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Prenatally diagnosed pulmonary atresia with intact ventricular septum

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Abstract:

Congenital heart disease is the most common birth defect, affecting 1%–1.2% of live born infants. Pulmonary atresia with intact ventricular septum (PA-IVS) accounts for <1% of all total heart defects. The cause of PA-IVS has been unclear. Thus, experience for prenatal diagnosis of PA-IVS is limited in any single institution. This is the case of a 28-year-old gravida 1 para 0 who came in at 34 + 5 weeks of gestational age. Fetal two-dimensional (2D) echocardiography revealed Type II PA-IVS, higher risk for univentricular circulation postnatally. She gave birth at term by vaginal delivery, with confirmed findings through a 2D echocardiography. Prenatal diagnosis of PA-IVS allows options for the termination of pregnancy, fetal cardiac interventional therapy, early postnatal initiation of prostaglandin E1, and planned early neonatal interventional surgeries for palliation and repair. Early assessment of fetal cardiac features is useful for a better outcome.

Keywords:

Intact ventricular septum, prenatal diagnosis, pulmonary atresia

Introduction

Congenital heart disease (CHD) is the most common birth defect, affecting nearly 10–12 per 1000 (1%–1.2%) live born infants.[1,2] The actual prevalence is undetermined because not all CHDs are diagnosed prenatally or early in the neonatal life. However, in the advent of widespread availability of ultrasound, improving imaging capabilities, and rigorous training for sonologists, prenatal diagnosis of CHD has been more detailed. This improvement in fetal detection of various CHDs is in part due to the standardization of outflow tract imaging outlined in the 2013 American Congress of Obstetricians and Gynecologists fetal imaging guidelines as well as the global thrust of the International Society of Ultrasound in Obstetrics and Gynecology publishing the guidelines for performing the "basic" and "extended basic" cardiac scan since 2006 and updated sonographic screening of the fetal heart in 2013.[3-5] According to the study of Chu *et al*. (2017) regarding the evaluation of performance of detailed fetal echocardiography by skilled obstetric physician sonologists in the diagnosis of CHD in a Chinese population, the detection of CHD in low-risk population has a 33.9% sensitivity and 99.8% specificity, whereas in high-risk population, as high as 68.8% sensitivity and 99.4% specificity.[6]

Early fetal diagnosis of a treatable CHD reduces the risk of perinatal morbidity and mortality.[7] Prenatal diagnosis of CHD is crucial as it optimizes prenatal patient counseling, multidisciplinary team preparation, and referral to a tertiary hospital prior to delivery for close monitoring and further management. 50%–60% of CHDs will require surgical correction, and of these, 25% are critical requiring early intervention.[7] The early successful intervention, whether medical or surgical, in these diseases, contributes to the prolongation of life and eventual prevalence into adulthood. With modern surgeries, approximately 90% of those with CHD survive to childbearing age.[2]

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There are ten general classifications of fetal cardiac malformations.[8] One of which pertains to right heart obstructive lesions, which involves the anomalies of the tricuspid valve (TV), right ventricle (RV), pulmonary valve (PV) and pulmonary arteries, and the ductus arteriosus. Anatomical variants can be divided into those with intact ventricular septum and those with ventricular septal defects (VSDs).[9] Pulmonary atresia with intact ventricular septum (PA-IVS) is a rare form of CHD accounting for 4–8 per 100,000 live births or <1% of all total heart defects, but the third most common cyanotic CHD. The cause of PA-IVS has been unknown or unclear. Several theories have been postulated including primary insult to the PV, abnormal venous valve, or abnormal coronary arterial development.[10]

Review of PubMed/Medline, and EBSCO databases for the past five years using keywords Prenatal Diagnosis + Pulmonary Atresia (PA) + Intact Ventricular Septum yielded 20 journal articles. Twelve out of the 20 articles were not included as it pertained to either an absent PV or with an Ebstein's anomaly or those with coronary sinus connections.

In the Philippines, there are no official published articles with a prenatally diagnosed case. Thus, there is no single institution with adequate experience in the detailed prenatal diagnosis of this kind of CHD. Therefore, we present a case of such with the subsequent management undertaken.

Case Report

This was the case of a 28-year-old gravida 1 para 0 who came in for fetal two-dimensional (2D) echocardiography to verify the status of the fetal heart. The patient had previously consulted with a general obstetrician gynecologist since her first trimester in Cebu City. Her fetal congenital anomaly scan done by a maternal fetal medicine specialist showed a hypoplastic left heart syndrome. She was subsequently referred to a cardiology specialist, who performed a fetal 2D echocardiography, which confirmed the cardiac anomaly but claimed that the findings were consistent with a TV atresia with pulmonic valve stenosis. The conflicting findings led the patient to seek a third opinion at our institution for a fetal echocardiography.

