

Atrial Septal Defect: A Literary Review of Congenital Heart Disease

Dr.Uzma Tabassum

CSMSS Ayurved Mahavidyalaya,
Kanchanwadi, Aurangabad

Abstract:

Atrial septal defect is a common congenital abnormality that occurs in the form of ostium secundum, ostium primum, sinus venosus and rarely coronary sinus defects. Atrial septal defects are the third most common type of congenital heart disease. Included in this group of malformations are several types of atrial communications that allow shunting of blood between the systemic and pulmonary circulation. Most children with isolated atrial septal defects are free of symptoms but the rate of exercise intolerance, atrial tachyarrhythmias, right ventricular dysfunction and pulmonary hypertension is increased with advanced age and life expectancy is reduced in adults with untreated defects. Surgical closure is safe and effective and when done before age 25 years is associated with normal life expectancy. An isolated atrial septal defect can occasionally go undiagnosed for decades. It accounts for 25-30 % of congenital heart disease cases diagnosed in adulthood. Transcatheter closure offers a less invasive alternative for patients with a secundum defect who fulfill anatomical and size criteria. Patent foramen ovale is a normal communication during fetal life and is commonly encountered after birth. Abnormalities in genes essential to cardiac septation have been associated with atrial septal defects. Echocardiography is central to diagnosis and also informs the interventional approach. Percutaneous or surgical ASD closure may be indicated in presence of right heart volume overload, paradoxical embolism, orthodeoxia-platypnea or an elevated pulmonary systemic flow ratio.

Keywords : *Ostium primum, Ostium secundum, Septal defects, Transcatheter closure, Echocardiography, Paradoxical embolism, Orthodeoxia platypnea.*

Introduction :

Atrial septal defects belong to a group of congenital cardiac anomalies that allow communication between the left and right sides of the heart. These inter atrial communications include several distinct defects in the cardiac terminations of systemic and pulmonary veins (sinus venosus and coronary sinus defects) and in inter atrial septum (atrial septal defects). Patent foramen ovale is a normal communication during fetal life and is commonly encountered after birth.

Defects of atrial septum are the third most common type of congenital heart disease with an estimated incidence of 56 per 100000 live births [1]. With improved recognition of clinically silent defects by echocardiography, recent estimates are about 100 per 100000 live births [2]. About 65 – 70% of patients with a secundum defect, roughly 50 % of those with a primum atrial septal defect and 40 – 50 % of those with a sinus venosus defect are female.

Most atrial septal defects are sporadic with no identifiable cause. Reports of familial clusters of secundum defects have noted different modes of inheritance, most notably autosomal dominant [3, 4]. Abnormalities in genes essential to cardiac septation have been associated with atrial septal defects [5]. The risk of secundum defect is increased in families with history of congenital heart disease, especially when an atrial septal defect is present in a sibling [3]. In patients with trisomy 21, secundum and primum defects are the more frequent lesions, accounting for 42% and 39% of major congenital heart disease, respectively [6]. Exposure to several substances has been associated with atrial septal defects, including fetal alcohol syndrome [7], first trimester maternal cigarette consumption [8,9], and some anti depressants [10-12]. Other maternal risk factors include diabetes, increased dietary glycemic index in women without diabetes [35,36] and advanced maternal age.(more than or equal to 35 years) [15,16].

Normal development of atrial septum results in formation of fossa ovalis, which include two

anatomical elements: first, muscular boundaries contributed by septum secundum, and second, the valve of fossa ovalis, which attaches on left atrial aspect of septum secundum – septum primum. A patent foramen ovale is seen in almost all newborn babies, but its frequency decreases with advancing age [17-18]. Complete anatomical closure of foramen ovale occurs in 70-75% of adults [20].

Secundum atrial septal defect is a defect within the fossa ovalis usually due to one or several defects within septum primum. With the exception of patent foramen ovale, secundum atrial septal defect is the most common cause of an atrial - level shunt. The size of secundum defects varies from several millimeters to 2-3 cm. Large defects usually associated with substantial deficiency, or even complete absence of septum primum.

