Review Article on Pre-natal Diagnosis in Congenital Heart Defects

Placental abnormalities in congenital heart disease

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Contributions: (I) Conception and design: C Limperopoulos; (II) Administrative support: C Limperopoulos; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Congenital heart disease (CHD) remains the most common birth defect in infants, and critical CHD is associated with significant rates of morbidity and mortality. With the advent of powerful yet noninvasive advanced fetal imaging, it is becoming increasingly evident that the presence of CHD in utero disrupts typical development and contributes to the lifelong morbidity in this population. Across healthy and high-risk populations, intrauterine influences can permanently alter fetal development that may manifest in complex morbidities later in life, the so-called fetal-onset-of-adult-disease (FOAD) phenomenon. The placenta plays a critical role in not only supporting fetal development, but also by adapting to specific intrauterine conditions. The role of placental health, adaptation and dysfunction, however, in CHD is not well understood. In this article, we will review current evidence relating placental health in CHD, appraise existing knowledge-gaps in the field and highlight promising new avenues to better understand the impact of placental function on fetal well-being. We will review evidence of *ex vivo* human placental studies that describe abnormal placental findings in pregnancies complicated by CHD, as well evidence for *in vivo* assessments of the human placenta. While overall clinical *in vivo* assessments of placental development are rather limited, we will also review emerging evidence from advanced quantitative and functional magnetic resonance imaging that are bringing new insights into placental structure and function throughout gestation. By providing novel information about placental development, we can now explore the maternal-fetal-placental connection in greater detail, and better understand the multi-factorial mechanisms that may contribute to adverse outcomes seen in survivors of CHD.

Keywords: Placenta; congenital heart disease (CHD); imaging; ultrasound; magnetic resonance imaging

Submitted Oct 20, 2020. Accepted for publication Nov 05, 2020.
doi: 10.21037/tp-20-347
View this article at: http://dx.doi.org/10.21037/tp-20-347

Introduction

The placenta is a critical organ necessary for the healthy development of any fetus; not only does it provide the necessary nutrients to promote growth and clear the fetal circulation of metabolic byproducts, it serves as gatekeeper to protect the fetus from a hostile intrauterine environment—including toxic stress, infection, inflammation and other damaging mediators, and to regulate early metabolic and endocrine functions (1-8). Deviations from normal placental function, especially if coupled with adverse intrauterine exposures, can result in significant physiologic changes of fetal development that increase the risk of cardiovascular, metabolic and neuropsychiatric disease across the lifespan (9,10). For children born with congenital heart disease (CHD), placental dysfunction is yet another mechanism by which

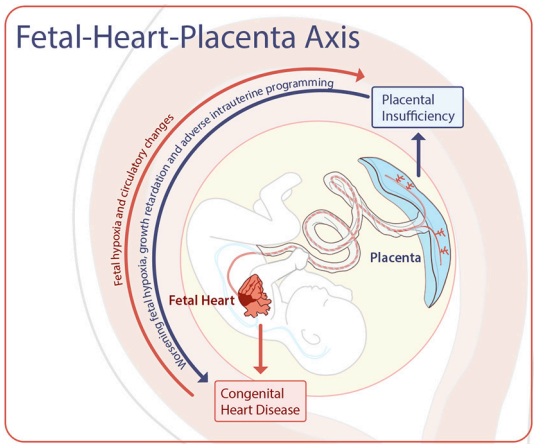

Figure 1 A diagram of the Fetal-Heart Placenta Axis, where fetal hypoxia and circulatory changes from congenital heart disease may contribute to placental insufficiency (red arrow), while ongoing placental insufficiency may further contribute to worsening fetal hypoxia, growth retardation and adverse intrauterine programming (blue arrow).

typical development may be disrupted, and a potential contributor to the lifelong morbidity and mortality seen in this fragile population.

