Placental Vascular Malperfusion is Common in Neonates with Critical Congenital Heart Disease

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Background: The placenta and heart develop concurrently and share developmental pathways, but the association between placental abnormalities and congenital heart disease (CHD) is not clear.

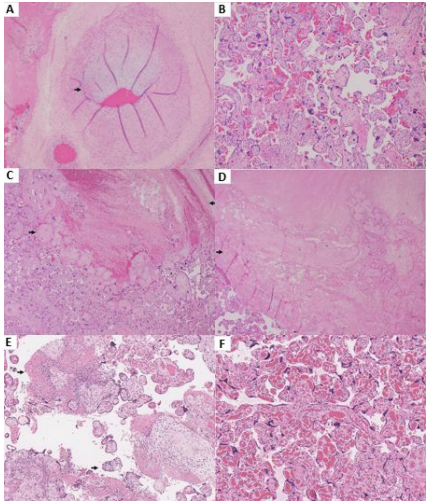
Aim: This study seeks to understand the prevalence of placental abnormalities in mothers of fetuses with critical CHD and associated in utero ultrasound abnormalities.

Methods:

- Pregnant mothers of fetuses with critical CHD were prospectively enrolled to evaluate placental function by US and pathology.
- US of maternal uterine artery and fetal extracardiac Dopplers of the umbilical artery, umbilical vein, ductus venosus and middle cerebral artery were obtained. Pulsatility index (PI) Z-scores for gestation age (GA) were analyzed as markers for vessel resistance.
- Placentas analyzed by pathology postnatally.
    - Fetal vascular malperfusion (FVM): intramural fibrin deposition, stem vessel obliteration, recent or remote thrombus formation, avascular villi, villous-stromal-vascular karyorrhexis; this was graded as low vs high per Amsterdam criteria.
    - Maternal vascular malperfusion (MVM): accelerated villous maturation, villous infarction, infarction hematoma, or decidual arteriopathy/vasculopathy.

Results:

- Seventeen mothers and infants had complete data.
- Mean maternal age was 31 years.
- Seven (41%) had maternal conditions including two type 2 diabetes, four gestational diabetes, one medication-dependent depression.
- Mean GA at ultrasound was 34 5/7 weeks [27 0/7-38 5/7 wks].
- Mean GA at birth was 39 weeks and mean birth weight 3309 (+/- 476) grams.



A-B. Fetal vascular malperfusion pathology of intramural fibrin deposition in stem vessel (A, black arrow, H&E, 20x) and group of avascular villi (B, blue stars, H&E, 20x).
C-D. Maternal vascular malperfusion pathology of infarction hematoma (C, black arrows, H&E, 4x) and remote villous infarction (D, black arrow, H&E, 4x).
E. Chronic villitis with lymphohistiocytic infiltrates (black arrows, H&E, 4x).
F. Chorangiosis, capillary hyperplasia in terminal villa in response to chronic placental hypoperfusion (H&E, 4x).

Congenital Cardiac Diagnoses	**Number (%)**
Biventricular without TGA	3 (18%)
Biventricular with TGA	2 (12%)
Single ventricle with left heart obstruction	7 (41%)
Single ventricle with right heart obstruction	5 (29%)
Abnormal Fetal Ultrasound Flow or Resistance	
Umbilical Artery PI Z score >2	7 (41%)
Umbilical Vein Mean Velocity Z score >2	5 (29%)
Middle Cerebral Artery PI Z score >2 or <-2	2 (12%)
Ductus Venosus Absent/Reversed Diastolic Flow	3 (18%)
Uterine Artery PI Z score >2	2 (12%)
Placental Outcomes	
Small for gestational age (<10%ile)	6 (35%)
Large for gestational age (>90%ile)	2 (12%)
Maternal Vascular Malperfusion	14 (82%)
Fetal Vascular Malperfusion, total High grade	7 (41%) 5 (29%)
Hypervascularity (chorangiosis, delayed villous maturation)	11 (61%)
Chronic inflammation (villitis of unknown etiology, chronic deciduitis with plasma cells)	4 (23%)
Acute inflammatory pathology with significant fetal inflammatory response (stage 2)	3 (18%)
Abnormal umbilical cords	4 (24%)

Conclusions:

- Placental defects, including MVM & FVM, are common in fetal CHD.
- Abnormal maternal and fetal extracardiac Dopplers were observed, however, they do not match the degree of placental abnormalities.
- Further evaluation in a larger cohort and more refined imaging modalities (for example, with placental MRI) are needed to better understand placental function and the placental-cardiac interactions.