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Prevalence of Secundum Atrial Septal Defect and Associated Findings

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1. Introduction

The goal of this chapter is to review data regarding the *current* prevalence estimates for secundum type atrial septal defect (ASD) and to give the reader a sense as to how these prevalence data compare relative to other common cardiac defects. This chapter will also review the current understanding of cardiac and non-cardiac findings known to be associated with secundum ASD. It is recognized that the prevalence estimates of cardiac defects have been impacted by the routine utilization of color flow Doppler-echocardiography in current clinical practice. This is particularly true for certain cardiac anomalies such as secundum ASD that frequently occur in asymptomatic infants and children. Several studies have indeed documented a significant increase in the apparent prevalence of congenital heart defects in general and specifically for certain common phenotypes including secundum ASD (Hoffman & Kaplan, 2002; Wren et al., 2000; Correa et al., 2007). Further, these studies have concluded that much of these increases are likely secondary to better ascertainment in recent years. This chapter will review the most recent estimates of the prevalence of secundum ASD using information obtained from a population-based surveillance system using strict definitions of what constitutes a secundum ASD. This chapter will also review a detailed list of what is presently known about the associated findings and potential risk factors for the development of secundum ASD.

2. Definition of what constitutes a secundum ASD

One of the difficulties recognized with the utilization of standard trans-thoracic color-Doppler echocardiography is the inability to differentiate a small secundum ASD from the physiologic communication (the patent foramen ovale) seen in most newborn infants. In other words, deciding what constitutes a "true" ASD has obvious implications for making accurate estimates of prevalence. In a recently revised heart classification system, the diagnosis of secundum ASD was made only when the atrial defect is greater than or equal to 4 mm in diameter (Riehle-Colarusso et al., 2007). If the specific size of the defect is not indicated in the imaging study, the diagnosis of ASD can also be made in the presence of documented right heart enlargement. In clinical practice, one can sometimes detect a flap associated with patent foramen ovale even in defects larger than 4 mm. However, as this finding is not reliably reported, the utilization of the 4 mm size requirement for secundum ASD was chosen. While admittedly arbitrary, this size is based on previous published studies showing that most (if not all) defects less than this size close spontaneously and are therefore not considered anatomic atrial defects (Ghisla et al., 1995; Radzik et al., 1993). The prevalence data that are reported for

secundum ASD in this chapter utilized this strict size cutoff. Investigations that do not make this distinction between small ASD and patent foramen ovale would be expected to give much higher estimates for the prevalence of secundum ASD.

It is well recognized that secundum ASD commonly occurs with other congenital cardiac defects. When it occurs with other presumed "independent" heart defects (such as with ventricular septal defects), most investigators, when assessing prevalence, would count ASD as a distinct cardiac defect. However, when a secundum ASD occurs as an *obligatory* shunt (such as with the diagnoses of tricuspid and pulmonary atresia, transposition of the great arteries, complex single ventricle with mitral atresia, or hypoplastic left heart syndrome), it is typically *not* counted as a distinct cardiac defect. The prevalence data reported in this chapter were made using these same distinctions.

3. Background and methods

One challenge in assessing differences in prevalence of congenital cardiac defects across population groups and over time has been the variation in nomenclature and classification systems that have been utilized. The prevalence data reviewed in this chapter were obtained utilizing the Metropolitan Atlanta Congenital Defects Program (MACDP) using data that were analyzed for births that occurred between 1998 and 2005 (the most recent time-frame studied) (Reller et al., 2008). A major strength of the MACDP is that it is a population-based surveillance system that includes structural birth defects, chromosomal abnormalities, and clinical syndromes. It was established in 1967 by the Centers for Disease Control and Prevention (CDC), Emory University, and the Georgia Mental Health Institute (Correa et al., 2007). This program has conducted surveillance for birth defects among live born and stillborn infants greater than 20 weeks gestation born to residents of the 5 central counties of metropolitan Atlanta through the use of active case-finding methods. While many of the cardiac defects in MACDP are diagnosed in infancy, cases can be ascertained *up to 6 years of age*. The MACDP recently completed a re-classification of all heart defects in its database (Riehle-Colarusso et al., 2007). All cases underwent a detailed review by pediatric cardiologists to classify congenital heart defects according to standard nomenclature used by the Society of Thoracic Surgeons congenital heart surgery database (Jacobs et al., 2004).

4. Prevalence of secundum ASD

Prevalence estimates are reported per 10,000 live births with the numerators representing the number of *infants* with secundum ASD (or any other cardiac defect) per 10,000 live births. The current overall prevalence of congenital heart defects is estimated to be 81.4 infants per 10,000 births (~0.8% of live births). The prevalence of secundum ASD is estimated to be 10.3 per 10,000 births. As a frame of reference, the most common cardiac defect is muscular ventricular septal defect (VSD) with a prevalence of 27.5 per 10,000 live births. It is noteworthy that the prevalence of secundum ASD is comparable to peri-membranous VSD (prevalence of 10.6 per 10,000 live births) and greater than any other specific cardiac defect (Reller et al., 2008). Based on current prevalence data, secundum ASD is the third most common cardiac defect, and together with muscular and peri-membranous VSD, account for slightly more than half of all recognized cardiac defects.