The placenta-heart axis refers to the parallel development of the placenta and heart, two critical vascular structures with a shared ontogeny. Molecular and genetic studies have identified multiple shared pathways critical to both early placental and cardiac development, including critical micronutrients, such as folate (11,12). Early changes in the embryonic development of the fetal and placental circulations can influence placental shape, size, cord insertion and ultimately placental efficiency (12). Similarly, spiral artery remodeling of the maternal uterine circulation also occurs within the first few weeks of pregnancy, and if this process goes awry increases the risk of pre-eclampsia, fetal growth restriction (FGR), preterm labor and stillbirth (12). In addition, there is potential for ongoing placental injury from poor implantation, hypoxia and circulatory changes that can result in "multi-hit" mechanisms of placental dysfunction and fetal harm (*Figure 1*). In the sections below, we will review the supporting clinical evidence of placental injury and mal-development in CHD, as well as promising new fields of investigation to better understand the clinical implications of placental health and dysfunction in the fetus with CHD.

Ex vivo studies: placental pathology

Placental weight

Placental pathology can provide great insight into intrauterine conditions, especially for high risk pregnancies, yet relatively little is known about placental pathology in CHD. Among the few studies reported, several of these have noted smaller placentas in newborns born with CHD (13-15). One early study of placental pathology in CHD from the Danish Medical Birth Registry compared placental findings in newborns with and without CHD (13). In this work, the authors found that mean placental weight was lower in newborns with CHD compared to newborns without CHD, with the greatest decrease in placental weight was in infants with tetralogy of Fallot (TOF), followed by double-outlet right ventricle (DORV) and major ventricular septal defects (VSD) (13). Another smaller study specific to hypoplastic left heart syndrome (HLHS) also found a significant reduction in placental weight in infants with HLHS compared to age matched controls (15). Similarly, Rychik *et al.* described placental characteristics among 4 sub-types of CHD and found that 77% of CHD cases had placental weights less than the 10th centile for gestational age and nearly half had placental weights less than the 3rd centile (14). Among healthy and high-risk populations, placental size is highly associated with fetal growth, with over a third of birth weight variation due to placental weight alone (16). Birth weight variation, in turn, is associated with neonatal outcomes, with increased risk of adverse outcomes for infants born small for gestational age (SGA) (17-19).

Placental efficiency

Two of these studies further evaluated the relationship between placental weight and birth weight specifically in CHD (13,14). In the Danish Birth Registry study, the authors also described a significant association between placental weight and both birth weight and head circumference, and the case series on HLHS also noted both decreased birth weight and placental weight when compared to controls (13,15). Interestingly, the association between placental weight and fetal growth varied significantly across sub-groups, with the greatest association among infants with TOF, DORV, major VSD and lowest among infants with transposition of the great arteries (TGA) or (HLHS) (13). Rychik *et al.* also presented the placental

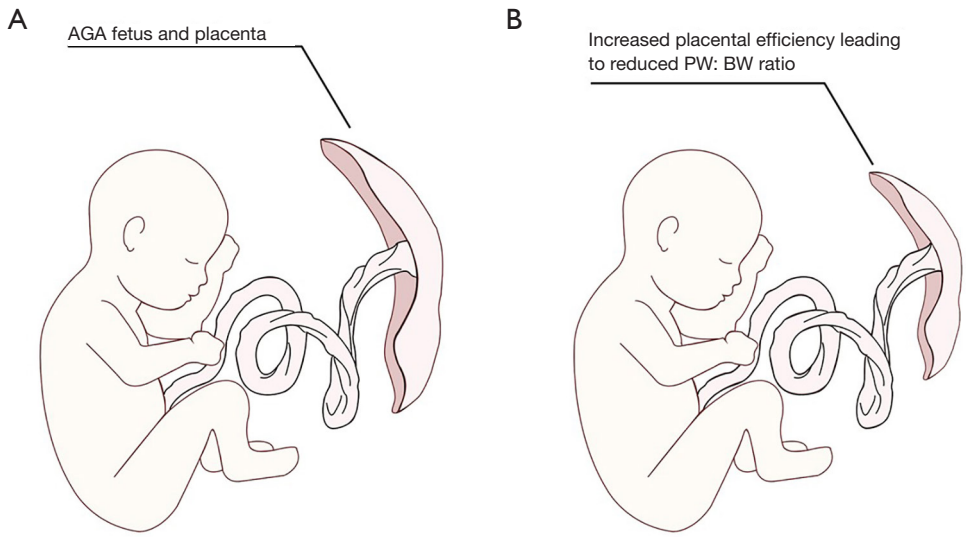

Figure 2 A diagram of placental efficiency. Panel (A) shows a typically developing fetus and placenta (appropriate for gestational age, AGA), while panel (B) shows a smaller placenta relative to fetal development, that would result in a lower placental weight (PW) to birth weight (BW) ratio. A reduced PW:BW ratio may reflect a highly efficient placenta that can support adequate fetal growth despite smaller placental size.

