Fetal Counseling Provider Information
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Authors: Ann Kavanaugh-McHugh, MD and Stacy A.S. Killen, MD, MSCI

DIAGNOSIS:

Absent Pulmonary Valve Syndrome

Note: The majority of this document addresses Tetralogy of Fallot (TOF) with absent pulmonary valve (APV), which accounts for ~92% of fetal diagnoses with absent pulmonary valve. Unless specifically mentioned, these data do not apply to rare variants.

Incidence (1-9)

- 1/100,000 live births
- 1% of CHD and 15-20% of TOF diagnosed prenatally
- 0.2-1% of CHD and 2.5-6% of TOF diagnosed postnatally (due to fetal loss/termination)

Subtypes (1-9)

- Most commonly seen in association with TOF
- In 8-17% occurs with intact ventricular septum (IVS), most commonly with associated tricuspid stenosis/atresia and right ventricular myocardial abnormalities
- Even more rarely occurs in association with tricuspid valve dysplasia, double-outlet right ventricle, unbalanced atrioventricular septal defect, or absent aortic valve

Available Fetal Interventions

None

Fetal Imaging Predictors of Postnatal Interventions/Outcomes (2, 6-9, 14)

- Echocardiographic hallmarks of TOF/APV include a dysplastic or rudimentary pulmonary valve with severe pulmonary insufficiency, right ventricular dilation, and severe branch pulmonary artery dilation

- Pulmonary artery dilation is a constant feature after 20-22 weeks but may be absent before this time
- First trimester diagnosis may depend on identification of a ventricular septal defect, abnormal aortic arch situs, to-fro flow in the ductal arch, or reversed flow in the ductus venosus, umbilical artery, or middle cerebral artery
- Left ventricular (LV) dysfunction is an independent predictor of fetal demise and may progress over gestation
- Right ventricular (RV) dysfunction is an independent predictor of overall mortality
- Other factors associated with prenatal and postnatal mortality that do not change significantly through gestation: mediastinal shift [related to airway obstruction and abnormal lung development], LV/RV dilation, increased CT area ratio, hydrops, pericardial effusion, tricuspid valve regurgitation, and Doppler abnormalities (decreased tricuspid inflow duration/cardiac cycle length [marker of diastolic dysfunction], increased pulmonary valve forward to reverse velocity time integral (VTI) [less pulmonary valve insufficiency], decreased aortic valve VTI, decreased MCA pulsatility indices, abnormal ductus venosus flow pattern, and lower cerebroplacental ratio [CPR])
- Pulmonary artery diameters do not appear to correlate with outcome but in one small series a higher pulmonary valve to aortic valve ratio predicted mortality (14)
- Factors associated with fetal demise: hydrops, pericardial effusion, LV or RV systolic dysfunction, tricuspid valve regurgitation, mediastinal shift, moderate or severe RV dilation, and any LV dilation

Prognosis (6-8, 14, 17-22)

- Therapies
  - Available therapies and resulting outcomes depend on the subtype and may vary significantly by center
  - Most require respiratory and/or hemodynamic support in the first 24 hours of life

- Survival
  - Perinatal risk factors for mortality include respiratory distress at birth, presence of a genetic syndrome, and presence of hydrops
  - Earlier gestation and lower birth weight at delivery are associated with postnatal mortality
  - 64% overall survival for prenatally diagnosed fetuses with intention to treat

  - 9-14% in utero death (with prenatal intention to treat) in largest series
    - Hydrops and higher mortality more common in the first trimester
    - Late mortality between 26 and 38 weeks
  - 70% survival for liveborn infants (15% die before surgery; 9% die with neonatal surgery; remainder die before or after late surgery) in a recent US multicenter series (6); mortality risk is highest in the perinatal period
  - 92% 10-year survival in 2 recent series
  - Freedom from re-intervention:
    - 62% at 10 years with freedom from pulmonary artery intervention 83% and from pulmonary valve replacement 74% in one series (17)
    - 89% at 10 years in another series (18)
  - Underlying single-ventricle physiology strongly predicted need for heart transplantation

- Hospital LOS
  - Available therapies and resulting outcomes, including hospital length of stay, depend on the subtype and may vary significantly by center

- Neurodevelopmental outcomes
  - Up to 50-60% with learning differences in 2 small series; half of those had a genetic syndrome

<u>Associated Problems (2; 6-8; 10-16; 21-22)</u>

- Chromosomal abnormalities
  - Abnormal karyotype in ~35-45% of fetuses
  - 22q11 most common (15-50%); look for absence of the thymus
  - Trisomy 13, trisomy 18, Alagille's syndrome, and other chromosomal microdeletions have been reported

- Extracardiac abnormalities
  - Airway abnormalities
    - 40% of infants have perinatal respiratory distress postnatally
    - Secondary to compression of mainstem bronchi by dilated branch pulmonary arteries and segmental arteries "entwining and compressing" their associated bronchi; associated tracheobronchomalacia, abnormal bronchial development, air trapping, and potential ventilator dependence

        - No prenatal predictors of severity of airway abnormalities (pulmonary artery size is not predictive)
        - Respiratory complications may persist after surgical repair with need for long-term ventilation in up to 30%
        - Early neonatal ventilator dependence may predict mortality independent of the cardiac surgical result
    - CNS, genitourinary, gastrointestinal, musculoskeletal and craniofacial abnormalities (8-16%; as high as 51% in series with first trimester diagnoses)

