THE PLACENTA &

Congenital Heart Disease

Pathophysiology, Clinical Assessment & Emerging Science

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Fetal Cardiology · Maternal-Fetal Medicine · Developmental Biology

PRESENTATION OVERVIEW

01
The Placenta–Heart Axis
Shared developmental origins & hemodynamic coupling

02
Placental Pathology in CHD
Morphological abnormalities, malperfusion, and growth restriction

03
Molecular & Genetic Mechanisms
Shared signaling pathways, epigenetics, and gene variants

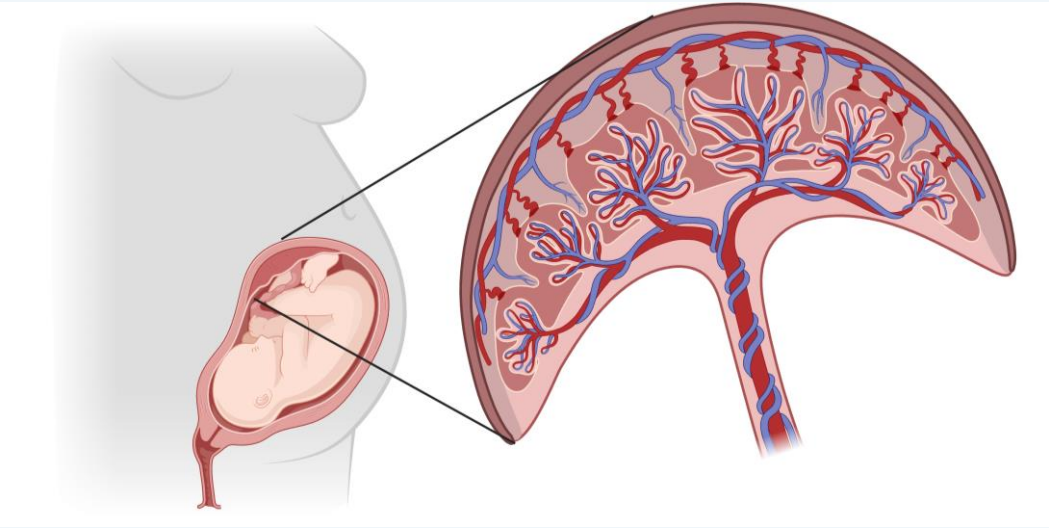
04
Clinical Assessment Methods
Ultrasound, Doppler, MRI, biomarkers & histopathology

05
Neurodevelopmental Consequences
Brain injury risk mediated through placental insufficiency

06
Basic Science Research Frontiers
Animal models, organoids, omics, and therapeutic targets

07
Clinical Implications & Future Directions
Monitoring, counseling, and translational opportunities

ROLE OF PLACENTA



01 | THE PLACENTA–HEART AXIS

Simultaneous Development

The heart begins beating at ~22 days gestation; placental circulation is established by weeks 8–10. Both organs share critical developmental windows.

Common Progenitor Signals

Trophoblast invasion and cardiomyocyte specification share key signaling molecules

Hemodynamic Coupling

The placenta receives ~40% of fetal combined cardiac output. Placental vascular resistance directly modulates fetal cardiac preload and afterload.

KEY STATISTICS

~8 weeks	gestational age when placental-cardiac feedback begins
~1 in 100	Live births affected by CHD globally
~30–45%	of CHD fetuses show placental weight reduction
2–3×	increased risk of placental malperfusion in CHD
40%	of fetal cardiac output directed to placenta

02 | PLACENTAL PATHOLOGY IN CHD

Reduced Placental Weight

- Mean placental weight is 10–15% lower in CHD pregnancies compared to controls, even after adjusting for birth weight.
- Reduced villous surface area limits gas and nutrient exchange.

Villous Maldevelopment

- Dysmorphic villi, increased syncytial knots, fibrin deposits, and accelerated villous maturation are hallmarks of CHD-associated placentas.
- These indicate chronic hypoxia.

Maternal Vascular Malperfusion

- Inadequate spiral artery remodeling leads to reduced uteroplacental perfusion.
- Associated with fetal growth restriction and abnormal umbilical artery Doppler waveforms.

Fetal Vascular Malperfusion

- Thrombotic vasculopathy and avascular villi reflect abnormal fetal cardiac hemodynamics.
- More prevalent in left-sided obstructive lesions (HLHS, AS, CoA).