weight to birth weight ratio (PW:BW) (14). Typically, the PW:BW has been cited as a marker of placental efficiency (*Figure 2*), with reduced ratios reflecting more efficient nutrient transfer from placental to fetus (9). In the study by Rychik *et al.*, the PW:BW was lower in CHD compared to expected norms, particularly for infants with TGA (14). This is in contrast to the findings in a case-control study of infants with and without CHD by Albalawi *et al.*, that found no different in the absolute PW:BW ratio between infants with CHD and healthy controls (20). The study by Albalawi, however did note increased rates of fetal growth restriction among CHD cases, and for all subjects with FGR (cases and controls), the PW:BW ratio was higher in the setting of FGR (20). These conflicting findings may represent limitations from inherent differences in CHD, particularly when grouping distinct CHD diagnoses into sub-types for adequate power analysis. While the utility of the PW:BW as a surrogate of placental efficiency has been questioned (9,21), it nonetheless has been linked with adverse cardiovascular health in adults (9). The relevance of these findings, however, in CHD, remains poorly understood.

Placental shape

Albalawi *et al.* also noted significant differences in cord insertion sites between CHD placentas and healthy controls (20), with higher rates of eccentric, marginal and velamentous insertion sites in CHD (20). Sub-group evaluation noted that the relative risk of CHD subtype in the setting of abnormal cord insertion was highest for conotruncal defects (relative risk, RR =3.08), followed by left heart disease, namely HLHS and coarctation of the aorta (RR =2.4) and right heart disease, including Ebstein anomaly, tricuspid atresia, pulmonary atresia with intact ventricular septum, and critical pulmonary stenosis (RR =2.22) (20). Abnormal cord insertions sites, particularly marginal and velamentous insertion sites, have been associated with adverse pregnancy outcomes, including preterm birth, SGA infants, low birth weight (LBW) infants, emergency cesarean delivery and intrauterine fetal death, with velamentous cord insertion sites carrying the greatest risk (22,23). Similarly, eccentric and peripheral cord insertion sites have been variably associated with SGA and LBW (24), premature birth and decreased placental weight z-score (*Figure 3*) (25).

Histopathology

Several placental abnormalities have been noted on pathologic examination of CHD placentas. In the study by Rychik *et al.*, the most common lesion seen was thrombosis in 41% of CHD placentas as well as infarction (17%) (14). On histopathology, higher rates of both maternal and fetal