On review of her antenatal and medical histories, the patient had no known comorbidities, no known allergies to food and drugs/medications, and no previous surgical procedures done. Her family history was unremarkable. The patient was a nonsmoker and not an alcoholic beverage drinker who had been regularly menstruating since 12 years old consuming three pads per day lasting for 5–6 days with one sexual partner and no history of sexually transmitted infections or oral contraceptive use.

Her first prenatal checkup was at 4 weeks of gestational age, wherein folic acid and multivitamin supplementation was started daily. Pregnancy was confirmed with a transvaginal ultrasound at 6–7 weeks of gestational age with a pregnancy compatible with a last normal menstrual period of May 17, 2019. No maternal illnesses were noted for the duration of the first trimester with regular prenatal checkups.

The second trimester oral glucose tolerance test revealed normal results. Fetal congenital anomaly scan done at 30 weeks and 3 days gestational age by a maternal fetal medicine specialist revealed a fetus at 30 weeks and 3 days by fetal biometry, within the 10th–90th percentile for age, live, singleton, in cephalic presentation with an adequate amniotic fluid. Placenta was grade II, high-lying, and attached to the left posterolateral wall. There was note of a single umbilical artery, and a cardiac anomaly wherein the left ventricle (LV) appears smaller than the RV with minimal flow through the valve, to consider a hypoplastic left heart syndrome versus a mitral stenosis. The rest of the fetal ultrasound scan showed no other gross anomalies. The following day, the patient was referred to a cardiology specialist for fetal 2D echocardiography. The scan revealed a normal mitral valve (MV) giving rise to a well-developed ascending aorta, hypoplastic TV with TV atresia (Z-score 2), small right ventricular chamber (bipartite RV) giving rise to an adequately-sized main pulmonary artery with confluent branches, with mild pulmonic valve stenosis, and suspicious inlet-type VSD. The tricuspid annulus was 0.6 cm, and the mitral annulus was 1.3 cm, with absent tricuspid regurgitation (TR). There was no pericardial effusion. The rest of the findings were unremarkable.

The patient was seen at our institution by a maternal fetal medicine specialist for an ultrasound scan at 34 weeks and 5 days of gestational age. Biophysical profile scoring ultrasound showed a fetus at 34 weeks and 1 day gestational age by fetal biometry, within the 10th–90th percentile for age, live, singleton, in cephalic presentation with adequate amniotic fluid. The placenta was grade II, and attached posteriorly. There was note of a single umbilical artery. Biophysical Profile Score was 8 out of 8. Fetal 2D echocardiography [Appendix A] revealed a small TV orifice with minimal blood flow through the valve (TV atresia and absent regurgitation), hypoplastic RV (bipartite with small cavity), inlet-type VSD, nonpatent pulmonic valve with small orifice (pulmonic valve atresia), and retrograde flow in the ductus arteriosus (ductus dependent pulmonary circulation). The RV length was 0.98 cm, and the LV length was 2.2 cm.

Family counseling was done with the general obstetrician gynecologist and maternal fetal medicine

specialist. The patient opted to continue her prenatal care at our institution. She consulted with a pediatric cardiologist whose plan was to await delivery, and perform a diagnostic 2D echocardiography scan for the neonate at birth, and possible postnatal staged cardiac interventions. Thereafter, regular weekly prenatal checkup and monitoring was continued with a general obstetrician gynecologist and comanaged with a maternal fetal medicine specialist with an unremarkable prenatal course. A pelvic ultrasound was done at 36 weeks and 6 days gestational age for fetal surveillance. The scan revealed a fetus at 35 weeks and 3 days by fetal biometry, within the 10th–90th percentile for age, live, singleton, in cephalic presentation with an adequate amniotic fluid. The placenta was grade II–III and attached posteriorly. There was note of a single umbilical artery, and two nuchal cord coils.

The patient was admitted at 38 weeks and 2 days of gestational age for watery vaginal discharge that started approximately 2 h prior to consultation. She was managed as a case of prelabor rupture of membranes. On admission, she had labor pains and bloody show. The vital signs were stable. Prepregnancy body mass index was 20.3 kg/m^2. On physical examination, she had pink palpebral conjunctivae, anicteric sclera, regular heart sounds, and clear lung fields. The abdomen was globular, with a linea nigra, soft, nontender with normal bowel sounds. Fundic height was 31 cm. Leopold's maneuver reveals that the uterine upper pole contains the fetal buttocks with the fetal back in the maternal right position. The fetus was in a cephalic position but unengaged, with a flexed head. Fetal heart beat was 130 beats/min. The external genitalia was grossly normal. The speculum examination revealed pooling of clear amniotic fluid. On internal examination, cervix was 4 cm dilated and 60% effaced, with ruptured bag of water, cephalic in station -3/5. Admitting cardiotocography was category 1, based on American College of Obstetricians and Gynecologists classification, or normal, based on International Federation of Gynaecology and Obstetrics classification. Ampicillin 2 g intravenous loading dose was started and continued 1 g intravenously every 4 h until delivery. Venoclysis and continuous electronic fetal monitoring was done. As part of the pre-operative preparation, the patient was referred back to the neonatologist and pediatric cardiologist, who will be on stand-by for the neonate. Labor progress was monitored and uneventful for 8 h. The patient gave birth by normal spontaneous delivery with right mediolateral episiotomy and episiorrhaphy under epidural anesthesia. She delivered to a live male with Apgar score of 8 becoming 8, birth weight of 2690 g, birth length of 50.5 cm, Ballard score of 38 weeks, and appropriate for gestational age.