Inflammation & Chorioamnionitis

- Increased inflammatory infiltrates and cytokine dysregulation observed.
- May contribute to fetal neuroinflammation and adverse neurodevelopmental outcomes.

Growth Restriction (FGR)

- Fetal growth restriction occurs in ~15–25% of CHD pregnancies, amplifying perioperative risk and neurodevelopmental vulnerability in the neonatal period.

03 | MOLECULAR & GENETIC MECHANISMS

NOTCH Signaling

Endocardial cushion formation & trophoblast spiral artery invasion

Key genes: NOTCH1, JAG1, DLL4

TBX Transcription Factors

Cardiac septation and trophectoderm specification share TBX2, TBX3, TBX5 regulatory networks

Key genes: TBX1, TBX2, TBX5, TBX20

VEGF / Angiogenesis

Placental vasculogenesis and myocardial vascularization co-regulated; VEGF-A critical for both

Key genes: VEGFA, FLT1, KDR, HIF1A

Chromatin & Epigenetics

Placenta-specific imprinting and DNA methylation changes co-occur with cardiac gene dysregulation

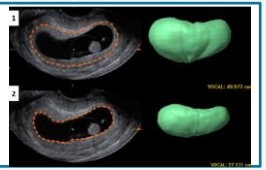
Key genes: KDM6A, CHD7, DNMT3A

04 | CLINICAL ASSESSMENT — ULTRASOUND & DOPPLER

GRAYSCALE ULTRASOUND

Placental Volume

Measured by 3D US at 11–14 wks;
reduced volume <10th centile predicts adverse outcome



Placental Texture

Grade III placentas, early calcification, and echogenic lesions warrant heightened surveillance

Placental Location

Anterior, fundal, or posterolateral placement affects accuracy of Doppler angle of insonation

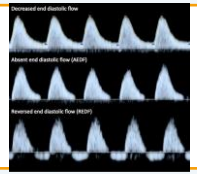
Placental Thickness

Abnormal thickness (<2 cm or >4 cm) is associated with growth restriction and structural anomaly

DOPPLER VELOCIMETRY

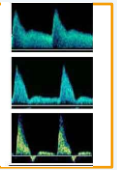
Umbilical Artery (UA) PI/RI

Elevated UA PI (>95th centile) reflects increased placental resistance; absent/reversed EDF signals critical FGR
Elevated RI indicates placental insufficiency



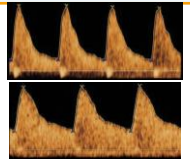
Uterine Artery (UtA) PI/RI

Bilateral notching and elevated UtA PI at 20–24 wks identifies maternal vascular malperfusion with 60–70% sensitivity for subsequent FGR
RI assesses maternal blood flow to placenta



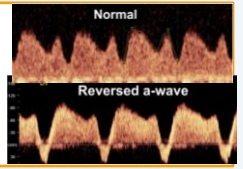
Middle Cerebral Artery (MCA)

Low MCA PI indicates fetal brain-sparing in response to placental insufficiency; CPR/cerebroplacental ratio (MCA PI/UA PI) <1.0 signals redistribution



Ductus Venosus (DV) Waveform

Absent or reversed a-wave reflects elevated cardiac afterload and venous pressure; terminal finding in severe IUGR/CHD



04 | CLINICAL ASSESSMENT — MRI, BIOMARKERS & HISTOPATHOLOGY

Fetal & Placental MRI

- Quantifies placental oxygenation
- Provides information about villous edema & infarction
- Placental perfusion correlates with UA Doppler
- Fetal brain volumes measured alongside placental parameters
- Research tool; clinical protocols actively being validated
- No ionizing radiation — ideal for longitudinal fetal studies

SERUM BIOMARKERS

PlGF (Placental Growth Factor)

↓ in placental insufficiency; used clinically for pre-eclampsia; explored in CHD

sFlt-1

Anti-angiogenic factor elevated with placental stress;

