CARDIOLOGY 2025

The Placenta in CHD: The Next Frontier

Rebecca Josowitz, MD PhD

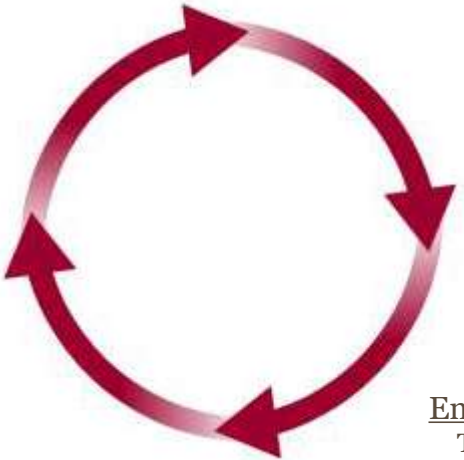
February 19, 2025

Children's Hospital of Philadelphia®
Cardiac Center

DISCLOSURES

- None

ORIGINS OF CONGENITAL HEART DISEASE

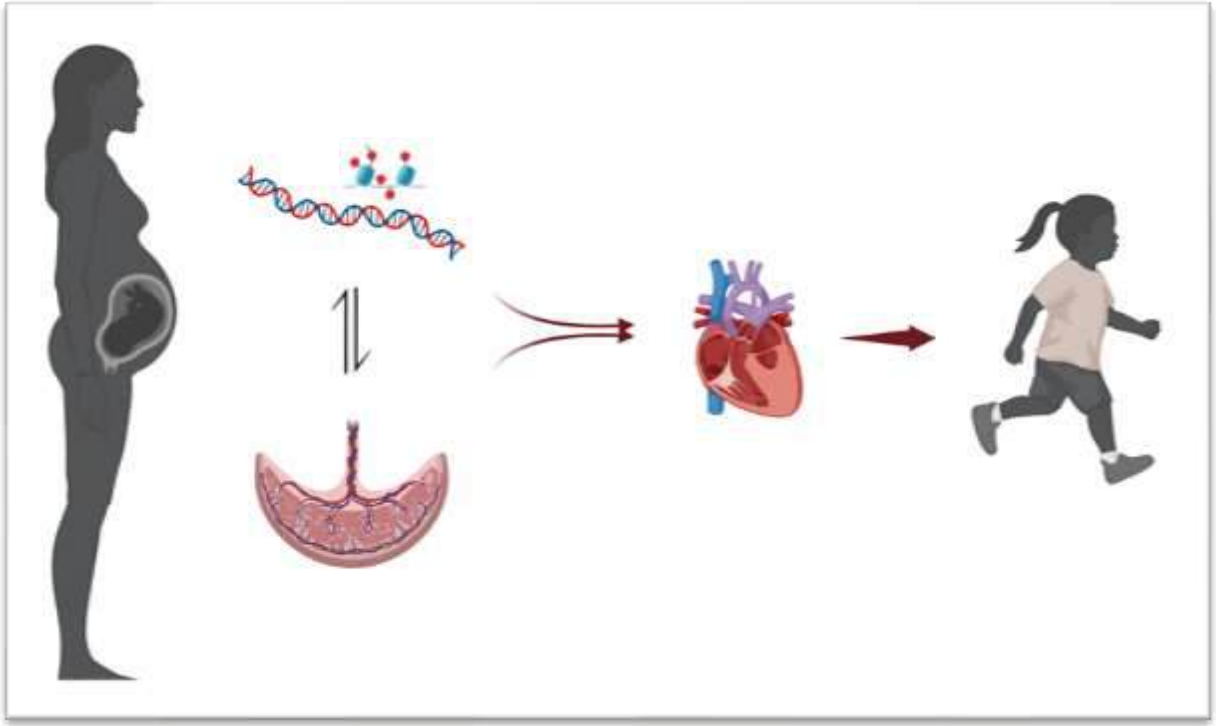


Genetics