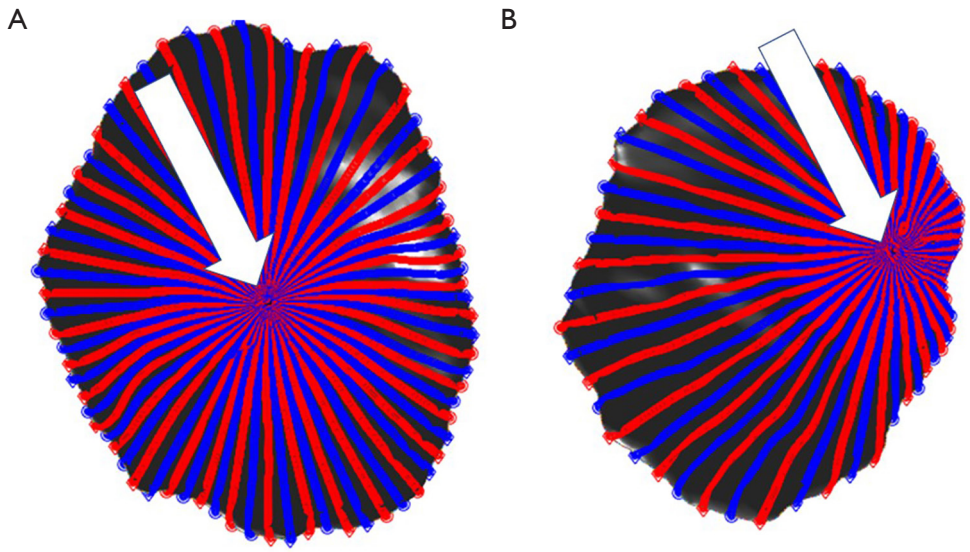

Figure 3 Three-dimensional reconstructions of *in vivo* placentas from MRI images, with the cord insertion site highlighted by a white arrow. Panel (A) demonstrates a placenta with central cord insertion site, and relatively symmetric fetal surface radii, while Panel (B) demonstrates a placenta with eccentric cord insertion site, and asymmetric fetal surface radii. These metrics have been used to develop a cord centricity score (unpublished data), as eccentric cord insertion sites are associated with growth disturbances of both the infant and placenta.

vascular malperfusion (MVM and FVM) were seen in a case control study of placentas from pregnancy terminations due to severe CHD compared to controls (26). FVM represents a group of placental lesions that can result from abnormal fetal perfusion to the villous parenchyma of the placenta. The most common cause of FVM is thought to be due to umbilical cord obstruction that limits fetal perfusion of the placenta, but CHD with accompanying flow abnormalities, cardiac insufficiency, and hyperviscosity from chronic hypoxia can also result in FVM (27). Segmental FVM consists of fetal vascular thrombi, villous stromal-vascular karyorrhexis subsequent avascular and ischemic villi (27). Regardless of the etiology, the mechanisms behind common lesions of FVM are venous congestion and stasis that results in focal ischemia and thrombosis, and in particular, segmental FVM has been associated with several adverse outcomes, including FGR and intrauterine fetal demise (27). Rychik *et al.*, also noted significant rates of chorangiosis (18%) and villous immaturity (15%) (14). Choriangiosis is characterized by increased vascularization of the distal villi, thought to occur after chronic hypoxia, and has been associated with avascular-ischemic villi seen in FVM (28) while villous immaturity is a lesion commonly seen in pregnancies complicated by diabetes mellitus, FGR, congenital malformations, and late gestational hypoxia (29). The Jones study of HLHS also noted increased fibrin and syncytial nuclear aggregates or syncytial knots in HLHS compared to controls (15). Both abnormalities of villous maturation and increased syncytial knots are associated with MVM. MVM, in contrast to FVM, is a constellation of placental findings that represent injury from altered uterine and intervillous flow from the maternal circulation. MVM is seen most often with preeclampsia and other hypertensive disorders of pregnancy, as well as spontaneous preterm birth and FGR. Interestingly, a study of 279 women carrying fetuses with CHD found significantly higher incidences of preeclampsia (OR 5.96), severe FGR (OR 3.32) and still birth (LR 9.45) compared to uncomplicated pregnancies (30). Collectively, these pathologic findings suggest that fetal flow anomalies and chronic hypoxia resulting in FVM, along with placental implantation anomalies resulting in MVM, may contribute to additional placental injury in CHD.

In utero studies

Doppler sonography

A common clinical approach to assess *in vivo* placental health is through Doppler interrogation of the umbilical arteries, either alone or relative to the fetal circulation as the cerebroplacental ratio (CPR) (31,32). In certain types