PAPP-A

Low 1st trimester PAPP-A (<0.4 MoM) associated with subsequent FGR and CHD

Cell-Free Fetal DNA

Elevated in maternal plasma with placental damage; research marker

NT-proBNP

Elevated in fetuses with CHD and hemodynamic compromise; reflects cardiac stress

HISTOPATHOLOGY

Amsterdam Consensus Classification

Maternal Vascular Malperfusion

Fetal Vascular Malperfusion

Delayed Villous Maturation

Inflammatory Lesions

05 | NEURODEVELOPMENTAL CONSEQUENCES

White Matter Injury

Microstructural Anomalies

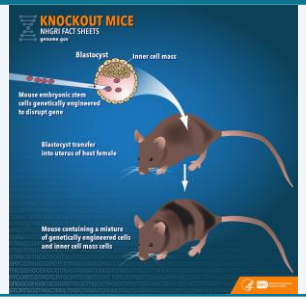
Cognitive & Motor Outcomes

Placental Weight as Predictor

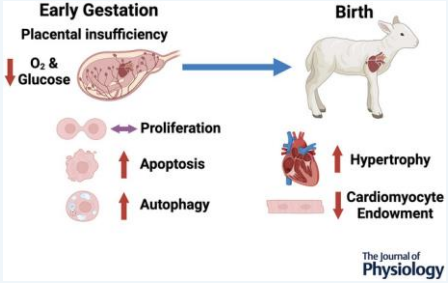
06 | BASIC SCIENCE — ANIMAL MODELS

Preclinical models have been instrumental in establishing causal links between placental dysfunction and cardiac maldevelopment:

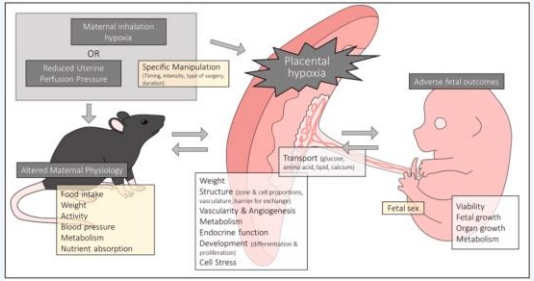
Mouse — Knockout Models



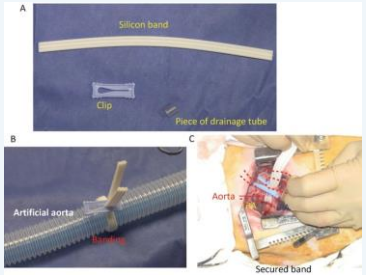
Sheep — Surgical Ligation



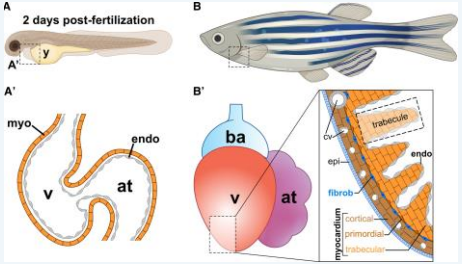
Rat — Hypoxia Chamber



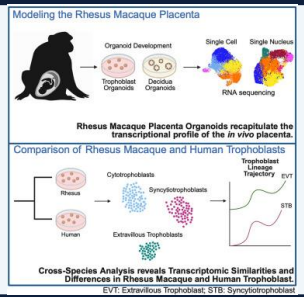
Pig — Surgical CHD



Zebrafish — Genetic Screens



Non-Human Primates



06 | BASIC SCIENCE — ORGANOIDS, OMICS & THERAPEUTIC TARGETS

Trophoblast & Cardiac Organoids

- Human trophoblast organoids (hTSC-derived) recapitulate syncytialization and invasion
- Cardiac organoids model early cardiomyocyte specification and CHD mutations
- Co-culture systems: trophoblast + cardiomyocyte interface studies now feasible
- Organ-on-chip: microfluidic placental-fetal circulation models replicate Doppler-like hemodynamics
- iPSC-derived models from CHD patients reveal patient-specific placental vulnerability
- CRISPR perturbation screens in organoids identify shared regulatory networks

Multi-Omics Approaches

Bulk RNA-seq:

Transcriptomic profiling of CHD placentas identifies dysregulated angiogenic and metabolic pathways

Single-cell RNA-seq:

Cell-type-specific transcriptomic changes in syncytiotrophoblast, EVT, and Hofbauer cells

ATAC-seq / ChIP-seq:

Open chromatin mapping reveals shared cardiac-trophoblast enhancer landscapes

DNA Methylation Arrays:

