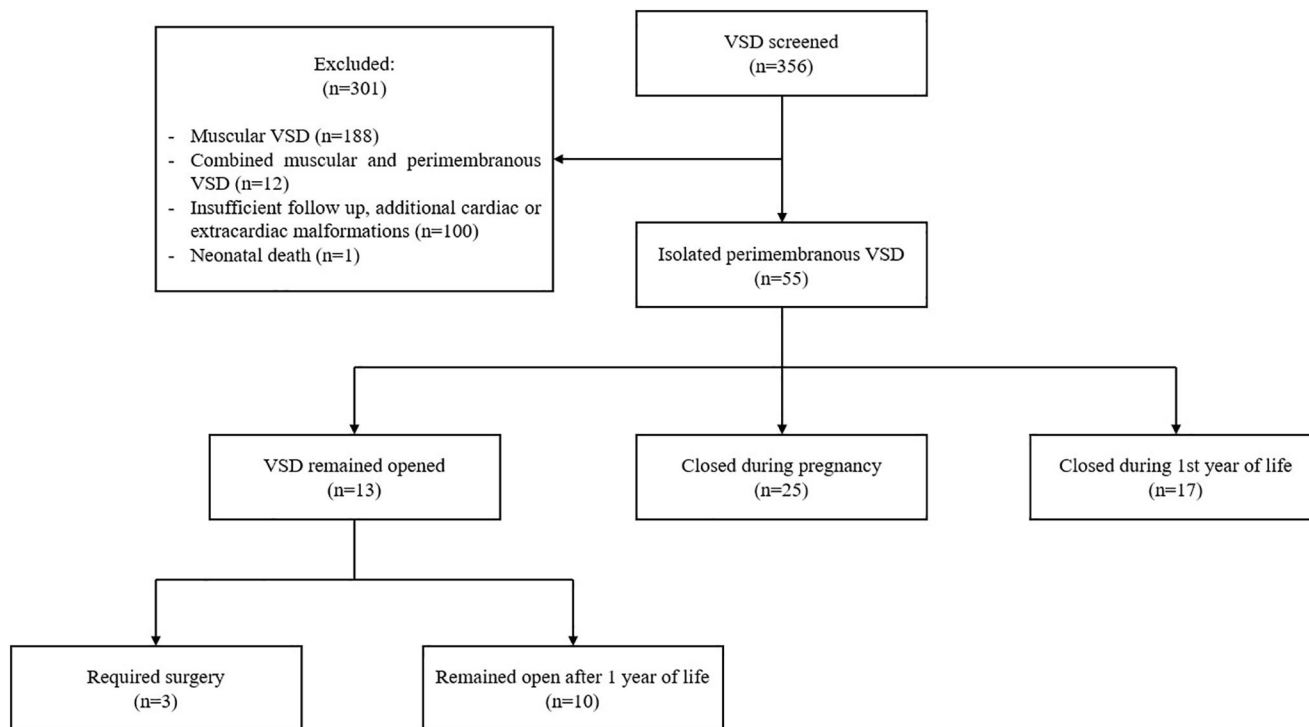
FIGURE 3 Study design and patient inclusion flow

infants had dysmorphic features or abnormal neurological findings on the postnatal pediatric evaluation, during the follow-up period of 2 years, that would have necessitated karyotype testing after birth. Maternal age difference was non-significant when comparing those who underwent genetic workup with those who declined it. ($p > 0.05$).

3.3 | Clinical outcomes

In 25/55 (45.4%) of the cases the VSD closed spontaneously in utero (12 before 30 weeks of gestation and 13 between 30 weeks of gestation and the first month of life). In 17/30 (56.7%) cases the VSD closed during the first year of life whereas in 13/55 (23.6%) cases, the VSD remained patent. When comparing the 3 groups, no significant differences in maternal or fetal parameters (such as GA of pVSD) were detected.

The comparison of the same parameters by closure status up to 1 year of age revealed no significant differences apart from the estimated prenatal VSD size. Most VSDs (50/55) were considered small, and most of these small VSDs (40/50small VSDs) closed either prenatally or during the first year. The VSD was more likely to close by one year of age if estimated prenatally as being small ($p = 0.045$; Table 2). Ten out of 13 (77%) of the VSDs that did not close spontaneously (during the first year of life) were estimated as small, and all were considered asymptomatic and they only required pediatric cardiologist follow-up.

