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# Ventricular septal defect: diagnosis and treatments in the neonates: a systematic review

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## Original Article

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## Abstract

*Background:* Medical advancements have encouraged minimally invasive surgical repair of congenital heart defects such as ventricular septal defects (VSDs), and the diagnostic process can now be carried out using non-traditional techniques such as pulse oximetry. This, in turn, has improved clinical outcomes with reduced complication rates post-surgery. However, the variations in type of VSDs, age of patient, comorbidities, and access to closure devices may limit the efficacy of surgical advancements. *Methods:* Articles were identified amongst Scopus, MEDLINE, and PubMed using various relevant search strings using PRISMA guidelines. Of the 115 articles initially extracted, 10 were eventually reviewed after duplicates and irrelevant studies were removed. *Results:* Of the 24 eligible articles, 10 papers were selected for analysis. Minimally invasive approaches to VSD repair was associated with satisfactory short-term outcomes when compared to open repair. For diagnosis of congenital VSD, whilst recent advances such as pulse oximetry method and genome analysis are more sensitive, the limited availability and access to such investigatory methods must be recognised. *Conclusion:* Pulse oximetry and fetal echocardiography are established non-invasive diagnostic tools for VSD. The recent advances in minimally invasive treatment options including periventricular approach and transcatheter techniques have improved patient outcomes, yet at the expense of higher residual rates. Careful patient selection for each technique and follow-up should be planned through multidisciplinary team meetings.

Ventricular septal defect (VSD) is the most common type of congenital heart defect, and is responsible for approximately 32% of all heart defects diagnosed during the first year of postnatal life.[1] VSD can occur sporadically or in association with TBX5 and GATA4 gene mutations, and is commonly associated with other congenital anomalies.[2] Foetal cardiac anomalies can be found in patients with no identifiable risk factors, and therefore examination of the foetal heart is an integral part of routine obstetric ultrasound.[3]

Echocardiographic prenatal diagnosis of congenital heart defects such as VSD is challenging. It requires a team of specialists and subspecialists as well as sonographers. Moreover, the sensitivity of detection is highly variable and depends on many factors such as operator experience, gestational age, and the position of the foetus. This can result in patients with clinically significant CHDs being missed, as approximately 10–30% of patients who die from CHD are undiagnosed until autopsy.[4]

To combat this, pulse oximetry measurements can be utilised in order to aid the identification of newborns who may benefit from early treatment of CHD. This is a painless and easily accessible examination that can be effortlessly fitted into the assessment of newborns. It is used to measure the capillary concentration of oxygen-saturated haemoglobin in an extremity, and the reading is expressed as a percentage.[5]

Surgical intervention may be required if the infant fails to gain weight and develop adequately, or symptoms of heart failure develop requiring pharmacological treatment.[6] Traditionally, treatment for large muscular VSDs consisted of open surgical closure, through sternotomy (an incision made in the middle of the sternum giving access to the heart), with cardiopulmonary bypass. The defect is usually accessed through the atrioventricular or semilunar valves, and this has the benefit of avoiding the need for ventriculotomy.[7] Potential complications of open surgery include complete heart block, residual VSD, neurologic injury, or even death.[8] New minimally invasive techniques of VSD repair have increasingly become a viable management option. This eliminates the need for cardiopulmonary bypass and can potentially decrease the length of recovery and hospital stays.



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### Aim of this study

The primary aim of this literature review is to explore and discuss existing diagnostic and therapeutic options for neonatal ventricular septal defects.

## Methodology

### Search strategy and selection

Using the search strings "Congenital VSD diagnosis", "Congenital VSD screening", "congenital VSD management", and "congenital VSD treatment" on Scopus, PubMed, and MEDLINE, 115 articles were initially identified following PRISMA guidelines. These databases were used as they are large and easily accessible. The references of studies found were also searched to identify additional studies that may be of interest. It was decided to use these search strings as they allowed the acquisition of an appropriate number of papers whilst also ensuring the results were narrowed down and relevant to the aims of the review.