Secundum ASD is by far the most common of the atrial septal defects, accounting for greater than 80% of all atrial defects where the specific sub-type is identified. Secundum ASD is ~ 6 times more common than the ostium primum type ASD (1.7 per 10,000 live births) and ~ 25

times more common than the sinus venosus atrial septal defect (0.4 per 10,000 live births) (Reller et al., 2008).

Last, it is recognized in clinical practice that many individuals with ASD are diagnosed later in life and indeed, are the most common un-diagnosed congenital cardiac defect presenting in adult congenital cardiology clinics (Rosas et al., 2004). Thus, while the prevalence data obtained from the MACDP database are the most current available, it is clear that these data (diagnosed in infants and children), are under-estimates of the "true" prevalence of secundum ASD.

5. Associations and risk factors

The cause(s) of secundum ASD, as is true for most congenital heart defects, remain largely unknown. Nonetheless, there are clearly recognized associations between secundum ASD and other cardiac and non-cardiac findings that are worth reviewing and may ultimately help to elucidate an etiology for at least some of the causes for secundum ASD. These associations are discussed in the paragraphs that follow.

5.1 Associations with other cardiac defects

Several investigations have documented the association of secundum ASD with peri-membranous VSD as well as with valvular pulmonary stenosis (Botto et al., 2007). The relative frequency and non-randomness of these associations suggest that they may have specific risk factor profiles. Indeed, there is some suggestion that the combination of secundum ASD and peri-membranous VSD *within families* may occur in greater frequency in the setting of the NKX2-5 genotype (Schott et al., 1998).

5.2 Genetic syndromes

Infants with secundum ASD are more likely to have a positive family history of congenital heart disease than most other cardiac defects (Ferencz et al., 1997). The finding of a positive family history obviously suggests the possibility of genetic causation(s) yet to be determined. There are several recognized genetic syndromes that have been shown to be associated with secundum ASD. While Trisomy 21 is more commonly associated with the finding of partial or complete atrio-ventricular septal defects, infants with Down syndrome also have an increased risk for isolated secundum ASD as well (Ferencz et al., 1997; Boldt et al., 2002). It is generally recognized that secundum ASD is also seen in greater frequency with the chromosomal anomalies Trisomy 13 and 18.

Other recognized genetic syndromes associated with an increased risk of secundum ASD include the Holt-Oram syndrome, where the association of radial limb anomalies and cardiac defects, primarily secundum ASD, is seen in at least half of affected individuals (Basson et al., 1994). Secundum ASD is also seen with chromosome 22q11 deletion in association with DiGeorge syndrome and velo-cardio-facial syndrome (Borgman et al., 1999). Secundum ASD, occurring either in isolation, or in conjunction with pulmonary stenosis, is associated with Noonan syndrome (Mendez and Opitz, 1985). The NKX2-5 gene defect has been shown to be associated with *familial causes* of either isolated secundum ASD, or in combination with other cardiac defects, and with heart rhythm conduction anomalies (Schott et al., 1998; Benson et al., 1999).

5.3 Female gender

The association with female gender has long been recognized. In the current prevalence estimates, secundum ASD was significantly more common in girls (58.6%) than boys. (Reller et al., 2008). In the Baltimore-Washington Infant Study, 65.3% of children with secundum ASD were girls (Ferencz et al., 1997).

5.4 Non-cardiac malformations and pregnancy exposures/teratogens

Certain common non-cardiac malformations such as cleft palate are associated with an increased incidence of secundum ASD (Ferencz et al., 1997). Some of these infants will have chromosome 22q11 deletion, as noted above. Secundum ASD is the most common congenital cardiac defect associated with a constellation of non-cardiac anomalies recognized as the VACTERL (Vertebral anomalies, Anal atresia, Cardiac defects, Tracheal anomalies, Esophageal atresia, Renal anomalies, and Limb anomalies) association (Ferencz et al., 1997).

In addition, certain pregnancy exposures have been shown to be associated with secundum ASD and include maternal alcohol ingestion (fetal alcohol syndrome) (Mone et al., 2004). Exposure to certain viral infections such as cytomegalovirus (CMV) and rubella infections during pregnancy are also associated with an increased risk for secundum ASD (Ferencz et al., 1997). Last, the presence of maternal diabetes including gestational diabetes is associated with an increased risk of cardiac defects including secundum ASD (Ferencz et al., 1997; Loffredo al., 2001).

5.5 Other pregnancy and pre-pregnancy-related "risk factors"

As a group, infants with secundum ASD, compared to live-born infants in the general population, are significantly more likely to be born at a lower gestational age and have significantly lower birth weight (Reller et al., 2008; Ferencz et al., 1997). Further, infants with secundum ASD are more likely to be small for gestational age irrespective of their gestational age at delivery. Last, infants with secundum ASD (relative to infants in the general population), are more likely to be born of mothers of increased maternal age and are significantly more likely to be the product of a multiple gestation pregnancy (Reller et al., 2008; Mastroiacovo et al., 1999).