The general appearance of the neonate was cyanotic with a Grade 3/6 holosystolic murmur at the left sternal border. Newborn care was rendered, and the neonate was brought to the neonatal intensive care unit, where he was monitored every 15 min through a cardiac monitor. Stat 2D echocardiography revealed atrial septal aneurysm with right-to-left shunting, patent ductus arteriosus, intact ventricular septum, hypoplastic tricuspid annulus, patent TV, normal MV, and pulmonic valve atresia. Family counseling was done and the neonate was scheduled for stat atrial septostomy and patent ductus arteriosus stenting (first-stage cardiac operation). Prostaglandin drip at 0.1 ml/h (0.01 μg/kg/min) intravenously was started. Oxygen saturation was maintained at 80% and above. Laboratory workup including complete blood count, prothrombin time, partial thromboplastin time, chest X-ray, blood culture, and serum creatinine was done. The patient was started on intravenous ampicillin and cefotaxime every 12 h for presumed sepsis. Routine preoperative preparation was done. On the 1st day of life, the neonate underwent stent implantation into the ductus arteriosus and balloon atrial septostomy (BAS) under general endotracheal anesthesia. Baseline oxygen saturation was 80% preoperatively and increased to 94% after the stent was implanted. Postoperatively, prostaglandin drip was discontinued and neonate was hooked to a mechanical ventilator. Neonate was extubated and transferred to the isolette on the 2nd day of life. Post extubation, the neonate had stable vital signs with no desaturations or cyanosis, but with a grade 2–3/6 continuous murmur along the left sternal border. The rest of the hospital stay was unremarkable. Aspirin was started on the 5th day of life, while antibiotics were completed for 7 days and were discharged on the 10th day of life. Neonatal interval history was relatively unremarkable. Though, he still had occasional cyanosis and dusky extremities with a persistent Grade 2–3/6 systolic murmur at the left midclavicular line. He was readmitted at 5 months old for open heart surgery including the following procedures: takedown of patent ductus arteriosus stent, repair of left pulmonary artery, bidirectional Glenn shunt, and atrial septectomy (second stage of cardiac operation). The infant was discharged stable after 8 days. Interval history showed that the child did well following the first two stages of the single ventricle palliation. However, at 4 years old, he gradually developed deeper cyanosis with oxygen saturation as low as 70, especially when active. Therefore, it was decided that the child should undergo the third stage of cardiac operation, which is the Fontan procedure. The preoperative right cardiac catheterization showed good PA pressure at a mean of 11 mmHg with adequately sized pulmonary arteries and no discrete stenosis. Preoperative transesophageal 2D echocardiography revealed hypoplastic RV, pulmonic valve atresia, with atrial septal communication measuring

1.8 cm, and right-to-left shunting. The Glenn flow was demonstrated, and there was good contractility of the LV with no significant aortic or mitral regurgitation. The child underwent extracardiac Fontan procedure without any unexpected intraoperative events. Postoperative transesophageal 2D echocardiography revealed good Fontan flow with good cardiac contractility, collapsed right atrium, and no thrombus seen. Postoperative course was unremarkable and the child was discharged stable on the 16th postoperative day.

Case Discussion

PA-IVS is a rare complex cyanotic CHD with heterogeneous morphological variations of RV and TV hypoplasia and the absence or presence of ventriculocoronary artery communication (VCAC).[11] As part of the right-sided heart diseases with an intact ventricular septum variant, progression to right ventricular dysfunction and hypoplasia is more likely.[9]