The eligibility criteria utilised for this review were as follows:

- Studies published within the last 10 years (2010–2020).
- Any study design including randomised control trials, non-randomised control trials, prospective or retrospective cohort studies, or systematic reviews.
- Studies focusing on diagnostic investigations for VSD, and studies comparing transcatheter versus open surgical closure of defects.

Specific exclusion criteria were used in order to further reduce the numbers of papers, and these were as follows:

- Age – papers more than 10 years old were automatically excluded.
- Language – the paper must be in English, and not require translational services.
- Content – the paper must have a specific focus on the effectiveness of either the screening, diagnosis, or treatment processes.

The utilisation of the inclusion and exclusion criteria was followed by a manual analysis of the remaining papers, in order to deem if relevant to include in the analysis.

## Results

Searches of relevant databases and application of inclusion and exclusion criteria resulted in 24 papers being eligible. Ten of these papers were selected for analysis and in-depth review.

Searches were conducted without any date restrictions and identification of articles was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[9] The flowchart is illustrated in Fig 1. Of the initial 115 articles, 10 were eventually reviewed (Fig 1). The characteristics and outcomes of the selected studies are demonstrated in Table 1.

Critical Appraisal Skills Programme (CASP)[14–16] checklist for systematic review was employed to help analyse the studies selected. This particular programme was used as it allowed for a thorough, in-depth review of the literature.

## Discussion

### Risk factors for VSD

There are a variety of genetic and environmental factors predisposing to VSD. These are summarised in Table 2.

The majority of cases are attributed to multifactorial causes with Trisomy 21 being the commonest genetic association. VSDs commonly present with other septal defects, particularly ASDs in cases of genetic septal defects. Alcohol and illicit drug use is associated with septal malformation, thus, predisposing to VSDs. This may be explained by the effect of the teratogen on outflow tract formation and migration of neural crest cells resulting in a malformed cardiac septum. Sands et al[17] conducted a study to assess the incidence of VSDs in "low-risk" neonates, and to identify risk factors. The study also found a gender association, with girls having a higher incidence of VSDs (p=0.004) than boys in a population of 173 "low risk" infants.[17]

### Diagnosing VSD

Congenital heart defects are predominantly diagnosed in utero using foetal ultrasonography. However, there is a risk of clinically significant defects being missed on an initial investigation, which can have implications on the timing of treatment initiation. This is evidenced by Van Nisselroojj et al who found that many congenital heart defects are still missed in prenatal screening programmes.[18] It was found that the major reason for this was the inadequate quality of the second-trimester standard anomaly scans used in the missed group. In 49% of the missed cases, inadequate imaging was the main cause which raised the lack of detection of congenital heart defects.[18] This study concluded that congenital heart defects were being missed due to poor adaptation skills which caused poor quality SAS.[18] Missed congenital heart defects can have grave implications on the infants' health and delay the timing of treatment initiation. However, if left till late, missed congenital heart defects can result in severe morbidity or death.

A multicentre prospective cohort study was conducted in 2017 by Chu et al[13] which evaluated the effectiveness of foetal echocardiography in the prenatal diagnosis of congenital heart defects. Women in the first trimester of pregnancy were recruited for the study; those eligible were given detailed fetal echocardiography during the second trimester of pregnancy (18–28 weeks). A total of 10,259 pregnant women were included in the study, split into high and low-risk groups. The study found that fetal echocardiography was highly sensitive for detecting major congenital heart defects, but was less sensitive in diagnosing minor defects. When compared with muscular VSDs, perimembranous VSDs had greater sensitivities, but this was still markedly lower than major congenital heart defects such as Hypoplastic Left Heart Syndrome.[13] It was concluded that the utilisation of fetal echocardiography would be beneficial in the detection of major defects and would, therefore, aid parental counselling.[13] However, there was still a risk of delayed diagnoses due to the reduced sensitivity of echocardiography in detecting minor defects.