Primum atrial septal defect is one of the several variants of common atrio ventricular canal defects (also termed atrio ventricular septal defect) with an inter atrial communication between the anterior inferior margin of fossa ovalis and atrio ventricular valves. The defect is characterized by a common atrio ventricular orifice with two distinct atrio ventricular valve annuli completed by valve tissue adhering to crest of the ventricular septum. In addition to septal defect, the atrio ventricular valve in this anomaly are always almost abnormal, including a cleft in the anterior mitral leaflet. Unlike other types of atrial septal defects, the position and course of conduction axis is abnormal as in complete atrio ventricular canal defect.

In most patients, an atrial septal defect results in left -to- right shunt. The direction and magnitude of blood flow through an atrial communication are determined by the size of the defect and by the relative atrial pressures, which relate to compliances of left and right ventricles. Both the size of the defect and the compliance of the ventricles can change over time [21].

Pathophysiologic consequences of ASDs typically begin in adulthood, and include arrhythmia, paradoxical embolism, cerebral abscess, pulmonary hypertension and right ventricular failure .Two dimensional transthoracic echocardiography with Doppler is a central aspect of the evaluation. This non- invasive imaging modality often establishes

the diagnosis and provide critical information guiding intervention.

Clinical presentation:

Most patients remain asymptomatic throughout most of the childhood. Even those with a large left – to – right shunt might not have overt symptoms until adulthood. Rarely an isolated atrial septal defect is found in an infant with tachypnea, slow weight gain, or recurrent respiratory infections [23, 24].

By contrast, most adult patients with a large defect present with symptoms, including fatigue, exercise intolerance, palpitations, syncope, shortness of breath, peripheral oedema, manifestations of thromboembolism and cyanosis.

Exercise capacity and peak oxygen consumption are decreased in most adults with unpaired secundum defect, often at 50-60% of predicted values in healthy controls [27].

Major arrhythmias are uncommon in children with atrial septal defects. The most common arrhythmias are atrial flutter and fibrillation, incidences of which increase with age. Pulmonary hypertension is uncommon in children with an isolated atrial septal defect. In adults with large defects, mild or moderate pulmonary hypertension is common and tends to increase with age and in those living at high altitude [28-30]. Although uncommon, dyspnea in patients with ASD may be triggered by an upright position in orthodeoxia-platypnea syndrome and linked to arterial desaturation. Late post- operative atrial fibrillation or flutter tends to occur in those who undergo closure after the age of 40 years [2].

On physical examination, most young patients with an isolated secundum atrial septal defect are acyanotic and can have few or no symptoms. Characteristic electrocardiographic features of atrial septal defect include a tall P wave indicative of right atrial enlargement, incomplete right bundle branch block pattern and right axis deviation. Left axis deviation with superior axis is suggestive of primum defect.

Echocardiography :

Transthoracic echocardiography is a primary diagnostic method for determining the presence, location, size and haemodynamic characteristics of atrial septal defects. Contrast echocardiography with

injection of agitated saline through a peripheral venous cannula during imaging of atria and ventricles can assist in the diagnosis of atrial septal defect, especially in patients with restricted acoustic windows [32].

MRI and CT:

Advanced in cardiac and MRI techniques allow anatomical delineation of atrial septal defects and quantitative assessment of their haemodynamic consequences [33,34]. In patients with isolated secundum or primum defects, cardiac MRI is seldom necessary. Exceptions include those in whom the location of defect or its haemodynamic burden is in question. However, the risk of cancer related to ionizing radiation limits its application to only carefully selected patients in whom other modalities are insufficient [35].

Treatment:**Indications and contra indications of defect closure:**

Closure of an atrial septal defect is indicated in the presence of a haemodynamically significant shunt that causes enlargement of right heart structures, irrespective of symptoms [35, 36]. Other indications include suspicion of paradoxical embolism in the absence of other causes or in the rare instance of documented Orthodeoxia – platypnoea (dyspnea and hypoxaemia accompanying a change to a sitting or standing from a recumbent position) irrespective of shunt size.