Aneuploidy ~13%
CNV ~10%
De novo SNVs ~10%

Environment
Teratogens
Intrauterine infection

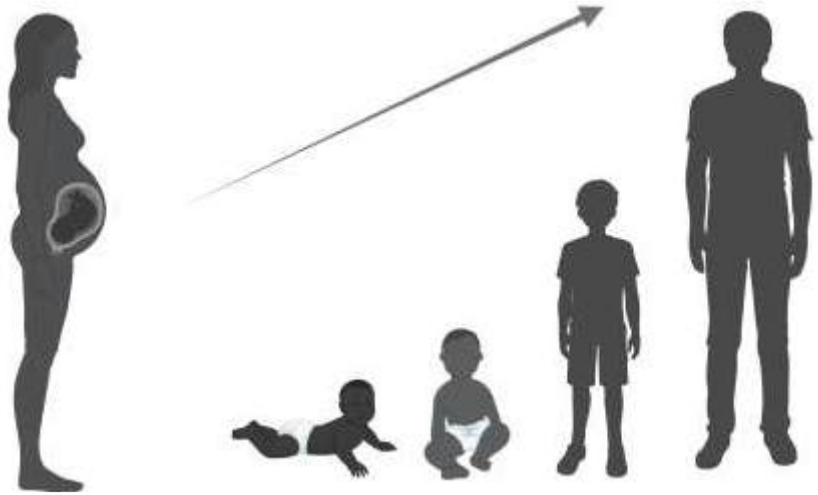
Unknown
??
Epigenetics
Gene-environment

ORIGINS OF CONGENITAL HEART DISEASE



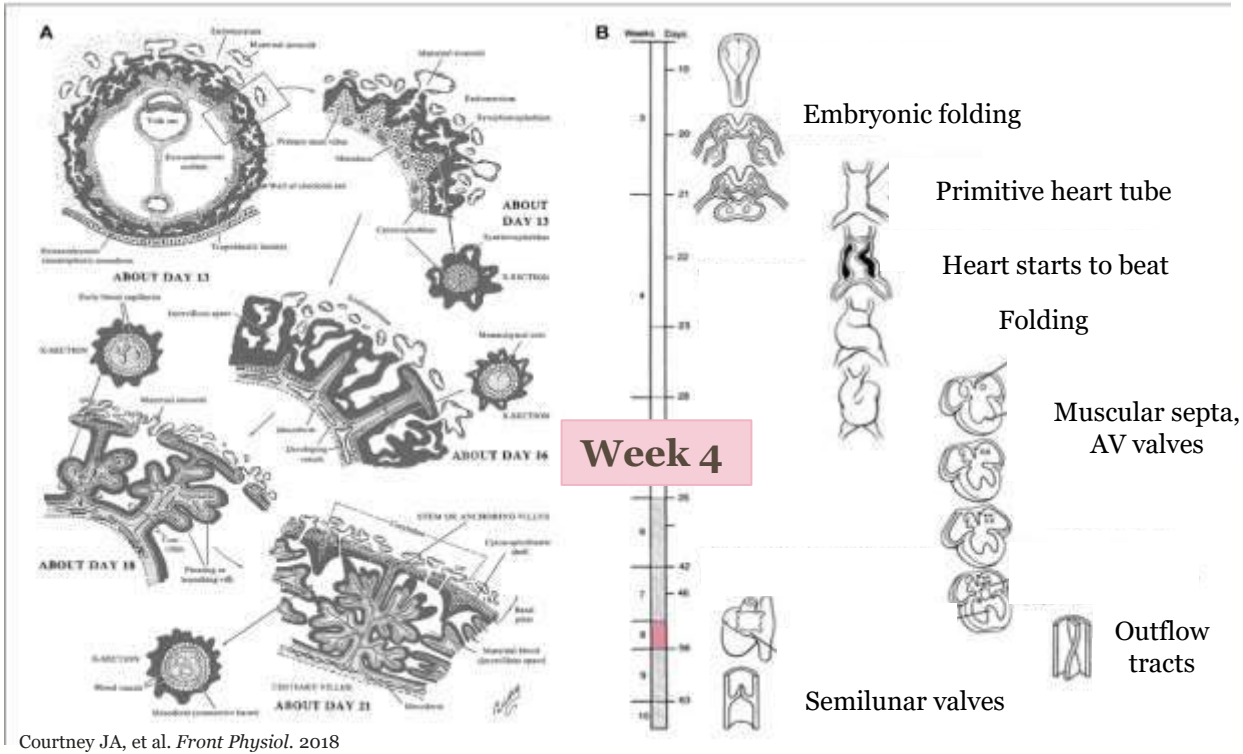
THE BARKER HYPOTHESIS

"FETAL ORIGINS OF DISEASE"