of placental pathology, blood flow through the placenta may encounter increased resistance and thus increasing the Doppler measures of the umbilical artery (33,34). Changes in the CPR reflect redistribution of the feto-placental circulation, and can reflect early adaptation to placental insufficiency, but also decreased Doppler measures of the middle cerebral artery (MCA) (32). Furthermore, abnormal CPR values have been associated with adverse perinatal and neurologic outcomes (31). In one study by Donofrio *et al.*, only 44% of fetuses with CHD were found to have normal CPR values, with increased rates of abnormal MCA Dopplers (35). In this study, larger fetuses with CHD with a reduced CPR also had smaller head circumferences (35). This is in contrast to another study of pregnancies complicated by fetal CHD, serial measures of fetal biometry and cerebroplacental Doppler flow were measured in the second half of pregnancy showed normal Doppler flow patterns, and did not find any significant relationship between placental function (as measured by Doppler studies of the UA and CPR) and fetal head growth (36). More specifically, even though MCA Doppler values varied between sub-groups of CHD, there was no association between MCA Doppler values and head growth in this population of CHD (36). Differences between studies may reflect differences in sample size (44 *vs.* 181, respectively), but again, also differences in CHD sub-types and sub-group classification. Similarly, the study by Rychik *et al.*, that described placental abnormalities in CHD on pathologic examination, did not find a significant association between fetal Doppler measures and postnatal placental anomalies (14). Despite the relatively few studies on Doppler sonography in CHD, there is no clear connection between fetal Doppler findings and placental health. The one study that did identify an association between increased rates of abnormal CPR values in CHD noted that UA values did not differ significantly between groups, with differences in MCA Dopplers driving differences in CPR (35). However, Doppler assessments of the UA remain indirect measures of placental health and may explain the variability in reliably predicting adverse pregnancy outcomes (32).

Magnetic resonance imaging (MRI)

The application of *in vivo* MRI in the living fetus has augmented prenatal sonography for the clinical diagnosis of many maternal-fetal conditions. Advances in both the application and interpretation of advanced MRI sequences are providing unparalleled access to detailed placental structural and functional development in healthy and high-risk pregnancies, including those complicated by fetal CHD.

Placental volume

In one study of *in vivo* placental imaging, 43 cases of fetal CHD were compared to 112 healthy controls (37). For all subjects, no placental anomalies were detected on conventional MRI and while overall placental volume did not differ significantly between groups, placental volume was positively associated with gestational age at birth, as well as birth weight in fetuses with CHD (37). Furthermore, the relationship between placental volume and birthweight, a proxy for placental efficiency in supporting fetal growth, revealed different trajectories between fetuses with CHD and healthy controls, suggesting functional differences in the CHD placenta (37). Interestingly, this study did not find an association between fetal brain volume and placental volume in CHD (37), although a comparable study of *in vivo* placental volumes and fetal brain volumes in healthy pregnancies and pregnancies complicated by fetal growth restriction found a positive association between placental volume and both total brain and cerebral volumes (38), further evidence to suggest that the normal associations between placental growth and fetal growth are disrupted in CHD.

Placental perfusion

Velocity-selective arterial spin labeling (VSASL) is a non-invasive technique to quantify global and regional perfusion (*Figure 4*); this technique has been successfully applied to the study of placental development in CHD (39). In this study, global placental perfusion decreased significantly over the second half of gestation in CHD, while regional variation in placental perfusion increased; most importantly these findings were not seen healthy controls (39). While the etiology of these differences are unclear, changes in placental perfusion in the second half of pregnancy may represent late manifestations of early developmental deviations or evidence of progressive placental dysfunction from abnormalities of the fetal circulation. These findings nonetheless support distinct functional aberrations of the CHD placenta, and emerge at a time of exponential fetal growth. Any changes in placental function that may accompany these changes in perfusion can increase the risk of late-onset fetal growth restriction, which increases