The remaining 3 cases were the only VSDs in the cohort that were defined as large in size (VSD measured on greyscale/color Doppler >3 mm). All 3 cases suffered from congestive heart failure symptoms and required postnatal treatment with medications and later on surgical repair, with uneventful outcome.

4 | DISCUSSION

Ventricular septal defects is the most common CHD diagnosed postnatal, with an incidence of 1/1000 live births.[1] Among the 34 with either NIPS or CMA, no genetic etiology was identified, and the clinical outcomes of pVSD measuring less than 3 mm were favorable. To the best of our knowledge, this is the largest reported cohort of isolated pVSD prenatally diagnosed and postnatally followed. The following parameters can help explain the growing numbers of prenatal diagnoses of isolated minor CHD in the last few years: 1. The use of more advanced ultrasound equipment in terms of resolution and precision. 2. Better training of both doctors and technicians. 3. An increased number of ultrasound scans per woman for each pregnancy. These factors increase the prenatal detection rate of even minor cardiac anomalies (small VSD) and may even result in an earlier prenatal diagnosis.[11] Furthermore, the 5-chamber view included in the International Society of Ultrasound in Obstetrics and Gynecolo gy (ISUOG) anomaly scan of the heart guideline, has improved the pVSD detection rate.[12] This has resulted in the need for a more precise parental consultation in terms of management, which is directly outcome-related.

TABLE 1 Demographic parameters

Variables		Median	IQR	Number (%)
Maternal age (years)		32	9	
VSD exist at 1st exam or follow up	Only 1st exam			16 (29.1%)
	Both exams			24 (43.6%)
	Only follow up			4 (7.3%)
GA at 1st echo (weeks)		25.1	6.7	
GA at 2nd echo (weeks)		29.4	5.4	
Indication for fetal echo	Susp cardiac malformation			9 (16.4%)
	Soft marker			18 (32.7%)
	Family history (HX)			12 (21.8%)
	Teratogenic event			9 (16.4%)
	Others			7 (12.7%)
Gravity	1–3			44 (80%)
	>3			7 (12.7%)
Parity	0			19 (34.5%)
	1–3			33 (60%)
Abortion	0			34 (63.0%)
	1–2			14 (26%)
	>3			2 (3.6%)
Wight at birth (gram)		3175	480	
GA at birth (weeks)		39	2	
Fetal gender	Female			24 (53.3%)
	Male			21 (46.7%)
Child current age (years)		2.0	3.5	
Familial HX of CHD	Non			45 (81.8%)
	Exists			9 (16.4%)
Genetic workup	Non			21 (38.2%)
	CMA			30 (54.5%)
	NIPS			4 (7.3%)
Estimated VSD size prenatally	Small			50 (90.9%)
	Medium			2 (3.6%)
	Large			3 (5.5%)

Note: VSD-ventricular septal defect; Teratogenic event (diabetes/ART/DRUGS); Others (technical/anti ro/no indication); GA -gestational age; CMA-chromosome microarray; NIPS-Noninvasive prenatal screening; IQR–interquartile ratio.

Perimembranous ventricular septal defect may be associated with complex cardiac as well as extracardiac anomalies.[13] Therefore, further recommended diagnostic tests including a detailed anomaly scan as well as fetal echocardiography. Two large studies concluded that a fetal isolated VSD diagnosis increases the risk of aneuploidy mainly when associated with extracardiac anomalies, thus requiring genetic consultation and further genetic diagnostic tests[5,6] Nevertheless, it remains unclear whether the diagnosis of isolated pVSD

warrants the same approach as these are studies from the years 2000, 2006 a time when the ultrasound resolution was inferior in comparison with our time and thus, might include fetuses with other anomalies that were missed. In order to be able to resolve this specific dilemma, the evolution of prenatally diagnosed isolated pVSD and its outcome must be definitively established. Studies on the association of isolated VSD with chromosomal aberrations have revealed a 1.2–5.5 fold risk increase.[7,13–17] However, these data