Intrauterine growth restriction associated with increased risk of adult-onset hypertension and cardiovascular disease

SHARED PLACENTAL AND CARDIAC DEVELOPMENT



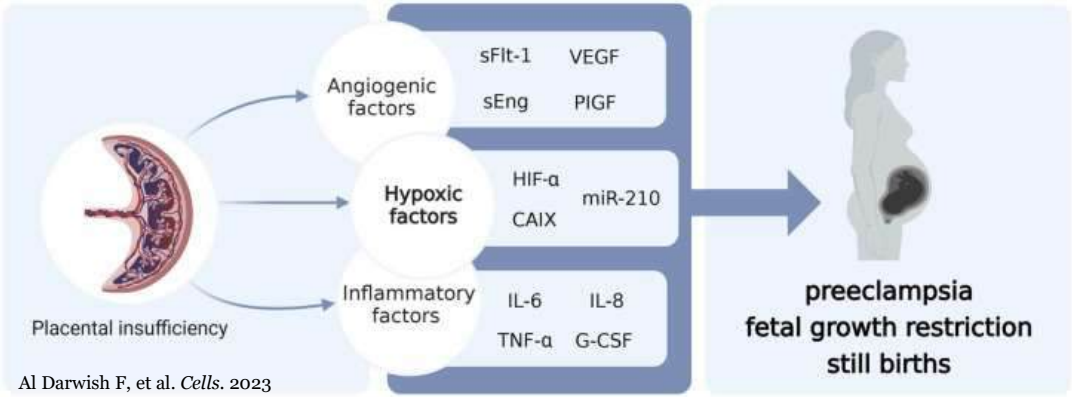
Courtney JA, et al. *Front Physiol.* 2018

NOTCH

WNT

VEGF

THE PLACENTA-HEART AXIS



Al Darwish F, et al. *Cells*. 2023

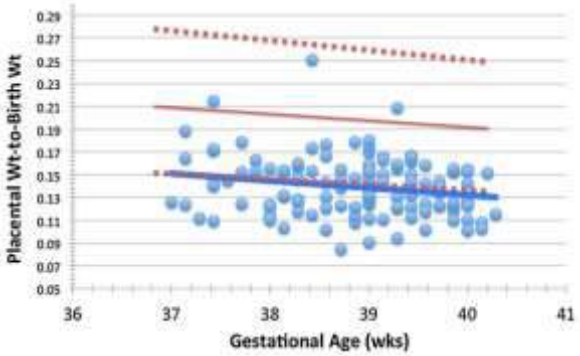
Phenotypes	No.	OR(95%CI)	*P* value	Measure of heterogeneity Q	*P* value	I^2(%)
CTD	5	1.55 (1.33–1.79)	<0.001	5.20	0.270	23
TOF	4	1.35 (1.05–1.72)	0.020	2.13	0.550	0
TGA	5	1.14 (0.86–1.52)	0.360	7.70	0.100	48
ASD	6	1.78 (1.11–2.87)	0.020	89.50	<0.001	94
VSD	5	1.31 (0.86–1.99)	0.200	36.84	<0.001	89
AVSD	3	2.20 (0.91–5.32)	0.080	8.90	0.010	78
HLHS	3	2.10 (1.29–3.42)	0.003	4.10	0.130	51
COA	4	1.73 (1.38–2.17)	<0.001	2.66	0.450	0
LVOTO	3	1.33 (1.06–1.67)	0.010	0.29	0.870	0
RVOTO	3	1.69 (1.31–2.18)	<0.001	2.38	0.300	16
Heterotaxia	4	1.12 (0.73–1.73)	0.600	1.23	0.750	0

FIGURE 3 | Forest plot of maternal HDP exposure and risk of most CHD phenotypes in offspring.