CpG hypomethylation at imprinted loci (H19/IGF2, PLAGL1) in CHD placentas

Spatial Transcriptomics:

Regional gene expression mapping in villous parenchyma vs. basal plate

Proteomics / Metabolomics:

Plasma proteome identifies placental-derived biomarkers specific to CHD type

Therapeutic Targets

Sildenafil (PDE5i)
Improves uteroplacental blood flow in FGR; discontinued STRIDER trial due to safety; research continues in CHD

PlGF Supplementation
Preclinical: exogenous PlGF enhances placental angiogenesis and fetal growth in rat ligation models

Pravastatin
Anti-inflammatory, pro-angiogenic; phase II trials in early-onset FGR show promising placental perfusion improvement

Antioxidants (NAC, MitoQ)
Reduce placental oxidative stress in animal hypoxia models; neonatal neuroprotection studies ongoing

Aspirin (low-dose)
Standard of care for UtA Doppler abnormalities; under investigation in CHD for placental preservation

Gene / RNA Therapies
Proof-of-concept: placenta-targeted nanoparticles deliver mRNA; trophoblast-specific therapeutic window being defined

06 | ONGOING RESEARCH PROGRAMMES

CCHD Genomics Consortium

Active

Multi-center, USA/UK

WGS of CHD trios including placental tissue; linking somatic placental mutations to cardiac defects via mosaic variant analysis.

FetoPlacental Heart Study (FETCH)

Recruiting

Boston Children's / Harvard

Longitudinal cohort linking prenatal placental MRI, Doppler, and histopathology to neurodevelopmental outcomes at 2 and 5 years in CHD.

PLACENTA-CHD Biobank

Active

Great Ormond Street, London

Systematic collection of placental tissue, cord blood, and maternal serum for multi-omic analysis across CHD subtypes.

Human Placenta Project (HPP)

Active

NICHD / NIH

Develops tools for real-time placental assessment including MRI biomarkers, optical coherence tomography, and cfDNA. Cardiology arm in development.

Cardiac Neurodevelopment Programme

Active

SickKids, Toronto

Prospective study examining placental morphometry, UA Doppler, and cord blood biomarkers as predictors of brain MRI findings and NDI in CHD neonates.

EuroCHD Placenta Study Group

Active

European CHD Consortium

Multi-center registry study standardizing placental examination protocols post-delivery in complex CHD; harmonized Amsterdam lesion classification.

07 | CLINICAL IMPLICATIONS & FUTURE DIRECTIONS

Prenatal Surveillance

- Offer serial growth scans and UA/UtA Doppler in all CHD pregnancies
- Consider placental MRI in centers with protocols for complex cases
- Low-dose aspirin from <16 weeks if UtA Doppler abnormal

Counseling Families

- Discuss neurodevelopmental risk attributable to placental factors in addition to cardiac anatomy
- Include placental pathology findings in post-delivery family discussions
- Placental health is a modifiable neurodevelopmental risk context

Perinatal Planning

- Placental growth restriction warrants early NICU involvement planning
- Timing of delivery should balance lung maturity vs. placental insufficiency
- Optimize fetal reserve before elective cardiac surgery in neonates

Future: Placenta-targeted therapies · AI-driven placental image analysis · Placental genomic biomarkers integrated into prenatal CHD management pathways

KEY TAKEAWAYS

Summary for Clinical Practice

1. The placenta and heart share developmental origins, signaling pathways, and genomic regulatory elements — making them jointly vulnerable in CHD.
2. Placental pathology is prevalent in CHD, with reduced weight, malperfusion lesions, and dysmorphic villi serving as measurable markers.
3. Multi-modal assessment (Doppler, MRI, biomarkers, histopathology) provides complementary windows into placental function.
4. Placental insufficiency is an independent contributor to neurodevelopmental impairment in CHD, beyond cardiac anatomy alone.
5. Basic science using organoids, multi-omics, and animal models is rapidly defining therapeutic targets at the cardio-placental interface.
6. Clinicians should integrate placental assessment into CHD prenatal care pathways and post-delivery management planning.

"The placenta is the fetal heart's first physiological partner."

Questions & Discussion

Thank you

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"The placenta is the fetal heart's first physiological partner."

Questions & Discussion

Thank you

Happy to take questions

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