Prevalence

There are multiple case series and retrospective studies found in literature. Tuo *et al*. (2011) reviewed medical records from the period of January 1993 to December 2009 in two referral centers located in Italy, which included 36 patients prenatally and 24 patients postnatally diagnosed with PA-IVS, wherein all neonates had a normal karyotype.[12] In the study of Gottschalk *et al*. (2019), two tertiary referral centers in Germany reported 50 fetuses with PA-IVS during the period of 14 years (2003–2016) with one diagnosed postnatally.[13] In the study of Liu *et al.* (2019), the Cardiac Center of Henan Province in China was able to identify 51 fetuses with PA-IVS from the period 2012–2019, wherein all neonates had a normal karyotype.[14] There are no official published cases diagnosed prenatally that were reported in the Philippines. There is a study from the Philippine Heart Center (2015) of 930 cases of CHD from 2004 to 2014 who underwent transcatheter interventions which detailed 10 cases who underwent single procedure PDA stenting and 21 with multi-interventional procedures (PDA stenting + BAS + percutaneous pulmonary balloon valvuloplasty (PPBV)). In total, there were 163 neonates and infants who underwent BAS and 26 who underwent PPBV, covering right-sided obstructive cardiac lesions that ranged from PV atresia, critical pulmonary stenosis (CPS), tricuspid stenosis and TV atresia, and dextro-transposition of the great arteries as well as some total anomalous pulmonary venous return cases. Even though PA-IVS is the third most common cause of CHD worldwide and encompassing approximately <1% of all CHD, it is not a negligible cause of perinatal and neonatal morbidity and mortality, and there is no single institution with adequate experience in the detailed prenatal diagnosis of this kind of CHD.

Pathogenesis

The precise morphogenesis of PA-IVS has been unclear. The PV may initially have been patent and then becoming stenotic and eventually atretic. It was postulated to be acquired later in gestation, beyond the 4th developmental week, after the closure of the interventricular communication due to the well-developed pulmonary trunk.[11] The markedly elevated right ventricular pressure may develop sinusoidal connections between right ventricular cavity and coronary arteries creating the VCAC.[8] Eventually, PA with an IVS, as compared to PA with a VSD, shows more progression to hypoplasia of the TV and RV, which develops into myocardial damage that leads to a possible univentricular circulation postnatally, requiring complex and multiple interventions at birth.[9]

Sonographic prenatal diagnosis

Sonographic prenatal diagnosis of CHD remains to be a challenge even in the present day and typically requires a skilled eye and technique. In the same study of Liu *et al*. (2019), the diagnosis of PA-IVS has a mean gestational age of 26 + 6 weeks (biventricular repaired PA-IVS) to 27 + 5 weeks (univentricular repaired PA-IVS).[14] While in the study of Tuo *et al*. (2011), 17 out of the 36 prenatally diagnosed PA-IVS were diagnosed at a mean gestational age of 23 weeks with the rest diagnosed and referred within the third trimester.[12] Similarly, prenatal ultrasound was a feasible screening tool for the presence of PA-IVS as the study did not have any false positive reading, and in only one case, the RV morphology was described incorrectly. In our case, the patient was already 30 weeks and 3 days gestational age at initial diagnosis. Then, the findings were finally confirmed in our institution at 34 weeks and 5 days gestational age. There is a male gender predilection for PA-IVS with a 1.5:1 ratio.[11] In the study of Tuo *et al*. (2011), 18 out of the 33 (55%) cases diagnosed prenatally and 18 out of the 24 (75%) cases diagnosed postnatally were male.[12] As in our case, the fetus was male.

Fetal cardiac intervention/therapy

Interventions in fetal life can alter the natural history of PA-IVS which can improve postnatal adaptation and status.[9] Interventional fetal therapy in cases of PA-IVS or CPS involves fetal cardiac intervention (FCI) in the form of fetal pulmonary valvuloplasty (FPV), which may relieve the RV tract obstruction.[13] The goal of this intervention is to stimulate and promote RV growth and function to avoid significant RV hypoplasia and to increase the likelihood of a biventricular circulation, wherein the RV is the only source of pulmonary blood flow in the absence of right-sided heart failure, postnatally.[13,15] In the fetal stage, the promotion of RV growth and cardiac remodeling through hyperplasia increases myocyte production, which may improve long-term function with better potential for

postnatal adaptation. However, FCI does not improve cardiac growth relatively beyond the body size of the fetus, which means catch-up growth does not occur.[9] For those with failed FCI or no FCI, biventricular circulation can still be attempted postnatally, but RV function may remain abnormal as potential for RV growth postnatally is limited.[15] Criteria for FPV include either membranous atresia (imperforate valve) or a critical stenosis of the PV with a recognizable RVOT, retrograde flow in the ductus arteriosus, and a hypoplastic hypertrophic RV with suprasystemic pressures as assessed by the velocity of the TR jet.[15]