Timing of defect closure:

A haemodynamically significant atrial septal defect should be closed electively once the diagnosis is confirmed. Although, there is no lower limit of age for defect closure, many clinicians choose to refer asymptomatic children for the procedure at age 3-5 years. At the other end of the age spectrum, evidence indicates that with the exceptions of contraindications noted above, defect closure is safe and effective in improving symptoms, even in elderly patients. [29, 37-39].

Sinus venosus, primum and coronary sinus septal defects need surgical closure. Secundum defects can be closed either by surgery or by percutaneous route using an occluding device delivered by a catheter. Transcatheter closure might not be feasible in some large secundum defects or small infants.

Clinical and haemodynamic results of defect closure:

Patients commonly report subjective improvement in symptoms after closure of atrial septal defects [27, 37]. A younger age at closure and a lesser degree of chamber enlargement before repair are associated with a higher likelihood of normalization of right ventricular size [43].

Studies have shown improvements in symptoms and exercise capacity decrease in right atrial and left ventricular size and improvement in pulmonary hypertension in most but not all patients [29, 30, 45, 50, 51]. Although, these benefits are less pronounced after age 60 years [29, 30], symptomatic improvement and increase in 6 min. walking distance coupled with a low procedural risk provide the rationale for defect closure in elderly patients [29, 37,52].

Maternal complications are uncommon in isolated atrial septal defects not complicated by pulmonary hypertension [55]. Yap and colleagues [56] found similarly low rates of maternal complications in women with repaired and unrepaired defects, including arrhythmias (4%) and transient ischaemic attack (1%). Pre - pregnancy history of arrhythmia and maternal age older than 30 years were risk factors for maternal cardiac complications. The women with an ASD who have severe pulmonary arterial hypertension should be counseled to avoid pregnancy due to excess maternal and fetal mortality [13, 27].

Discussion:

Defects of atrial septum are the third most common type of congenital heart disease with an estimated incidence of 56 per 100000 live births [1]. With improved recognition of clinically silent defects by echocardiography, recent estimates are about 100 per 100000 live births [2]. In most patients, an atrial septal defect results in left -to-right shunt. The direction and magnitude of blood flow through an atrial communication are determined by the size of the defect and by the relative atrial pressures, which relate to compliances of left and right ventricles. Both the size of the defect and the compliance of the ventricles can change over time [21]. Left ventricular systolic dysfunction can develop late in patients with a large atrial septal defect [22].

Surgical closure is safe and effective and when done before age of 25 years is associated with normal life expectancy. Transcatheter closure offers a less invasive alternative for patients with a secundum defect who fulfill anatomical and size criteria. The diagnostic sensitivity of transthoracic echocardiography is excellent in young patients, but lower in those with restricted acoustic windows due to obesity, large body habitus and previous thoracic surgery. Closure of an atrial septal defect is indicated in the presence of a haemodynamically significant shunt that causes enlargement of right heart structures, irrespective of symptoms [35, 36]. The primary indication for ASD closure is right heart volume overload, whether symptoms are present or not. ASD closure may also be reasonable in other contexts, such as paradoxical embolism.

American and European practice guidelines state that an atrial septal defect can be closed if the pulmonary vascular resistance is lower than two-thirds of the systemic vascular resistance and there is evidence of pulmonary-to-systemic flow ratio greater than 1.5. Some studies have shown an increase in exercise capacity in adults after defect closure [40], but in asymptomatic children the change has been minimum or none. Conversely, studies on respiratory symptoms and pulmonary function in children have shown a significant improvement after closure [41, 42]. A younger age at closure and a lesser degree of chamber enlargement before repair are associated with a higher likelihood of normalization of right ventricular size [43]. Atrial flutter and fibrillation are important causes of morbidity, seen in 21% of adults older than 40 years with a rising frequency over time [49].