TABLE 2 Comparison of 2 groups: ventricular septal defects (VSD) closure versus non-closure until the age of 1 year

	Variables	VSD closed prenatally or till the age of 1 year			VSD still open			p
		Median	IQR	Number (%)	Median	IQR	Number (%)	
Maternal age (years)		32	7		32	8.0		>0.05
GA at 2nd echo (weeks)		29.4	5		29.8	5.9		>0.05
GA at 1st echo (weeks)		23.6	6		28.0	6.0		>0.05
Indication for fetal echo	Susp cardiac malformation			6 (14.3%)			3 (23.1%)	>0.05
	Soft marker			16 (38.1%)			2 (15.4%)	>0.05
	Family history (HX)			8 (19%)			4 (30.8%)	>0.05
	Teratogenic event			7 (16.7%)			2 (15.4%)	>0.05
	Others			5 (11.9%)			2 (15.4%)	>0.05
Gravidity	1–3			35 (83.4%)			9 (69.3%)	>0.05
	>3			5 (11.9%)			2 (15.4%)	>0.05
Parity	0			16 (38.1%)			3 (23.1%)	>0.05
	1–3			24 (57.2%)			9 (69.3%)	>0.05
Abortion	0			27 (64.3%)			7 (58.3%)	>0.05
	1–2			12 (28.6%)			2 (16.7%)	>0.05
	>3			0 (0%)			2 (16.6%)	>0.05
Weight at birth (gram)		3165	505		3393	760		>0.05
GA at birth (weeks)		39	2		39	1		>0.05
Fetal sex	Female			21 (55.3%)			3 (42.9%)	>0.05
	Male			17 (44.7%)			4 (57.1%)	>0.05
Child current age (years)		2.0	4.5		2.5	1		>0.05
Familial HX of CHD	Non			34 (81.0%)			11 (84.6%)	>0.05
	Exists			7 (16.7%)			2 (15.4%)	>0.05
Genetic workup	None			17 (40.5%)			4 (30.8%)	>0.05
	CMA			23 (54.8%)			7 (53.8%)	>0.05
	NIPS			2 (4.8%)			2 (15.4%)	>0.05
Estimated VSD size prenatally	Small			40 (95.2%)			10 (76.9%)	**0.045**
	Medium			2 (4.8%)			0 (0%)	>0.05
	Large			0 (0%)			3 (23.1%)	>0.05
First echo age (years)		0	0		0	1		>0.05
Last echo age (years)		3	6		5	11		>0.05
Cardiac operation	None			42 (100%)			10 (76.9%)	>0.05
	Required			0 (0%)			3 (23.1)	>0.05

Note: IQR-interquartile ratio; VSD-ventricular septal defect; Teratogenic event (diabetes/ART/DRUGS); Others (technical/anti ro/no indication); GA-gestational age; CMA-chromosome microarray; NIPS-Noninvasive prenatal screening.

were collected from small cohorts, without a uniform definition of isolated VSD or a categorization by VSD type. Gomez et al. evaluated the risk of associated chromosomal anomalies in 32 prenatally diagnosed isolated pVSD cases; only one had a chromosomal anomaly with a 3.1% risk and no T21 cases.[7] The same fetus also had an increased nuchal translucency on the first trimester scan and the indication for performing echocardiography was the abnormal karyotype. Another study (with a smaller cohort) that focused on isolated VSD genetic outcomes with a categorization by VSD type revealed that 1/11 (9.1%) had a risk of T21 with a prenatal diagnosis of isolated pVSD.[19] While the majority of VSD diagnosed with T21 are membranous and perimembranous, Shen et al. specifically raised

the issue of the risk of T21 when isolated VSD was diagnosed, based on a cohort of 92 cases. To note, one third of the VSD included in their study were the perimembranous type and the rest were either muscular VSD or ill-defined, with no case of T21 detected. Their conclusion was that T21 is uncommon when VSD is the only sonographic abnormality detected.[20]

Our study was composed of a cohort of 55 prenatally diagnosed isolated pVSD. Most women in the cohort 34/55 (61.8%) underwent either NIPS or CMA testing that revealed no chromosomal aberration. Moreover, the 21 women who refused prenatal genetic testing, reported postnatal normal development and no dysmorphic features as detected by pediatricians spanning an age range when most infants and children would have genetic testing initiated if physical and neurologic exam was of concern. This is in line with the argument put forward by Shen et al. that when pVSD is the only finding in the fetus identified during an anomaly scan and screens for aneuploidy are normal, the risk of chromosomal aberration (mainly trisomy 21) is not increased above the background risk. While reassuring, our and all prior studies are limited by sample size. For trisomy 21 alone (1/600), a cohort of ~1000 fetuses with pVSD would need to be included in the assessment to detects a 2-3-fold increase in the probability to develop trisomy 21 at a confidence level of 0.9.