Tulzer *et al*. (2018) retrospectively reviewed medical records in Children's Heart Center Austria during the period October 200 to July 2017 with a total of 129 fetal intracardiac interventions, of which 35 involved cases of PA-IVS or CPS, wherein the median gestational age at the time of intervention was 28 + 4 weeks (range of 23 + 6–32 + 1 weeks).[15] Similarly, in the case reports of Pang *et al.* (2018), two cases underwent prenatal interventional therapy, one for PA-IVS and the other for CPS at Guandong General Hospital from September 2016 to February 2017. The two cases underwent FPV at 28 weeks of gestational age.[16] Moon-Grady *et al*. (2015) created an International Fetal Cardiac Intervention Registry, involving 25 fetal surgery and fetal interventional programs worldwide that spanned from January 2001 to June 2014, which included 245 maternal–fetal patients underwent FCI. Thirty patients were diagnosed with PA-IVS or CPS, but only 16 patients underwent pulmonary valvuloplasty with a median gestational age of 26 weeks (range: 23–29 + 6 weeks) at the time of intervention.[17] The initial fetal echocardiography results in this case at 30 weeks and 4 days of gestational age seemed a viable candidate for FPV. Unfortunately, the patient was seen late in the third trimester at our institution, which is past the usual gestational age for intervention. Although FCI is available for PA-IVS, the benefit of prenatal intervention versus postnatal intervention is still contentious as there are only a small number of treated fetuses, nonstandardized pre- and postnatal management, nonstandardized inclusion and exclusion criteria, lack of control groups, and limited follow-up data.[13] However, there is increasing evidence, with technological advancements and further training, that FCI can alter the natural history of fetuses with PA-IVS.[18] Therefore, early assessment of fetal cardiac features would be useful for the proper timing of FCI with the opportunity for a better outcome.[12]

Prenatal diagnosis of fetal cardiac anomalies

Prenatal diagnosis also allows for options of termination of pregnancy, interventional fetal therapy, early postnatal initiation of prostaglandin E1 (PGE1), and planned early neonatal intervention.[11,12] Although prenatal diagnosis is invaluable, solely, it has not been shown to decrease mortality rate.[11] Termination of pregnancy or medical abortion is not allowed in the Philippines. Interventional fetal cardiac therapy experience in the Philippines is scarce, but options abroad are available, which should be offered to patients as part of counseling if maternal and fetal status permits.

Prenatal diagnosis of PA-IVS aids in a patient-specific counseling including specific fetal characteristics that determine morbidity and mortality. Most fetuses with PA-IVS will survive until birth without major problems, as in our case.[9] However, some will develop or present with severe TR, leading to significant hydrops and eventually intrauterine fetal demise due to a right-sided heart failure.[11] In the study of Tulzer *et al*. (2018), no fetal death occurred, as prenatal diagnosis of PA-IVS enabled heightened fetal surveillance. All fetuses were born alive at a mean gestational age of 38 + 2 weeks (range of 30 + 1–40 + 4 weeks), as in our case, fetus was delivered live at 38 weeks and 2 days.[15] However, there were fetuses who developed pericardial effusion and persistent bradycardia during FCI. Similarly, there were six preterm deliveries due to preterm prelabor rupture of membranes, pregnancy-induced hypertension, and uncontrolled preterm labor. They also noted that, in almost all fetuses, progressive PV stenosis or re-atresia can be expected with advancing gestation as evidenced by 2 out of 17 fetuses with successful pulmonary valvuloplasty and 2 out of 4 fetuses with partially successful pulmonary valvuloplasty, owing to discrepancies in the balloon–valve ratios. Published survival rates include the 1-year survival rate is 65% to 92% and the 10-year survival rate is 43% to 73%.[9]

Prenatal risk stratification for neonatal intervention therapy

Similarly, prenatal diagnosis helps in the risk stratification of the most ideal postnatal palliative and corrective approach. This is determined by the initial TV morphology, RV morphology, form of the PV atresia (membranous atresia– imperforate valve versus muscular atresia– atresia of the entire outflow tract), and the presence or absence of VCAC.[11] These parameters determine the postnatal circulation and repair either biventricular, 1.5 ventricular, or univentricular. In the study of Liu *et al*. (2019), echocardiographic classification of PA-IVS includes Type I to III. Type I is PA + with RV inlet, trabecular and infundibulum portion + absence of VCAC. Type II is PA + absence of RV trabecular portion + with RV inlet and infundibulum portion but small cavity + absence of VCAC. Type III is PA + absence of RV trabecular and infundibulum portion, but only a small inlet portion + presence of VCAC.[14] Type I outcomes tend to be biventricular. Type II outcomes tend to be univentriuclar but biventricular are feasible. Type III outcomes tend to lean toward univentricular.

The fetal 2D echocardiographic report done at 30 weeks and 4 days gestational age, and that done at 34 weeks and 5 days gestational age is consistent with a Type II classification of PA-IVS. A Type II PA-IVS indicates a possible univentricular circulation outcome, as in our case.