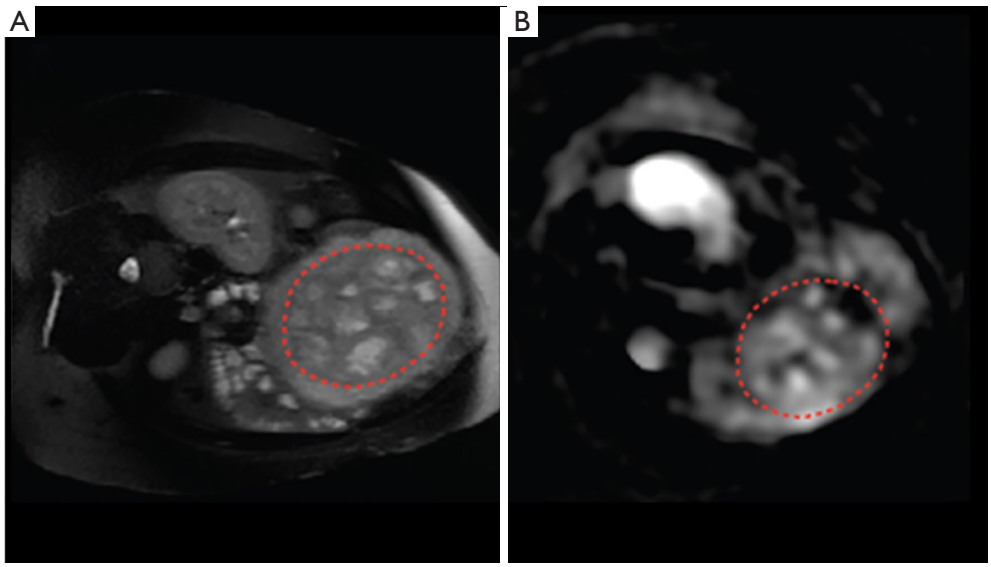

Figure 4 Anatomic (A) and arterial spin labeling images (ASL) (B) of the placenta in a pregnant woman with fetal congenital heart disease diagnosis, with the placenta outlined by the dotted line.

the risk of fetal distress, neonatal acidosis, and perinatal hypoxic injury, as well as long-term neurodevelopment and metabolic impairments (40).

Feto-placental oxygenation

Several MR sequences can estimate oxygen saturation and blood flow, all without the exogenous administration of contrast, including phase-contrast MRI, T2 mapping and blood-oxygen level dependent (BOLD) imaging. The successful application of these techniques to the fetus has allowed for the direct, yet non-invasive, interrogation of fetal-placental oxygenation. In a study by Sun *et al.*, imaging flow and oximetry data were used to calculate umbilical and fetal vessel oxygen content, delivery and consumption in fetuses with CHD (41). This study revealed a significant decrease in oxygen content returning to the fetus from the placenta, which resulted in decreased cerebral oxygen delivery and decreased fetal brain volumes (41). Another study by You *et al.*, used BOLD imaging during a maternal hyperoxia design (*Figure 5*) to measure regional oxygenation in healthy controls and pregnancies complicated by CHD (42). In this study, placental oxygenation increased significantly during maternal hyperoxia for all fetuses, and fetuses with single-ventricle CHD had the greatest response to maternal hyperoxia (42). This study suggests that the placenta has the capacity for increased oxygen delivery under certain circumstances, but also highlights the hypoxic state of the SV feto-placental unit at baseline.

While there are only a handful of advanced MRI studies on placental structure and function in CHD, collectively, these works provide hitherto unseen insights into *in vivo* placental structure and function and offer a promising opportunity to continue to understand the complex relationship between CHD and the placenta.

Conclusions & future directions

It is becoming increasingly evident that placental structure and function is impaired in CHD, however much less is known regarding the onset and mechanism of placental injury and/or maldevelopment. Despite advances in fetal diagnostic techniques, there are no current clinical tools that directly and non-invasively assess placental function in utero (43). This remains a major void in the field given the significant role of placental health to fetal well-being. Filling this void is necessary to enhance our ability to optimize fetal growth and long-term health outcomes, including in infants with CHD. Emerging tools intended to detect early deviations of normal placental function, such as those discussed in this review, may provide new insights into placental health overall, but especially to pregnancies complicated by CHD.