Studies have shown improvement in symptoms and exercise capacity, decrease in right atrial and right ventricular size, and improvement in pulmonary hypertension in most but not all patients [29, 30, 45, 50, 51]. Pregnancy should be avoided in women with an atrial septal defect and severe pulmonary hypertension. Maternal deaths tended to occur shortly after delivery and were often caused by heart failure, thromboembolism, pulmonary hypertensive crisis and sudden cardiac death.

The 2008 American College of Cardiology and American Heart Association (ACC/AHA) adult

congenital heart disease guidelines provide detailed clinical guidance on ASDs [1]. An interesting association of ASD with Klippel - Feil Syndrome was recently reported, which has the major physical examination features of a short neck, limited range of motion in the neck, and low hair line at the back of the head [64].

Conclusion:

ASDs are a common congenital abnormality that most commonly occurs as an ostium secundum defect. About 65-70% of patients with a secundum defect, roughly 50% of those with a primum atrial septal defect, and 40-50% of those with a sinus venosus defect are female. Exercise intolerance is uncommon in young children with an isolated atrial septal defect. Nonetheless, pulmonary function is often impaired in this age group [26]. Major arrhythmias are uncommon in children with atrial septal defects. Pulmonary hypertension is uncommon in children with an isolated atrial septal defect. Enlargement of right heart structures are evident on chest radiography in patients with haemodynamically significant atrial septal defects. Sinus venosus, Primum and coronary sinus septal defects need surgical closure. Secundum defects can be closed either by surgery or by percutaneous route using an occluding device delivered by a catheter. Transcatheter closure might not be feasible in some large secundum defects or small infants. The risk of atrial tachyarrhythmias, especially atrial flutter and fibrillation, remains high after defect closure in adulthood. Risk factors include atrial arrhythmia before closure and age at closure older than 40 years [53, 54]. By comparison with general population, women with unpaired atrial septal defects had an increased risk of pre-eclampsia, fetal loss and low birth weight. A comprehensive echocardiogram includes evaluation of anatomical ASD characteristics, flow direction, associated abnormalities (e.g. anomalous pulmonary veins), right ventricular anatomy and function, pulmonary pressures and pulmonary or systemic flow ratio. ASD types strictly include ostium secundum (75% of cases), ostium primum (15-20%), while rare coronary sinus defects are closely related [1]. The overall prevalence of diagnosed ASDs has been estimated at 3.89 per 1000 children and 0.88 per 1000 adults, which may be underestimated due to

clinically silent and unidentified cases [3]. Sick sinus syndrome may also develop in ASD patients due to long standing right heart overload [1]. A patent foramen ovale was much more common and present in 81%. Complete heart block is characteristic of familial ASD [15]. Echocardiography is central to diagnosis and also informs the interventional approach. Percutaneous or surgical ASD closure may be indicated in presence of right heart volume overload, paradoxical embolism, orthodeoxia-platypnea, or an elevated pulmonary or systemic flow ratio.

References:

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease . J Am Coll Cardiol 2002; 39: 1890-900.
2. Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects . Pediatrics 2001;107:E32.
3. Caputo S, Cappozzi G, Russo MG, et al. Familial recurrence of congenital heart disease in patients with ostium secundum atrial septal defect. Eur Heart J 2005;26:2179-84.
4. Chen Y, Han ZQ, Yan WD, et al. A novel mutation in GATA 4 gene associated with dominant inherited familial atrial septal defect. J Thorac Cardiovasc Surg 2010;140:684-87.
5. Maitra M, Schluteman MK, Nicholos HA, et al. Interaction of GATA 4 and GATA 6 with Tbx5 is critical for normal cardiac development. Dev Biol 2009;326:368-77.
6. Freeman SB, Bean LH, Allen EG et al. Ethnicity sex and incidence of congenital heart defects: a report from the national Down Syndrome Project. Genet Med 2008;10:173-80.
7. Burd L, Deal E, Rios R, Adickes E, Wynne J, Klug MG. Congenital heart defects and fetal alcohol spectrum disorders. Congenital Heart Dis 2007;2:250-55.
8. Alverson CJ, Strickland MJ, Gilboa SM, Correa A. Maternal smoking and congenital heart defects in the Baltimore-Washington infant study. Pediatrics 2011;127:e647-53.
9. Lee LJ, Lupo PJ. Maternal smoking during pregnancy and the risk of congenital heart defects in offspring: a systemic review and meta analysis. Pediatr Cardiol 2013;34:398-407.
10. Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA. First trimester use of Serotonin-