Prenatal prognostic models for neonatal ventricular outcome

Several prognostic models have been described to predict biventricular outcome versus a single ventricle outcome in the setting of PA-IVS [Appendix B]. One of those is the Roman *et al*. scoring system, which is based on four parameters: TV/MV annular diameter (TV/MV) ratio <0.7, RV/LV length ratio <0.6, RV filling time <31.5% of cardiac cycle length, and presence of right ventriculo-coronary artery communication (RVCAC).[19] This scoring system predicts 100% sensitivity and 75% specificity of a non-biventricular outcome if three of the four criteria are fulfilled.[17] Gottschalk *et al*. (2019) likewise confirmed in their study that an RV/LV ratio ≤0.6 corresponded to RV hypoplasia, while absence or mild TR of < 2 m/s corresponded to impaired RV function, and high risk for VCAC, and presence of VCAC corresponded to additional risk for an outcome of univentricular circulation.[13] In our case, the fetal echocardiographic report done at 30 weeks and 4 days gestational age did not have the measurement of the RV length. But that done at 34 weeks and 5 days gestational age revealed an RV/LV ratio of 0.45 with absence of TR, which corresponds to additional risk for a univentricular outcome.

Meticulous care should be taken when using the prognostic models, as prediction of a poorer outcome may result to an overly pessimistic counseling. Hence, a PA-IVS with a good ventricular function offers a relatively good prognosis. In the study of Strainic (2019), he summarized the three largest FCI results for PA-IVS, wherein 70% to 83% of those with successful procedures had a biventricular outcome while those with failed procedures or no procedure at all had biventricular outcome in 40%.[9] However, it is important to note that specific fetal characteristics as well as possible cardiac compromise affect the success rate of biventricular outcome. The ultimate goal to achieve a biventricular circulation is only feasible in 32% to 63% of reported cases. Hence, there is a percentage of cases with small but functional RVs, who undergo the one and a half ventricular repair (1.5 V). The one and a half ventricle type diverts some of the systemic venous return straight to the pulmonary artery, while maintaining some flow through the RV toward the pulmonary artery.[9] In the study by Gottschalk *et al*. (2019), the overall long-term outcome of univentricular circulation is as good as biventricular group with 81% and 86% survival rates after 15 years, respectively, while 95% of those with univentricular circulation live with New York Heart Association Class I or II. However, the risk of death is highest in the first 6 months of life, decreasing over the next 12 months with no deaths after 4 years of age.[14]

Prenatal diagnosis of fetal cardiac anomalies' effects on maternal mental health

Maternal psychological state is in general positively affected by prenatal diagnosis of CHD in women who elect to continue a pregnancy to term because they are spared the guilt associated with decision-making as they are given time to prepare for the arrival or death of the neonate. Studies about the effect of prenatal diagnosis of anomalies conclude that short-term increase in anxiety may be observed as both the parturient and her partner learn of the fetal state, while waiting for confirmatory scans. They noted that the levels of anxiety significantly improved to resolution after subsequent discussion of specific antenatal diagnosis and discussion of specific postnatal outcome and surgical management.[20] In part due to a heightened fetal surveillance, prenatal diagnosis of CHD ultimately seems to produce more hemodynamically stable neonates with better outcomes than those undetected before birth, as it provides opportunity for detailed cardiac malformation analysis and fetal intervention. Similarly, the time interval from diagnosis to delivery gives the opportunity for family education, financial procurement, and detailed planning for immediate post-birth interventions to be done in tertiary specialty hospitals, which alleviates concerns of parturients and families. However, the time interval is likewise a double-edged sword. In the cross-sectional study of Rychik *et al*. (2013) of 59 parturients in the Children's Hospital of Philadelphia, 39% exhibited traumatic distress, 22% developed depression, and 31% had anxiety during the interval from diagnosis to delivery.[21] Significant anxiety was demonstrated in women referred for fetal echocardiography, and though a decrease was noted after the procedure, the level of anxiety thereafter is still higher than in women whose neonate was diagnosed after birth. The initial prenatal diagnosis of CHD conveyance method and technique influences the degree of stress and trauma to the parturient. The uncertainty of the diagnosis, lack of full management strategy, and unknown outcome of particular CHD worsens the initial psychological impact. Maternal outcome is improved if there is healthy partner relationship, emotional social support, and obtaining financial stability prior to delivery.[21] In another longitudinal, prospective, case-controlled study by Wu *et al.* (2020), 48 women carrying fetuses with CHD exhibited stress (65%), anxiety (44%), and depression (29%).[22] Depression scores were higher for women whose fetuses had high-risk for single-ventricle CHD. Maternal stress and anxiety led to impaired

fetal brain development, decrease in cerebellar and hippocampal volume. Hence, maternal psychological distress from prenatal diagnosis of CHD is a potentially modifiable risk factor in high-risk population that should be addressed.[21]

Mode of delivery

Mode of delivery was not discussed in the studies reviewed. However, in our case, continuous intrapartum fetal monitoring was done, and cesarean section was only considered for obstetrical indications. In our case, the patient had an uneventful course of labor and delivered successfully by vaginal delivery.