Early measurement of pulse oximetry can be utilised as an option to promote early detection of congenital heart defects including VSD.[19] The PulseOx study[12] was a prospective test accuracy study aiming to assess the accuracy of pulse oximetry as a screening tool for congenital heart defects such as VSD. The study analysed all asymptomatic babies born at six maternity units in the United Kingdom (20,055 babies in total), who were screened with pulse oximetry prior to discharge. Subsequently, infants not achieving predetermined oxygen saturations were given echocardiography after clinical examination.[12] The results of the study found that 50% of the babies with critical congenital heart defects had already been suspected at the antenatal screening, but 36% of those with major congenital heart defects (critical and serious) had been detected at screening. Six babies with critical congenital heart

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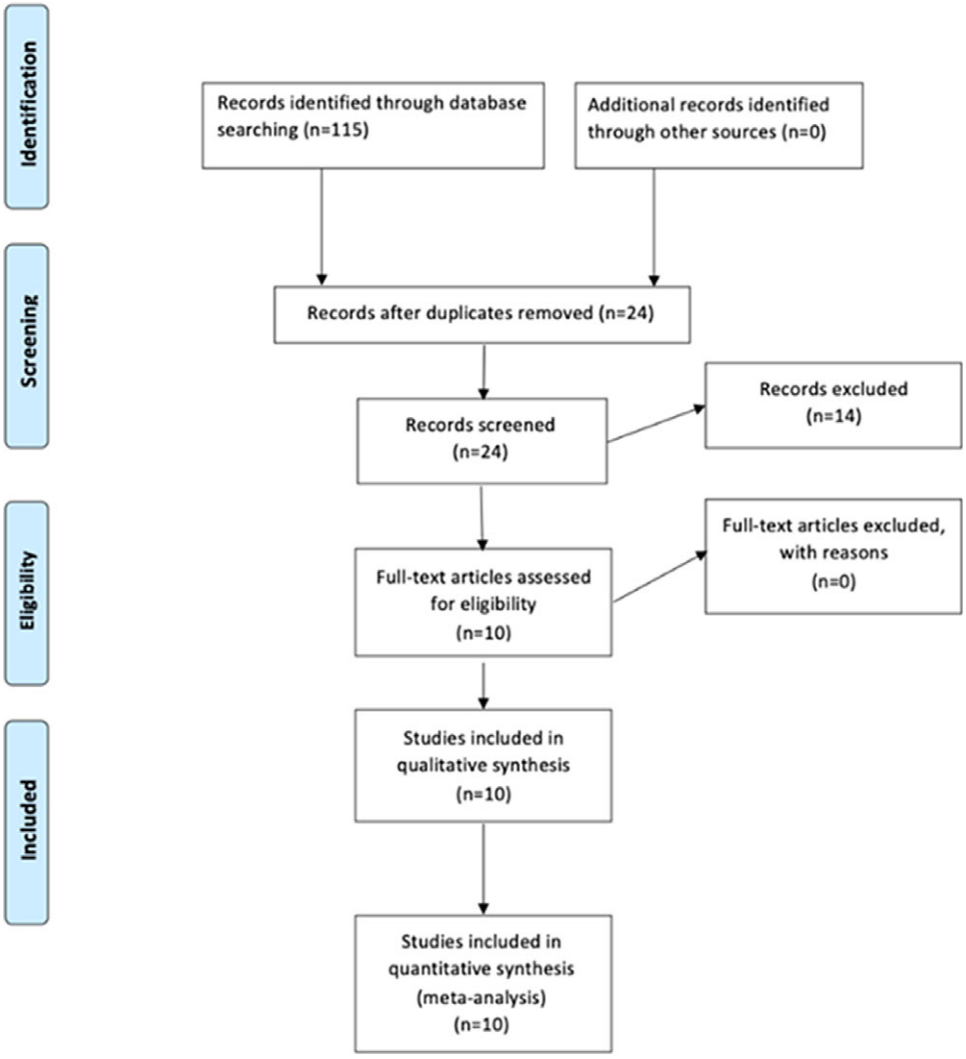


