Incidence and risk factors for ventricular septal defect in “low risk” neonates

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Abstract

Aims—To quantify the incidence of ventricular septal defect in “low-risk” neonates; and to define any associated risk factors.

Methods—One hundred and seventy three patients with ventricular septal defects from a scanned population of 3971 clinically normal neonates were compared with scanned controls, considered to be clinically normal. A subset of the group with defects was compared with normal infants delivered over the same period, to identify any seasonal variation.

Results—Ventricular septal defects were detected in 4.36% of the “scanned” group (173 out of 3971). Ten had perimembranous defects and the remainder apical or muscular lesions. Eleven neonates had multiple defects. The incidence of ventricular septal defect was independent of most tested risk factors. There were significantly more girls in the group with defects compared with the controls (p = 0.004). The defects group also contained fewer infants born during summer months (p = 0.04).

Conclusions—The incidence of ventricular septal defects was much higher than might be expected, given that “high risk infants” were excluded. The observations that gender and season of birth affect the rate suggest that both genetic and environmental factors may be involved in the aetiology.

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Keywords: ventricular septal defect; risk factors

Ventricular septal defects are the most common form of congenital heart disease and among the most frequently seen congenital abnormalities. Prevalence is higher in neonates than it is in older children due to the rate of spontaneous closure. A closure rate of 50–75% has been cited for small defects among older children. About 10 years ago the overall rate of congenital heart disease seemed to be increasing, because of a rise in the numbers of ventricular septal defects diagnosed.1–4 The consensus was that any increase could be explained on the basis of better detection, particularly using colour flow Doppler.1–5

In this study ventricular septal defects were not sought exclusively, but examination of the ventricular septum was part of each assessment. Two notable studies in recent years have used colour Doppler interrogation, solely to identify muscular defects.6–7 An exceptionally high prevalence was found in both term and preterm infants. This study broadly supports these findings, although the populations under investigation were not entirely comparable.3

Methods

Each year around 2600 babies are born in the Royal Maternity Hospital, Belfast (the regional maternity and neonatal unit). This represents about one tenth of the Northern Ireland total. Since November 1994 deliveries at this institution have been randomly assigned to one of two groups. The first group received an echocardiographic assessment (with parental consent) in addition to clinical examination(s). The second group received only clinical examination. Infants were not scanned unless they had at least one normal clinical examination.

Infants with ventricular septal defects were managed according to clinical need. As most defects were small and the infants were otherwise well, management typically entailed a 6 month review with repeat echocardiography and physical examination, as required. Those with more clinically significant lesions were examined by a paediatric registrar or senior house officer and managed with referral to the regional paediatric cardiology service. Most of these infants were also examined by a consultant paediatric cardiologist before discharge or kept in hospital for further assessment or treatment.

Mothers approaching delivery with the following features were excluded from scanning.

• Insulin dependent diabetes mellitus (n = 29)
• Strong family history of congenital heart disease: (usually fatal or surgically treated congenital heart disease in a first degree relative) (n = 7)
• Detected antenatal abnormality relating to the cardiovascular system (n = 7)
• Intrauterine death (n = 18)
• The following exclusions were applied to infants:
• Down’s syndrome (n = 6)
• Stillbirth (n = 49)
• Perinatal death (n = 13)
• Admission to special care baby unit (n = 471)
• Detection of postnatal abnormality relating to the cardiovascular system (n = 7); note crossover with special care baby unit admissions
• Mother refused scan (n = 48)
• “Domino” delivery—with discharge occurring 6 hours after delivery (n = 34)
• Other early discharge (n = 93)

The birthweight and gestation were noted for all infants. Maternal age at delivery and booking details such as previous obstetric
### Table 1 Effects of gender and risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No in defects group</th>
<th>No in control group</th>
<th>p Value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>41/173 (23.7%)</td>
<td>39/139 (28.1%)</td>
<td>0.381</td>
<td>0.8 (0.48–1.33)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>18/173 (10.4%)</td>
<td>20/139 (14.4%)</td>
<td>0.285</td>
<td>0.69 (0.35–1.36)</td>
</tr>
<tr>
<td>Low parity</td>
<td>76/173 (43.9%)</td>
<td>58/142 (40.8%)</td>
<td>0.501</td>
<td>1.13 (0.71–1.78)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>34/173 (19.7%)</td>
<td>23/142 (16.2%)</td>
<td>0.420</td>
<td>1.27 (0.71–2.27)</td>
</tr>
<tr>
<td>Female</td>
<td>84/173 (48.6%)</td>
<td>60/142 (42.3%)</td>
<td>0.002</td>
<td>2.06 (1.31–3.23)</td>
</tr>
</tbody>
</table>

Table 1: Effects of gender and risk factors

Figure 1: Effect of maternal history of smoking, alcohol consumption, low parity and previous miscarriage.