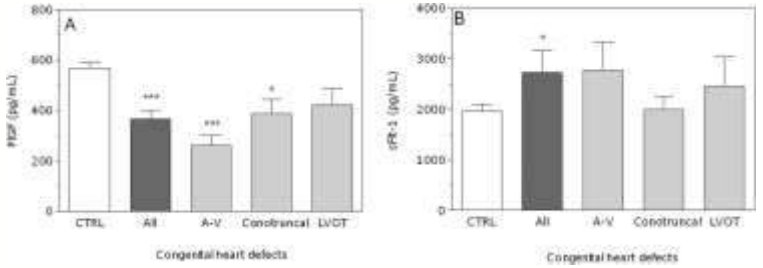
Zhang S, et al. *Front Cardiovasc Med*. 2022

THE PLACENTA-HEART AXIS

Josowitz R, et al. *Neoreviews*. 2023



Rychik J, et al. *Pediatr Cardiol*. 2018



Llurba E, et al. *Eur Heart J*. 2014

- Umbilical cord abnormalities
- Infarcts
- Villous hypoxic injury
- Abnormal villous maturation

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Damaging Variants in Proangiogenic Genes Impair Growth in Fetuses with Cardiac Defects

Mark W. Russell, MD[1], Julie S. Moldenhauer, MD[2], Jack Rychik, MD[3], Nancy B. Burnham, RN, MSN, CRNP[4], Erin Zullo, BSN[4], Samuel I. Parry, MD[5], Rebecca A. Simmons, MD[6], Michal A. Elovitz, MD[2], Susan C. Nicolson, MD[7], Rebecca L. Linn, MD[8], Mark P. Johnson, MD[2], Sunkyung Yu, MS[1], Matthew G. Sampson, MD[9], Hakon Hakonarson, MD, PhD[10], and J. William Gaynor, MD[4]

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THE PLACENTA-HEART AXIS

Placentation defects are highly prevalent in embryonic lethal mouse mutants

Article

Defects in placental syncytiotrophoblast cells are a common cause of developmental heart disease

RESEARCH ARTICLE

SLC25A1 regulates placental development to ensure embryonic heart morphogenesis

Wenli Fan[1,2], Zixuan Li[1,2], Xueke He[1,2], Xiaodong Wang[1,2], Ming Sun[3,*] and Zhongzhou Yang[1,2,*]

ORIGINAL RESEARCH ARTICLE

Placental Inflammation Leads to Abnormal Embryonic Heart Development

Eleanor J. Ward, PhD; Serena Bert, MSc; Silvia Fanti, MSc; Kerri M. Malone, PhD; Robert T. Maughan, PhD; Christina Gkantsinikoudi, MSc; Fabrice Prin, PhD; Lia Karina Volpato, MD, PhD; Anna Paula Piovezan, PhD; Gerard J. Graham, PhD; Neil P. Dufton, PhD; Mauro Perretti, PhD*; Federica M. Marelli-Berg, MD, PhD*; Suchita Nadkarni, PhD

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PLACENTAL PATHOLOGY IN CHD

- Maternal Vascular Malperfusion (MVM)
- Fetal Vascular Malperfusion (FVM)
- Delayed Villous Maturation (DVM)
- Maternal and Fetal Inflammation

Sampling and Definitions of Placental Lesions

Amsterdam Placental Workshop Group Consensus Statement

T. Yee Khong, MD; Eoghan E. Mooney, MB, FRCPath; Ilana Ariel, MD, PhD; Nathalie C. M. Balmus, MD; Theonia K. Boyd, MD; Marie-Anne Brundler, MD; Hayley Derricott, BSc; Margaret J. Evans, FRCPath (Paeds); Ona M. Faye-Petersen, MD; John E. Gillan, MD; Alex E. P. Heazell, MBChB, PhD; Debra S. Heller, MD; Suzanne M. Jacques, MD; Sarah Keating, MD; Peter Kelehan, MD; Ann Maes, MD; Eileen M. McKay, MD; Terry K. Morgan, MD, PhD; Peter G. J. Nikkels, MD, PhD; W. Tony Parks, MD; Raymond W. Redline, MD; Irene Scheimberg, MD; Mirthe H. Schoots, MD; Neil J. Sebire, MD; Albert Timmer, MD, PhD; Gitta Turowski, MD; J. Patrick van der Voorn, MD; Ineke van Lijnschoten, MD; Sanne J. Gordijn, MD, PhD