Neonatal management

Postnatally, the arterial duct remains the sole source of pulmonary blood flow. As PGE1 is administered, the ductus arteriosus is maintained prior to a surgical repair or palliation in the first few weeks of life. An atrial communication is likewise necessary to permit obligate right-to-left shunting of the systemic venous return, which results in cyanosis as seen in our case. Multistaged cardiac repair is expected for those CHD which cannot be successfully offered a biventricular circulation, as in our case. The first stage operation for repair involves atrial septostomy and patent ductus arteriosus stenting. Intermediate stage operation involves the Glenn procedure wherein the anastomosis between the superior vena cava and the right pulmonary artery is done. The last stage operation is the Fontan procedure, modified to the lateral tunnel technique, wherein an interatrial patch is placed in the right atrium. Another recent modification is the creation of an extracardiac conduit between the inferior vena cava and the right pulmonary artery.

Risk of recurrence in subsequent pregnancies

It is noteworthy that there is a 25% recurrence risk for CHD in subsequent pregnancies.[11] In the case report by Chitayat *et al*. (1992), two sisters born a year apart were both diagnosed with isolated PA-IVS and both with normal karyotype.[18] The first case had apparently normal ultrasound findings and was delivered at term but developed perioral cyanosis and mild respiratory distress on the 1st day of life. 2D echocardiography revealed a hypoplastic right heart with PA. She underwent a central aortopulmonary shunt, but the neonate died on the 2nd day of life due to persistent ventricular fibrillation. The second case had a fetal echocardiography at 22 weeks of gestational age which revealed the same findings as the first sibling. Hence, the parental decision was to terminate the pregnancy and autopsy findings confirmed the findings with no other abnormalities detected. This study suggested a possible autosomal recessive trait for PA-IVS. In another case report by De Stefano *et al*. (2008), PA-IVS was diagnosed in a monozygotic twin pregnancy with an uneventful prenatal course but delivered prematurely at 27 weeks of gestational age.[23] Both twins had identical cardiac findings with no other extra cardiac abnormalities. One twin died on the 3rd day of life and the other died on the 7th day of life. Genetic evaluation noted 55 kb deletion at WFDC8 and WFDC9 but the clinical significance of this gene deletion is unknown. PA-IVS is rarely associated with extracardiac anomalies and chromosomal abnormalities as seen across studies, but there is also a report of chromosome 22q11.2 microdeletion.[14] In our case, no other extracardiac anomalies were observed.

Conclusion

PA-IVS is a rare complex cyanotic CHD with heterogeneous morphological variations. The precise morphogenesis of PA-IVS has been unclear. As part of the right-sided heart diseases with an intact ventricular septum variant, progression to right ventricular dysfunction and hypoplasia is more likely, which can eventually lead to hydrops and intrauterine death. Encompassing approximately <1% of all CHD, it is not a negligible cause of perinatal and neonatal morbidity and mortality, and any single-center experience is limited.

Prenatal diagnosis of PA-IVS aids in a patient-specific counseling including specific fetal characteristics that determine morbidity and mortality. Prenatal diagnosis also allows for options of termination of pregnancy in countries where it is legal and FCI (pulmonary valvuloplasty). Early assessment of fetal cardiac features through detailed fetal cardiac evaluation would be useful for the proper timing of FCI. Although the benefit of prenatal intervention versus postnatal intervention is still contentious, there have been increasing evidence that it can alter the natural history of fetuses and provide an opportunity for a better outcome postnatally. Similarly, prenatal diagnosis positively affects maternal psychological state as it gives them time to prepare for the arrival of the neonate in terms of family education, financial procurement, and detailed planning for immediate postbirth interventions. As prenatal diagnosis of CHD has a psychological impact on the parturient, care should be undertaken so as not to predict a poorer neonatal outcome, which may result in an overly pessimistic counseling, thus highlighting the value of a detailed and accurate prenatal diagnosis of CHD with proper and thought-worthy patient counseling.

Authorship contributions

Vanessa Marie T. Lim – Involved in conceptualization, writing – original draft, review and editing, visualization.

Angelita R. Teotico – Involved in conceptualization, checking – original draft.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Appendices

Appendix A: Fetal two-dimensional echocardiography at 34 weeks and 5 days of gestational age

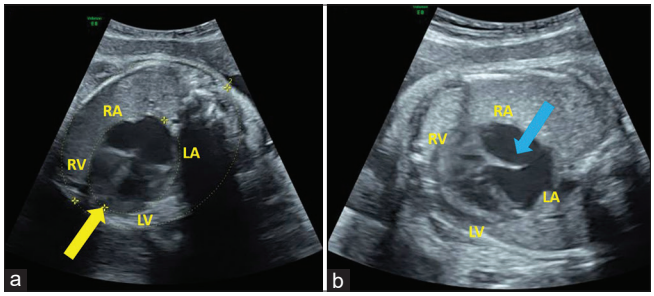

Figure 1: (a and b) The four-chamber heart view showed atrioventricular concordance, normal mitral valve, small tricuspid valve orifice, small right ventricle, normal left ventricle, with a suspicious inlet ventricular septal defect (yellow arrow) (a), normal atria, intact interatrial septum (blue arrow) with flap of foramen ovale, normal veno-atrial connections (b). RA – Right atrium, RV – Right ventricle, LA – Left atrium, LV – Left ventricle