**Figure 1.** PRISMA chart of search results.

defects were falsely negative on pulse oximetry, and a further 21 babies with normal pulse oximetry findings had serious congenital heart defects such as VSD. The overall sensitivity of pulse oximetry was found to be 76% for critical cases, and 49% for serious cases.[12] The study, therefore, concluded that pulse oximetry was a "safe, feasible test" that aids in the screening process by helping to detect cases of critical CHD that aren't detected by ultrasound.[12] These findings are further supported by another pulse oximetry study by Xiao-jing Hu et al who tested the use of pulse oximetry on 4128 newborn infants without a prenatal diagnosis of congenital heart defects.[20] Of these infants, 19 were found to have critical congenital heart defects.[20] However, if pulse oximetry was not used then there would have been seven missed cases of congenital heart defects.[20] Therefore, this study concluded that incorporating pulse oximetry into the screening process for congenital heart defects was vital in preventing delayed cases which would have been detrimental for those infants' health.

### *Indications for repair of VSD*

Indications for surgical intervention in VSD vary depending on the characteristics of the defect, such as the size and anatomical type. Small defects don't require surgical closure as they usually undergo spontaneous closure. However, intervention may be required if the defect is moderately sized. Indications for closure in these cases include failure to thrive and poor development, significant enlargement of the left atrium or ventricle and/or elevated pulmonary arterial pressure, or a pulmonary–systemic flow ratio of greater than 2:1.[21] Another indication for surgical repair is the development of significant aortic regurgitation due to prolapse of one of the aortic cusps. If congestive heart failure is present, it should be treated promptly. If the defect is large, a surgical closure is indicated in cases where systolic pressures in the right ventricle and pulmonary artery are close to left ventricular and aortic pressures.[21]

### *Open versus minimally invasive approaches to VSD closure*

Traditionally, patients with VSD requiring treatment underwent open surgical intervention, however with advances in medical technology, there are now minimally invasive options available. Liu H et al conducted an open-label randomised controlled trial comparing the traditional open surgical approach to the new minimally invasive periventricular approach.[10] This study found that

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**Table 1.** Summary of study characteristics included in this review.

| Author(s) | Study dsign | Cohort number | Baseline characteristics | Key outcome measures |
|---|---|---|---|---|
| Liu H et al[10] | Randomised control trial | 200 patients | Patients were aged between 5 and 60 months, with 104 girls and 96 boys. | VSD closure decreased adverse effects in the patients; however, open repair had a higher rate of complete closure. |
| Yang J et Al[11] | Prospective randomised controlled trial | 229 children with pmVSD | 465 patients aged between 3 and 12 years with VSD were assessed for eligibility, and 229 were included in the study. | Transcatheter device closure is the treatment of choice for pmVSD in children in this cohort due to decreased morbidity and hospital stay length. |
| Ewer AK et al[12] | Test accuracy study | 20,055 newborn babies. | Pulse oximetry testing was performed on 20,055 eligible patients. Children not achieving the oxygen saturation threshold underwent echocardiography. | Pulse oximetry was found to be 75% sensitive for diagnosing critical cases and 49% sensitive for the diagnosis of major congenital heart defects. |
| Chu et al[13] | Prospective cohort study | 10,259 pregnant women | Women were allocated to either high or low-risk groups. The high-risk group consisted of pregnant women between 18 and ≤28 gestational weeks. The low-risk group was randomly recruited pregnant women between 18 and 24 weeks gestation. | Fetal echocardiography was found to have a high detection rate for major congenital heart defects, but a lower detection rate for minor defects. |
| Hu et al[18] | Cohort study | 4128 infants | Newborn infants admitted to the neonatal ICU at a hospital in China. | The addition of pulse oximetry increased the detection of critical CHDs. |
| Van Nisselrooji et al[19] | Case-control study | 198 infants | All patients either had a prenatal diagnosis of CHD or postnatal diagnosis of severe CHD in the Amsterdam and Leiden regions. | Operator skills when performing imaging is an important factor causing CHD to be missed. |
| Moreno-Medina et al[23] | Cohort study | 157 children | Patients aged between 2 and 18 years with a confirmed diagnosis of CHD. | Quality of life in children with CHD can be lower than healthy children. |
| Mellion et al[24] | Cross-sectional survey | 1909 children and adolescents | Children and adolescents with CHD were compared with healthy controls. | Children and adolescents with CHD had a significantly lower health-related quality of life than healthy controls. Management must focus on both physical and psychosocial health. |
| Kovalenko et al[29] | Registry-based study | 52,253 newborns | All singleton births in Murmansk County, Russia between 1 January, 2006 and 31 December, 2011. | Alcohol abuse during pregnancy and diabetes mellitus are risk factors for VSD. Defects were more common in females. |
| Thakkar et al[30] | Cohort study | 24 infants | High-risk infants with isolated large muscular VSD. | Periventricular closure of isolated muscular VSD can be used in addition to the conventional approach or may be a feasible replacement. |