- Cardiac associations
    - Ductal agenesis is common in TOF/APV (80%)
    - Ductal persistence is associated with a poorer prognosis (associated with biventricular dysfunction); more common in the first trimester and associated with discontinuous branch pulmonary arteries
    - Intact ventricular septum associated with tricuspid stenosis/atresia and myocardial abnormalities carries a poorer prognosis due to associated RV dysfunction; in APV/IVS the ductus arteriosus is usually present with normal branch pulmonary artery dimensions; coronary arteries may be markedly abnormal (14)
    - Right aortic arch
    - Abnormal cardiac axis with leftward rotation (80-90%)

REFERENCES

1. Mivelaz Y, Lim KI, Templeton C et al. Population based review of tetralogy of Fallot with absent pulmonary valve: is prenatal diagnosis really associated with a poor prognosis. *Ultrasound Obstet Gynecol.* 2012;40:536-541.
2. Gottschalk I, Jehle C, Herberg U et al. Prenatal diagnosis of absent pulmonary valve syndrome from first trimester onwards: novel insights into pathophysiology, associated conditions, and outcomes. *Ultrasound Obstet Gyn*ecol 2017;49:637-642.
3. Lev M, Eckner F. The pathologic anatomy of Tetralogy of Fallot and its variations. *Chest.* 1964;45:251-261.
4. Rao B, Anderson R, Edward J. Anatomic variations in the tetralogy of Fallot. *Am Heart J.* 1971;81:361-371.
5. Allan LD, Sharland GK, Milburn A et al. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. *J Am Coll Cardiol.* 1994;23:1452-1458.
6. Chelliah A, Moon-Grady AJ, Peyvandi S, et al. Contemporary outcomes in tetralogy of Fallot with absent pulmonary valve after fetal diagnosis. In press: *JAHA* 2020.
7. Wertaschnigg ,D Jaeggi M, Chitayat D et al. Prenatal diagnosis and outcome of absent pulmonary valve syndrome: contemporary single center experience and review of the literature. *Ultrasound Obstet Gynecol.* 2013;41:162–167.
8. Axt-Fliedner R, Kurkevych A, Slodki M et al. Absent pulmonary valve syndrome – diagnosis, associations, and outcome in 70 prenatally diagnosed cases. *Prenatal Diagnosis.* 2017;37:812–819.
9. Galindo AG, Gutierrez-Larraya F, Martinez JM, et al. Prenatal diagnosis and outcome for fetuses with congenital absence of the pulmonary valve. *Ultrasound Obstet Gynecol.* 2006; 28:32-39.
10. Rabinowitz M, Grady S, David I et al. Compression of intrapulmonary bronchi by abnormal branching pulmonary arteries associated with absent pulmonary valves. *American Journal of Cardiology.* 1982;50:804-813.
11. Taragin BH, Berdon WE, Printz B. MRI assessment of bronchial compression absent pulmonary valve syndrome and review of syndrome. *Pediatr Radiol.* 2006;36:71–75.
12. Donofrio MT, Jacobs M, Rychik J. Tetralogy of Fallot with absent pulmonary valve: echocardiographic morphometric features of the right sided structures and their relationship to presentation and outcome. *JASE.* 1992;10:556-561.
13. Moon-Grady A, Tacy TA, Brook MM et al. Value of clinical and echocardiographic features in predicting outcome in the fetus, infant, and child with tetralogy of Fallot and absent pulmonary valve complex. *Am J Cardiol.* 2002;89:1280–1285.
14. Szwast A, Tian Z, McCann M et al. Anatomic variability and outcome in prenatally diagnosed absent pulmonary valve syndrome. *Annals of Thoracic Surgery.* 2014;98:152-158.
15. Chelliah A, Berger JT, Blask A, et al. Clinical utility of fetal magnetic resonance imaging in tetralogy of Fallot with absent pulmonary valve. *Circulation.* 2013;127:757-759.
16. Sun HY, Boe J, Rubesova E, Barth RA et al. MRI correlates with postnatal CT angiogram assessment of pulmonary anatomy in tetralogy of Fallot with absent pulmonary valve. *Congenital Heart Disease.* 2014;9:E105–109.

17. Dorobantu DM, Stoicescu C, Tulloh RM et al. Surgical repair of tetralogy of Fallot with absent pulmonary valve: favorable long-term results. *Seminars in Thoracic and Cardiovascular Surgery.* 2019;31:847-849.
18. Talwar S, Divya A, Choudhary SA. Mid-term results of correction of tetralogy of Fallot with absent pulmonary valve. *Indian Heart J.* 2017;69:767-771.
19. Yong MS, Yim D, Brizard C, et al. Long-term outcomes of patients with absent pulmonary valve syndrome: 38 years of experience. *Ann Thorac Surg.* 2014;97-1671-1677.
20. Norgaard MA, Alfonso N, Newcomb AE. Absent pulmonary valve syndrome: surgical and clinical outcome with long-term follow up. *European Journal of Cardiothoracic Surgery*. 2006;29:682-687.
21. Torok K, Brettle E, Deasi T, et al. Long-term outcomes in children with absent pulmonary valve syndrome: it is not just fixing the heart. *Arch Dis Child*. 2021;0:1-5.
22. Brettle E, Torok K, Desai T, et al. Long term respiratory and developmental outcomes of children with absent pulmonary valve syndrome. *European Respiratory Journal*. 2018;52: Suppl. 62, PA4654.