reuptake inhibitors and risk of birth defects. N Engl J Med 2007;356:2675-83.

11. Polen KN, Rasmussen SA, Riehle-Colarusso T, Reefhuis J, and the National Birth Defects Study. Association between reported Venlafaxine use in early pregnancy and birth defects, national birth defects prevention study, 1997-2007. Birth defects Res A Clin Mol Teratol 2013;97:28-35.
12. Bakker MK, Kerstiens-Frederikes WS, Buys CH, de Walle HE, de Jong-Van den Berg LT. First trimester use of paroxetine and congenital heart defects: a population based case control study. Birth defects Res A Clin Mol Teratol 2010;88:94-100.
13. Correa A, Gilboa SM, Besser LM, et al. Diabetes Mellitus and birth defects. Am J Obstet Gynecol 2008;199:237e231-39.
14. Parker SE, Werler MM, Shaw GM, Anderka M, Yazdy MM, and the National Birth Defects Study Dietary glycemic index and the risk of birth defects. Am J Epidemiol 2012;176:1110-20.
15. Miller A, Riehle-Colarusso T, Siffel C, Frias JL, Correa A. Maternal age and prevalence of isolated congenital heart defects in an urban area of the United States. Am J Med Genet A 2011;155A:2137-45.
16. Reefhuis J, Honein MA, Schieve LA, Correa A, Hobbs CA, Rasmussen SA, and the National Birth Defects Prevention Study. Assisted reproductive technology and the major structural birth defects in the United States. Hum Reprod 2009;24:360-66.
17. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17-20.
18. Connuck D, Sun JP, Super DM, et al. Incidence of patent ductus arteriosus and patent foramen ovale in normal infants. Am J Cardiol 2002;89:244-47.
19. Fisher DC, Fisher EA, Budd JH, Rosen SE, Goldman ME. The incidence of patent foramen ovale in 1000 consecutive patients. A contrast transesophageal echocardiographic study. Chest 1995;107:1504-09.
20. Schneider B, Zienkiewicz T, Jansen V, Hofman T, Noltenius H, Meinertz T. Diagnosis of patent foramen ovale by transesophageal echocardiography and correlation with autopsy findings. Am J Cardiol 1996;77:1202-09.