**Table 2.** Outline of the genetic and environmental factors attributing to VSD.

| Genetic | Environmental |
|---|---|
| Trisomy 18, 21 | Maternal diabetes |
| Microdeletion of long arm of Ch 22 | Maternal cigarette smoking |
| | Maternal alcohol consumption |
| | Maternal illicit drug use |

periventricular closure of ventricular septal defects was associated with a decreased rate of haemodynamic compromise, disorders of respiratory mechanics and cardiomyocyte viability, and tissue perfusion when compared with surgical closure.[10] However, it was also found that open surgical approaches were associated with a greater degree of complete defect closure than the periventricular technique. Continuous data were presented as means and standard deviations and compared by t-test by adhering to the normal Gaussian distribution.[10]

In 2014, Yang J et al randomised 229 infants into two treatment arms, one receiving open surgical closure and the other undergoing a minimally invasive transcatheter approach.[11] The infants were followed up for 2 years afterwards and a record was made of any major/minor adverse events, and laboratory testing was carried out measuring levels of CK-MB, ALT, BUN, and cTnI. Also, an echocardiogram was conducted 3 days after surgery to measure the degree of VSD closure. The results of the study found that neither the transcatheter or surgical procedures were associated with mortality or major adverse effects. However, there were 32 minor adverse effects in the surgical group and 7 in the transcatheter group (32.3% versus 6.9%). Fisher's exact test was used to establish statistical significance, and there was a significant difference in minor adverse events found ($p < 0.001$).[11] The study concluded that the transcatheter approach has a lower incidence of injury to the myocardium and is associated with a faster recovery and shorter hospital stay (Table 3).

## VSD and other pathologies

VSD results in a shunt creation between the right and left ventricles. The degree of blood shunted and the direction of flow can determine the severity and haemodynamic significance. The pathophysiology of VSDs arises from a failure of development

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**Table 3.** Comparative outcomes of studies reporting on minimally invasive versus open repair of ventricular septal defect (VSD).

| Study | Cohort | Key outcomes |
|---|---|---|
| Liu H et al[10] | Minimally invasive n=98<br>Open repair n=98 | – Mortality – 0.<br>– ICU stay – N/A.<br>– Residual – N/A.<br>– Complications – (periventricular closure had two major adverse events) – complete atrioventricular block, more than moderate valve regurgitation (open surgery had one major adverse event) – protamine reaction requiring cardiopulmonary bypass. |
| Yang J et al[11] | Minimally invasive n=101<br>Open repair n=99 | – Mortality – 0.<br>– ICU stay (hours) – 20.1 (open repair), 0 (trans catheter).<br>– Residual – 200 alive.<br>– Complications- (minimally invasive had 7 minor adverse events) – (open repair had 31 minor adverse events + 1 major adverse event) – major adverse event was thoracic re-exploration. |
| Thakkar et al[30] | Minimally invasive n=21<br>Open repair n=3 | – Mortality – 3.<br>– ICU stay (days) – 3.<br>– Residual – 21 alive.<br>– Complications – hypokalaemia, bronchopneumonia, gastroenteritis, complete heart block, LVOT obstruction, oesophageal tear. |

or fusion of the interventricular septum[22]. Membranous VSDs are the commonest subtype overall, whereas atrioventricular canal VSD (AVSD) are seen in Down syndrome. Muscular VSDs tend to occur in children due to the spontaneous closure with age. VSDs tend to occur in conjunction with other congenital heart defects. Most frequently, they are seen in tetralogy of Fallot, transposition of great arteries, and with pulmonary atresia.