Figure 2: Month of delivery of infants in septal defects and control groups.

Discussion

Ventricular septation is usually complete by the end of the sixth intrauterine week. It is believed that the formation of the trabecular septum is rather different from the membranous portion. The fusion of the embryonic inlet septum and the trabecular area is an integral part of embryonic septation, but development of the constituent portions of the septum is usually synchronous, and factors affecting the development of one portion might reasonably be expected to affect both.

In his review of the aetiology of ventricular septal defects, Newman points out that the incidence is considered to be remarkably consistent worldwide. However this can be corroborated only if equivalent investigation techniques are used—colour Doppler—for example, as it is now clear that many defects may go undetected in the neonatal period. Genetic factors do seem to play a part, with an increased risk of congenital heart disease for first degree relatives of children with ventricular septal defects (2–3% compared with 0.6–1% for the population as a whole). Despite this, it is striking to note the reportedly high degree of discordance even between mono-
zygoic twins.\textsuperscript{10} This study has limited the degree of genetic influence because of its exclusion criteria.

Attention has focused on environmental factors. It has been said that twin discordance for ventricular defect makes in utero insults less likely as aetiological factors. This is also seen in animals—similarly affected fetuses may not respond to teratogens in the same way. However, the degree of discordance may be partly explained by less sensitive detection methods.

Although maternal alcoholism does seem to cause ventricular septal defects and other forms of congenital heart disease, this study, in line with others, did not find any association between a positive history of alcohol consumption and the risk of defects.\textsuperscript{6,7} No attempt was made to categorise mothers further according to quantities of alcohol consumed. Maternal smoking, a risk factor investigated by several groups, again yielded a negative result. Again, the actual number of cigarettes smoked was not assessed as figures may well lack accuracy.

Few cardiac teratogens have been identified in humans. This contrasts with the animal world where septal defects can be induced by the injection of various substances, such as herxidices.\textsuperscript{11} Administration of sex hormones has been linked to septal defects and other congenital heart disease. Although not significant, there was a difference between the defects group and controls in terms of maternal obstetric history. Reproductive history seemed to be worse in the defects group. It may be that differing levels of maternal hormones are important. Maternal age showed no difference across the two groups, a finding supported by other workers.\textsuperscript{6-7} In this study female gender was associated with an increased risk of defects when compared with a control group of infants with an entirely normal scan. The control group in this instance might have been depleted of girls because of other minor defects. Although not significant, some difference has been documented by other authors dealing specifically with muscular ventricular septal defects.\textsuperscript{1} Seasonal variations in the birth of children with septal defects might imply the influence of teratogens, such as infection or atmospheric pollution. Summarising the pooled data from several studies, Newman found no link between ventricular septal defect and season.\textsuperscript{3} However, this work was again carried out before the routine use of echocardiography and Doppler ultrasonography. In contrast to other studies, our data clearly suggest that summer birth confers some protection from ventricular septal defect. This implies that is could be advantageous to conceive in September to November, as cardiac septation would then occur during autumn or early winter. This phenomenon is not easily explained on the basis of an absent infective agent or indeed reduced air pollution at this time of year. It seems likely, therefore, that other, less obvious factors are involved.

It has been suggested that muscular ventricular septal defects arise from cell death within an already formed ventricular septum while perimembranous defects may be the result of failed fusion secondary to transient interruption of the blood supply to the developing septum.\textsuperscript{13} Fetal echocardiography suggests that some small septal defects may close in utero.\textsuperscript{14} However, it seems less likely that they should form within an intact septum except perhaps in the presence of local ischaemia. Most authors agree that the aetiology of congenital ventricular septal defect is most likely multifactorial. The genetic component may well be quite weak.

Many would argue that small, muscular septal defects are of limited importance and as such do not merit diagnosis. However, if they reflect exposure to environmental teratogens, or help identify other influences harmful to the fetus, their true importance may lie in their role as markers of such an insult. It may also be that reproductive ability (maternal or perhaps paternal) is inversely related to the risk of ventricular septal defects, although the case is far from proved. Recently attention has focused on how an adverse intrauterine environment may leave an imprint on the individual for life, in terms of cardiovascular and other disease in later life.\textsuperscript{15} The case for ventricular septal defect as a marker of unrecognised intrauterine stress remains speculative. Long term follow up of a cohort such as this may well be productive.

14 Orie J, Flottor D, Sherman FS. To be or not to be a VSD. \textit{Am J Cardiol} 1994; 74:1284–5