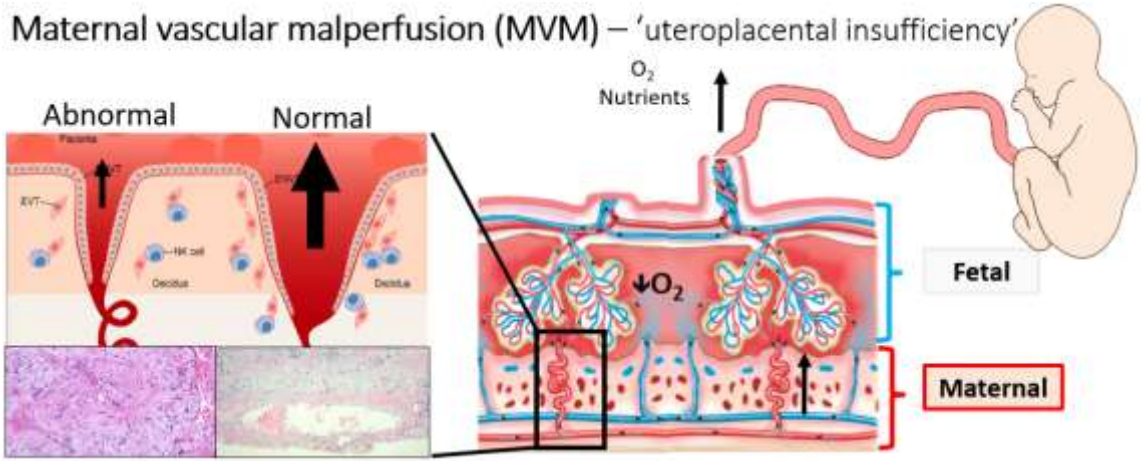

Image courtesy of Rebecca Linn, MD

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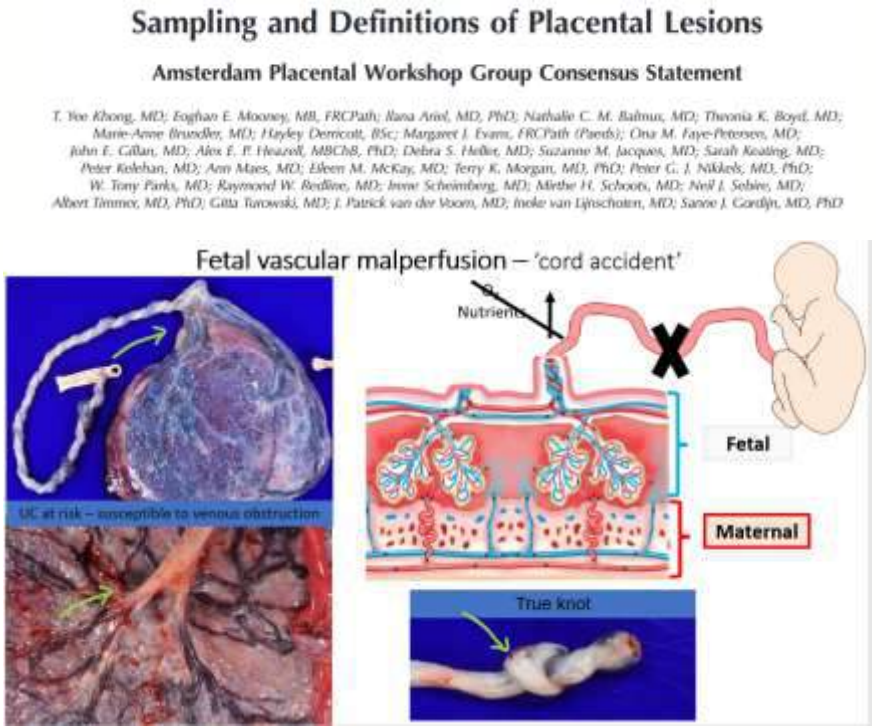

Image courtesy of Rebecca Linn, MD

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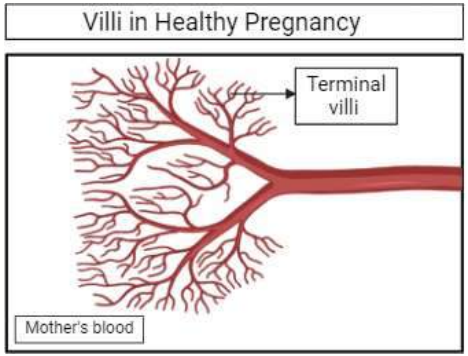