TOF involves a VSD along with right ventricular hypertrophy, overriding aorta, and pulmonary stenosis. Pulmonary atresia with VSD can occur as a congenital defect due to an underdevelopment of the right ventricular outflow tract along with atresia of the pulmonary valve and trunk. Management of VSD varies with associated syndromes and other cardiac defects. For instance, definitive management of transposition of the great arteries involves an arterial switch (Jatene) procedure whilst VSD in pulmonary stenosis requires the Rastelli procedure[23]. Multistep surgical correction is often required when VSD occurs in conjunction with other cardiac defects.

### *Prenatal screening*

Early detection of congenital heart defects such as VSD is crucial in ensuring the best possible outcomes for patients, therefore it is important to have an effective prenatal screening process. In most countries, the screening process consists of a scan taking place at approximately 20 weeks gestation.[24] Both high and low-risk pregnancies are screened, and this is critical as risk factors are identified in only 10% of patients diagnosed with defects.[25] Van Velsen et al[26] conducted a geographical cohort study evaluating the effectiveness of a national screening programme in the Netherlands implemented in 2007, which consisted of a uniform national ultrasound anomaly scan for all pregnancies. The anomaly scan utilised a four-chambered view of the heart, with right and left outflow tract views. If congenital heart defects such as VSD are suspected on this scan, patients were referred to a tertiary centre for more detailed fetal echocardiography. After the screening programme implementation, the prenatal detection rate of VSD increased by 10.3% (from 28.7 to 39.0%), with >90% of diagnoses occurring before 24 weeks gestation.[26] This demonstrates the beneficial effects of a uniform screening process for CHD in ensuring early diagnosis.

### *Quality of life of patients with VSD*

Moreno-Medina et al conducted a study to assess the effects of congenital heart defects on the quality of life of children. In this study, 157 children with CHD underwent quality of life (QoL) assessment with 112/157 (71%) achieving 1-year follow-up.[27] The PedsQL 4.0 scale, which included generic and cardiac-specific modules was used for QoL evaluation.[27] Results from both modules showed that the children with CHD showed a better perception in the QoL evaluation compared to their caregivers who showed a less prominent perception of their children's QoL. Overall, there was a lower score recorded for QoL in follow-up compared to baseline evaluation for both the children and their caregivers. Results showed that "emotional health" and "school functioning" were the most affected scores in the evaluation. In the cardiac-specific module, "cognitive status" showed the lowest scores in the evaluation both at baseline and follow-up.[27] Therefore, this shows that although children perceive their quality of life to be better than their caregivers, the overall quality of life of children with CHD was generally lower than that of a healthy child. This is also in line with a study carried out by Katelyn Mellion et al, which stated that children with CHD had a significantly lower score on QoL assessment compared to that of healthy controls.[28] In this cross-sectional survey study, there were 1138 patients in the CHD group (625 children and 513 adolescents) and 771 patients in the healthy group (528 children and 243 adolescents). Patients with CHD scored lower on the evaluation in "total", "physical health", and "psychosocial health" compared to the controls ($p < 0.0001$).[28] Therefore, this study showed the presence of worsened quality of life in children and adolescents with CHD and the need for intervention to improve the lower scores obtained.

## Conclusion

Pulse oximetry and fetal echocardiography are established non-invasive diagnostic tools for VSD. The recent advances in minimally invasive treatment options including periventricular approach and transcatheter techniques have improved patient outcomes than traditional open repair of VSD, yet at the expense of higher residual rates. Careful patient selection for each technique and follow-up should be planned through multi-disciplinary team meetings.

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