In terms of clinical outcomes, almost half of the pVSD closed prenatally with an additional 30.9% closure within the first year of life. Therefor a total of three fourths of the pVSD closed spontaneously either during the pregnancy or the first year of life without further medical or surgical intervention.

Our findings are consistent with several studies that have reported prenatal closure rates for perimembranous type VSD to be 50%–62%, with a higher probability of closure compared to muscular VSD (5,6,18). This relationship between the VSD type and spontaneous closure was speculated to be linked to the different closing mechanisms of each type of VSD. The mechanism of spontaneous closure of membranous type VSD is mainly due to reduplication of the tricuspid valve tissue and its adherence. This process is presumed to initiate prenatally, as suggested by Nir et al.[22] Young Sun Cho et al. considered that a perimembranous site as well as the small size of the VSD are 2 out of 3 good prognostic factors for fetal closure (the third factor was maternal age <25years).[18] Here as well, the prenatal evaluation of small pVSD was correlated with better chances of spontaneous closure up to the age of 1 year ($p < 0.05$). Studies have shown that VSD size is inversely proportional to the likelihood of spontaneous closure.[5,23] Although there is no universally accepted definition for the relationship between VSD size and its natural history, it was reported that 3 mm is the upper limit for VSD size to result in spontaneous closure.

The only cases described as large prenatally (>3 mm) required postnatal intervention in our cohort. These 3/55 cases (5.5%) did not close spontaneously and required surgical repair within the first few months of life, with favorable outcomes. Although previous studies have reported that 29%–36.3% of all prenatally detected pVSD required postnatal treatment (either surgery or catheterization), these studies were composed of smaller cohorts or non-isolated

malformations and in one, the follow-up was up to adulthood and therefore could be an over-estimation.[13,19,24]

This study has several limitations. Because it was retrospective, there could be a potential bias arising from incomplete data. While this study and the literature provide a starting point for parental counseling of pVSD, improved parental consult requires a prospective study with a larger cohort. In addition, the large percentage of intrauterine closure may suggest overdiagnosis. However, the examinations were conducted by an experienced single senior pediatric cardiologist, whose diagnosis was based on at least two different views of the IVS, and a bidirectional shunt across the defect.

Thus overall, to the best of our knowledge, this is the largest study in the last 5 years to link prenatal diagnosis and management of pVSD with postnatal outcomes.

These findings can contribute to more effective parental counseling by providing parents with a clearer picture of the expected outcomes. Although our and sample size cannot adequately address this question. Our current study would suggest the risk of aneuploidy for pVSD does not reach that of a fetus with multiple anomalies (15%–20%) or some categories of isolated cardiac anomaly (5%–10%). For small VSDs, our results confirm high intrauterine/postnatal closure rates and/or the lack of substantial morbidity within the first year of life which should help reassure parents. In contrast, large VSDs detected during prenatal assessment are likely to require postnatal intervention, with good outcomes. The increasing use of noninvasive prenatal diagnosis in the first trimester is changing the composition of second trimester fetuses presenting for survey. Additionally, improved imaging techniques are increasing the detection of subtle findings which may or may not be associated with aneuploidy or perhaps more likely pathogenic copy number variation or sequencing changes. Continued studies will need to consider these aspects in order to provide informed parental counseling.

CONFLICT OF INTEREST

None.

ETHICS STATEMENTS

Approved by local committee.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Noa Feldman https://orcid.org/0000-0002-7522-9171
Yaakov Melcer https://orcid.org/0000-0002-7014-5892
Ran Svirsky https://orcid.org/0000-0001-6884-6502

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