Future research intended to understand the timing,

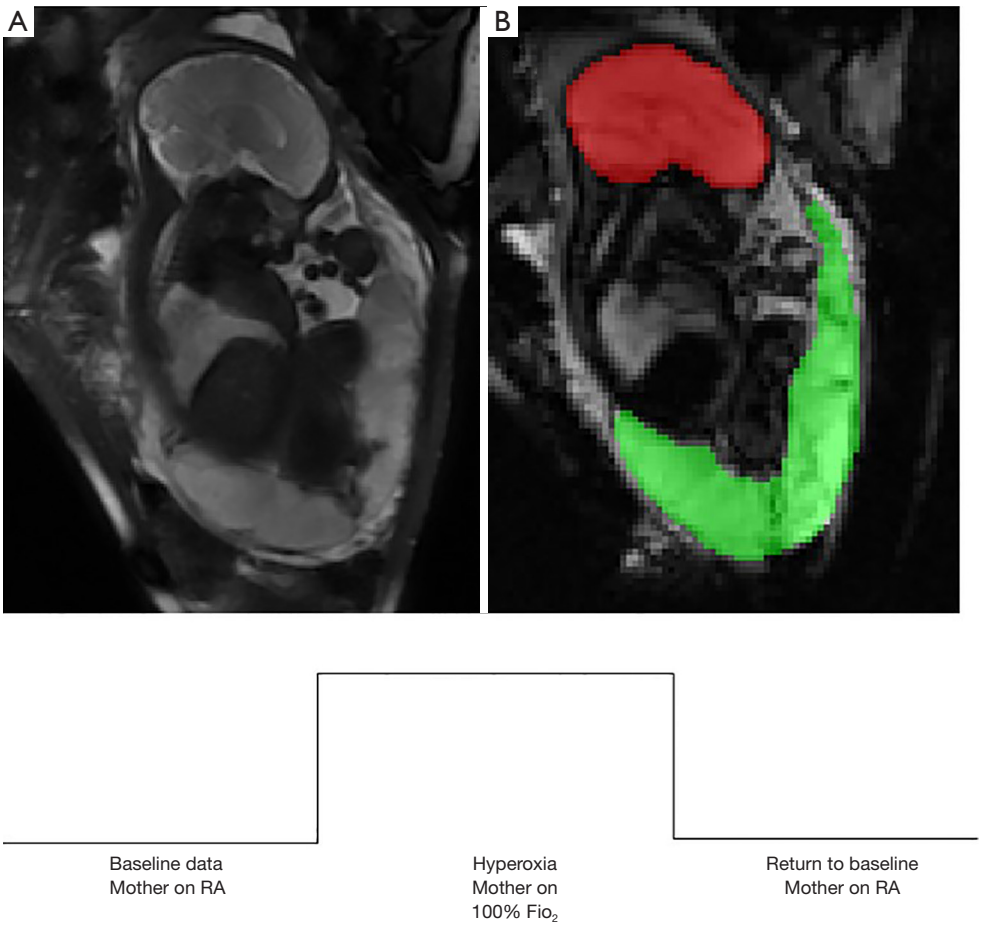

Figure 5 Anatomic image of fetus and placenta (A) and blood oxygen level dependent (BOLD) image of fetus and placenta (B) at 36 weeks gestation. Panel B highlights the fetal brain (red) and placenta (green) as regions of interest to measure BOLD signal. The maternal hyperoxia design collects BOLD signal at baseline, during maternal hyperoxia, and during return to baseline. Differences in BOLD signal reflect differences in regional oxygenation during each phase, which can be used to assess both baseline oxygenation, as well as capacity for oxygen transfer from mother to placenta and then fetus.

onset and progression of placental dysfunction in CHD is necessary, as is a better understanding of the direct impact of placental health on fetal well-being. As new research emerges with the intent to augment placental function in high-risk pregnancies, the biologic mechanisms underlying placental abnormalities in CHD will guide future clinicians on the relevance and applicability of novel placental treatments to this population. Moreover, successful development of early biomarkers of placental failure in the fetus with CHD is needed and will demand a comprehensive understanding of normal *in vivo* placental function across gestation, from which to reliably identify the onset and progression of placental dysfunction. Given the multi-factorial nature of morbidity related to CHD, the future will require a multi-factorial approach to both care and prevention.

Acknowledgments

We would like to thank Ben Scalise for his talented artwork. *Funding:* None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Antonio F. Corno) for the series "Prenatal Diagnosis in Congenital Heart Defects" published in *Translational Pediatrics*. The article has undergone external

peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-347). The series "Pre-natal Diagnosis in Congenital Heart Defects" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Andescavage NN, Limperopoulos C. Placental abnormalities in congenital heart disease. Transl Pediatr 2021;10(8):2148-2156. doi: 10.21037/tp-20-347