21. Fuse S, Tomita H, Hatakeyama K, Kubo N, Abe N. Effect of a secundum atrial septal defect on shunt volume. *Am J Cardiol* 2001;88:1447-50.
22. Masutani S, Senzaki H. Left ventricular function in adult patients with atrial septal defect: implication for development of heart failure after transcatheter closure. *J Card Fail* 2011;17:957-63.
23. Andrews R, Tulloh R, Magee A, Anderson D. Atrial septal defect with failure to thrive in infancy: hidden pulmonary vascular disease. *Pediatr Cardiol* 2002;23:528-30.
24. Lammers A, Hager A, Eicken A, Lange R, Hauser M, Hess J. Need for closure of secundum atrial septal defect in infancy. *J Thorac Cardiovasc Surg* 2005;129:1353-57.
25. Rhodes J, Patel H, Hijazi ZM. Effect of transcatheter closure of atrial septal defect on the cardio pulmonary response to exercise. *Am J Cardiol* 2002;90:803-06.
26. Lee YS, Jeng MJ, Tsao PC, et al. Pulmonary function changes in children after transcatheter closure of atrial septal defect. *Pediatr Pulmonol* 2009;44:1025-32.
27. Van De Bruaene A, Buys R, Vanhees L, Deloroix M, Moons P, Budtd W. Cardiopulmonary exercise testing and SF-36 in patients with atrial septal defect type secundum. *J Cardiopulm Rehabil Prev* 2011;31:308-15.
28. Khoury GH, Hawes CR. Atrial septal defect associated with pulmonary hypertension in children living at high altitude. *J Pediatr* 1967;70:432-35.
29. Humenberger M, Rosenhek R, Gaberiel H, et al. Benefit of atrial septal defect closure in adults: impact of age. *Eur Heart J* 2011;32:553-60.
30. Yalonetsky S, Lorber A. Comparative changes of pulmonary artery pressure values and tricuspid valve regurgitation following transcatheter atrial septal defect closure in adults and the elderly. *Congenit Heart Dis* 2009;4:17-20.
31. Campbell M. Natural history of atrial septal defect. *Br Heart J* 1970;32:820-26.
32. Rozensweig BP, Nayar AC, Varkey MP, Kronzon I. Echo contrast enhanced diagnosis of atrial septal defect. *J Am Soc Echocardiogr* 2001;14:155-57.
33. Valverde I, Simpson J, Schaffter T, Beerbaum P. 4D phase-contrast flow cardiovascular magnetic resonance: comprehensive quantification and visualization of flow dynamics in atrial septal defect and partial anomalous pulmonary venous return. *Pediatr Cardiol* 2010;31:1244-48.
34. Teo KS, Disney PJ, Dundon BK, et al. Assessment of atrial septal defect in adults comparing cardiovascular magnetic resonance with transesophageal echocardiography. *J Cardiovasc Magn Reson* 2010;12:44.
35. Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood and adolescence: data linkage study of 11 million Australians. *BMJ* 2013;346:f2360.
36. Baumgartner H, Bonhoeffer P, De Groot NM, et al, and the Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC), and the Association for European Pediatric Cardiology (AEPC) and the ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown up congenital heart disease (new version 2010). *Eur Heart J* 2010;31:2915-57.
37. Hanninen M, Kmet A, Taylor DA, Ross DB, Rebeyka I, Vonder Muhll IF. Atrial septal defect in the elderly is associated with excellent quality of life, functional improvement, and ventricular remodelling. *Can J Cardiol* 2011;27:698-704.
38. Nakagawa K, Akagi T, Taniguchi M, et al. Transcatheter closure of atrial septal defect in a geriatric population. *Catheter Cardiovasc Interv* 2012;80:84-90.
39. Nyboe C, Fenger Gron M, Neilson-Kudsk JE, Hjortdal V. Closure of secundum atrial septal defects in adult and elderly patients. *Eur J Cardio thorac Surg* 2013;43:752-57.
40. Takaya Y, Taniguchi M, Akagi T, et al. Long term effect of transcatheter closure of atrial septal defect on cardiac remodeling and exercise capacity in patients older than 40 years with a reduction in cardio pulmonary function. *J Interv Cardiol* 2013;26:195-99.
41. Zaquot M, De Baets F, Schelstraete P, et al. Pulmonary function in children after surgical and per cutaneous closure of atrial septal defect. *Pediatr Cardiol* 2010;31:1171-75.
42. Thomas VC, Vincent R, Raviele A, Diehl H, Qian H, Kim D. Transcatheter closure of secundum atrial septal defect in infants less than 12 months of age improves symptoms of chronic lung disease. *Congenit Heart Dis* 2012;7:204-11.
43. Du ZD, Cao QL, Koeing P, Heitschmidt M, Hijazi ZM. Speed of normalization of right ventricular volume overload after transcatheter

closure of atrial septal defect in children and adults. *Am J Cardiol* 2001;88:1450-53.