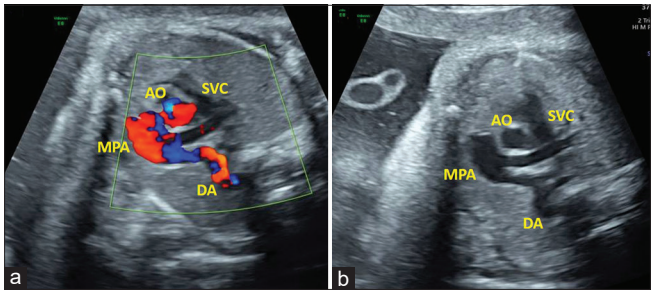

Figure 3: (a and b) Retrograde flow in the ductus arteriosus. Normal vessel alignment and sizes, normal V confluence to the left of trachea. MPA – Main pulmonary artery, AO – Aorta, SVC – Superior vena cava, DA – Ductus arteriosus

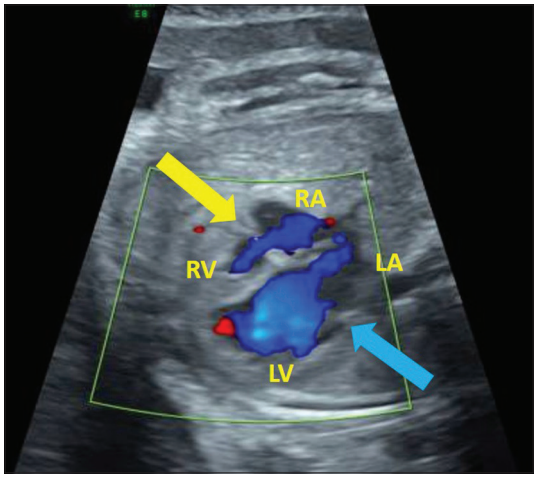

Figure 2: Color flow across the four-chamber heart view shows normal flow across mitral valve (blue arrow) and minimal flow across tricuspid valve (yellow arrow). RA – Right atrium, RV – Right ventricle, LA – Left atrium, LV – Left ventricle

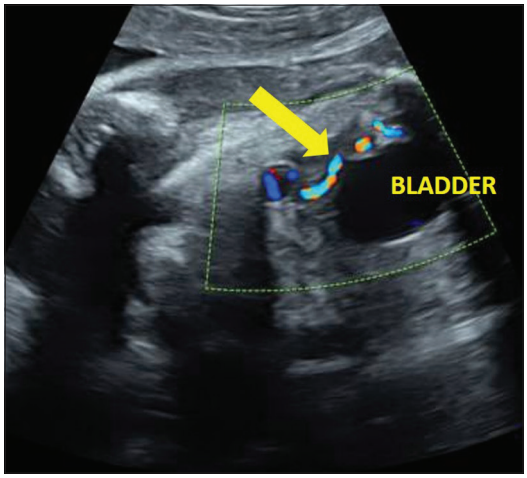

Figure 4: Single umbilical artery (yellow arrow)

Appendix B: Summary of morphologic and physiologic predictors of developing single ventricle in pulmonary atresia with intact ventricular septum[9]

	Fetal predictors of single ventricle outcome
Salvin *et al.* (2006)[24]	TV *Z* score ≤−3
Roman *et al.* (2007)[19]	TV:MV ratio <0.7
	RV:LV length ratio <0.6
	Tricuspid inflow duration to cardiac cycle length ≤31.5%
	Presence of VCAC
Gardiner *et al.* (2008)[25]	PV *Z* score <−1 or
	TV *Z* score <−3.4, before 23 weeks
	Median TV *Z* score <−3.95, before 26 weeks
	Median TV *Z* score <−2.8 and median TV:MV ratio <0.7, at 26–31 weeks
	Median TV *Z* score <−3.9 and median TV:MV ratio <0.59, after 31 weeks
Gomez Montes *et al.* (2012)[26]	TV:MV ratio ≤0.83
	RV:LV length ratio ≤0.64
	PV:AV ratio ≤0.75
	Tricuspid inflow duration/cardiac cycle length ≤36.5%

TV: Tricuspid valve, RV: Right ventricle, LV: Left ventricle, VCAC: Ventriculocoronary artery communication, MV: Mitral valve, PV: Pulmonary valve, AV: Aortic valve