The cause(s) of the association of secundum ASD with low gestational age and low birth weight is unclear at the current time. One possibility is that ASD might somehow impair normal fetal growth. Another possibility is that both altered fetal growth and secundum ASD represent co-outcomes of an associated causal risk factor. Clearly, more investigation is necessary.

Current data indicate that both older maternal age and multiple-gestation pregnancy are associated with secundum ASD. In addition, the association with older maternal age appears to be independent of the increased risk of genetic syndromes that occurs with older maternal age (Reller et al., 2008). It is recognized that older maternal age is more likely to be associated with the use of assisted reproductive technology, which is a strong risk factor for multiple gestation pregnancy. Thus, these findings of maternal age and multiple-gestation pregnancy may be inter-related. It is noteworthy that over the past 4 decades, one important demographic change has occurred in our society. In 1968, roughly 16% of mothers at the time of delivery were 30 years old or older compared with 42% in 2005 (Correa et al., 2007). During this same timeframe, the number of multiple-gestation pregnancies also nearly doubled from 1.8% to 3.4%.

Last, recent epidemiologic data suggest that pre-pregnancy maternal obesity may be a risk factor for a variety of birth defects including congenital heart defects. Of the cardiac defects,

maternal obesity is specifically associated with an increased risk for both atrial and ventricular septal defects (Cedergren and Kallen, 2003). While the mechanism of this finding is uncertain, the current "epidemic" of obesity in western society makes this association a potentially significant risk factor.

6. Natural history of secundum ASD

There are data indicating that secundum ASD (defined as defects ≥ 4 mm in size) when diagnosed in the first 6 months of life have a tendency to regress in size including the potential for spontaneous closure. In addition, the strongest predictor for spontaneous closure was shown to be *smaller size* at the time of initial diagnosis. In one study, over half of ASD's measuring between 4-5 mm at the time of diagnosis closed spontaneously and an additional 30% regressed to a size considered to be insignificant (≤ 3 mm) (Hanslik et al., 2006). None of the larger defects (> 10 mm) closed spontaneously and over 75% required surgical or device closure (Hanslik et al., 2006). These data certainly suggest that size of the secundum ASD at initial diagnosis directly impacts the natural history and specifically the potential need for closure. Last, the recognition that spontaneous closure of secundum ASD can occur is important, and has obvious implications for prevalence estimates.

7. Future trends regarding secundum ASD prevalence

A key question that remains unanswered is whether the true prevalence of secundum ASD is in fact increasing. Since 1975, the *reported* prevalence of secundum ASD (as well as some of the other common cardiac defects) has increased significantly (Correa et al., 2007; Hoffman & Kaplan, 2002; Wren et al., 2000). Because most of the increase in heart defect prevalence has been seen in asymptomatic infants, (while prevalence in more severe heart defects have been stable), better ascertainment using current color-Doppler echocardiography is clearly felt to be a significant contributing factor. However, there are preliminary evidence that the prevalence of secundum ASD may still be increasing in the most recent time-frame when imaging modalities have *not* changed significantly (Riehle-Colarusso T, unpublished observation). If true, some of the changing demographic factors referred to in this chapter may be contributing factors. However, at the current time, it is not possible to state with certainty whether the actual prevalence of secundum ASD is increasing.

8. Conclusion

This chapter has reviewed data assessing the prevalence of secundum ASD using current imaging modalities and strict guidelines for diagnosis. Secundum ASD is the third most common congenital cardiac defect and, based on the prevalence data reported in this chapter, accounts for greater than 10% of all cardiac defects. In addition, these data show that it is nearly as common as peri-membranous VSD. This chapter has also reviewed the common associations and risk factors that have been identified with secundum ASD. While some of the societal trends mentioned in the review of risk factors for ASD are of interest, knowing whether the prevalence of secundum ASD is in fact, increasing, and if so, what might be causing this, remain speculative at the current time.

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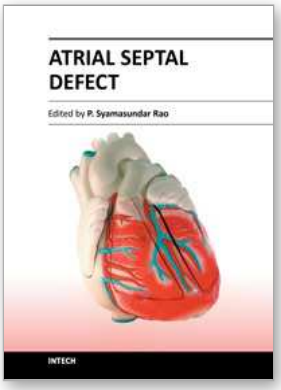

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Atrial Septal Defects (ASDs) are relatively common both in children and adults. Recent reports of increase in the prevalence of ASD may be related use of color Doppler echocardiography. The etiology of the ASD is largely unknown. While the majority of the book addresses closure of ASDs, one chapter in particular focuses on creating atrial defects in the fetus with hypoplastic left heart syndrome. This book, I hope, will give the needed knowledge to the physician caring for infants, children, adults and elderly with ASD which may help them provide best possible care for their patients.

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