44. Monfredi O, Luckie M, Mirjafari H, et al. Percutaneous device closure of atrial septal defect results in very early and sustained changes of right and left heart function. *Int J Cardiol* 2013;167:1578-84.
45. Veldtman GR, Razack V, Siu S, et al. Right ventricular form and function after per cutaneous atrial septal defect device closure. *J Am Coll Cardiol* 2001;37:2018-13.
46. Schoen SP, Kittner T, Bohl S, et al. Transcatheter closure of atrial septal defect improves right ventricular volume, mass, function, pulmonary pressure and functional class: a magnetic resonance imaging study. *Heart* 2006;92:821-26.
47. Lindsey JB, Hillis LD. Clinical update: atrial septal defect in adults. *Lancet* 2007;369:1244-46.
48. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates and prognostic implication. *Circulation* 2005;112:828-35.
49. Attie F, Rosas M, Granados N, Zabala C, Buendia A, Calderon J. Surgical treatment for secundum atrial septal defects in patients less than 40 years old. A randomized clinical trial. *J Am Coll Cardiol* 2001;38:2035-42.
50. Giardini A, Dotti A, Formigari R, et al. Determinants of cardiopulmonary functional improvement after transcatheter atrial septal defect closure in asymptomatic adults. *J Am Coll Cardiol* 2004;43:1886-91.
51. Schussler JM, Anwar A, Phillips SD, Vallabhan RC, Grayburn PA. Effect on right ventricular volume of per cutaneous Amplatzer closure of atrial septal defect in adults. *Am J Cardiol* 2005;95:993-95.
52. Khan AA, Tan JL, Li W, et al. The impact of transcatheter atrial septal defect closure in the older population: a prospective study. *JACC Cardiovasc Interv* 2010;3:276-81.
53. Silversides CK, Haberer K, Siu SC, et al. Predictors of atrial arrhythmias after device closure of secundum type atrial septal defects in adults. *Am J Cardiol* 2008;101:683-87.
54. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defect in adults. *N Engl J Med* 1990;340:839-46.
55. Drenthen W, Pieper PG, Ross-Hesselink JW, et al, and the ZAHARA Investigators. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007;49:2303-11.
56. Yap SC, Drenthen W, Meijboom FJ et al, and the ZAHARA Investigators comparison of pregnancy outcomes in women with repaired versus unrepaired atrial septal defect. *BJOG* 2009;116:1593-601.
57. Webb G, Gatzoulis MA. Atrial septal defect in the adult: recent progress and overview. *Circulation*. 2006;114:1645-53. [PubMed] [Google Scholar]
58. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115:163-72. [PubMed] [Google Scholar]
59. Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation*. 1968;37:805-15. [PubMed] [Google Scholar]
60. Fleg JL, Shapiro EP, O'Connor F, Taube J, Goldberg AP, Lakatta EG. Left ventricular diastolic filling performance in older male athletes. *JAMA*. 1995;273:1371-5. [PubMed] [Google Scholar]
61. Swinne CJ, Shapiro EP, Lima SD, Fleg JL. Age-associated changes in left ventricular diastolic performance during isometric exercise in normal subjects. *Am J Cardiol*. 1992;69:823-6. [PubMed] [Google Scholar]
62. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med*. 1993;340:839-46. [PubMed] [Google Scholar]
63. Daliento L, Somerville J, Presbitero P, et al. Eisen-menger syndrome. Factors relating to determination and death. *Eur Heart J*. 1998;19:1845-55. [PubMed] [Google Scholar]
64. Bejiqi R, Retkoceri R, Bejiqi H, Zeka N, Maluku A, Berisha M. Klippel-Feil Syndrome associated with atrial septal defect. *Med Arch*. 2013;67:141-2. [PubMed] [Google Scholar]
65. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systemic overview from 1978 through 1996. *J Am Coll Cardiol*. 1998;31:1650-7. [PubMed] [Google Scholar]