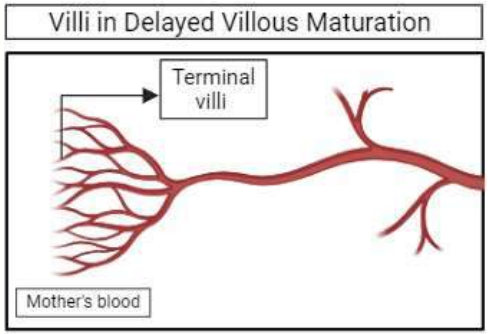

Image courtesy of Tommy's.org

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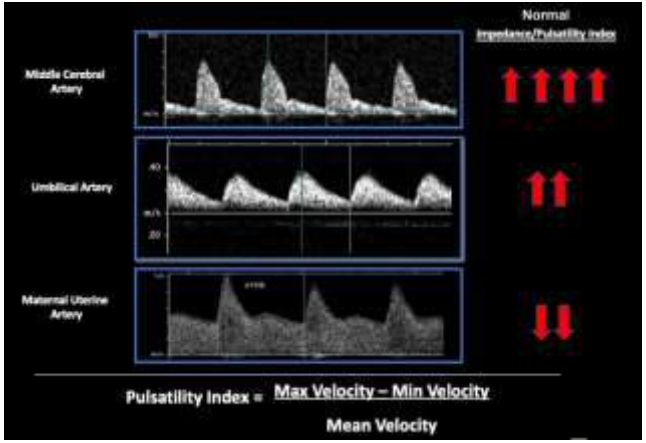
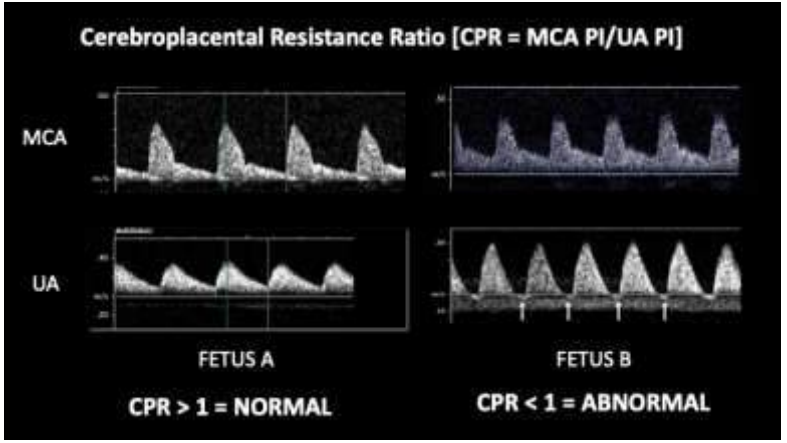
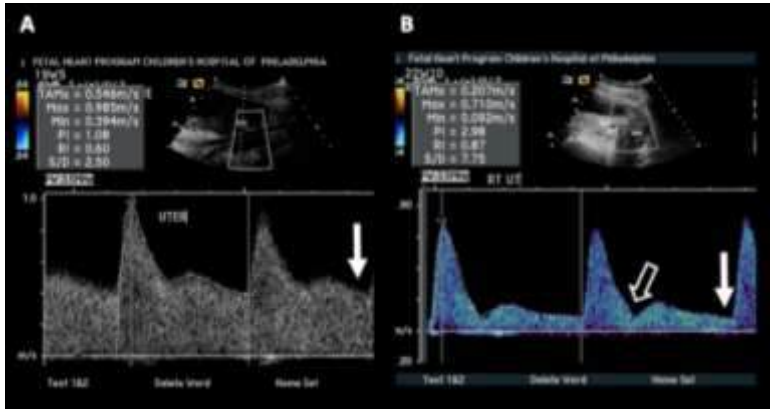
ASSESSING THE PLACENTA IN UTERO

TRADITIONAL DOPPLER INDICES







Josowitz R, et al. *Neoreviews*. 2023

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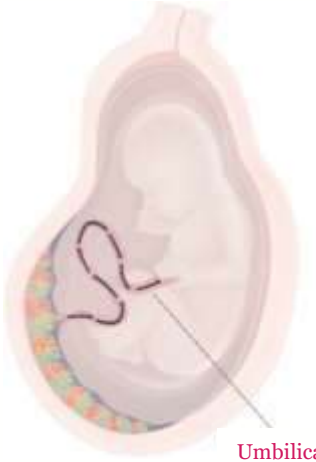
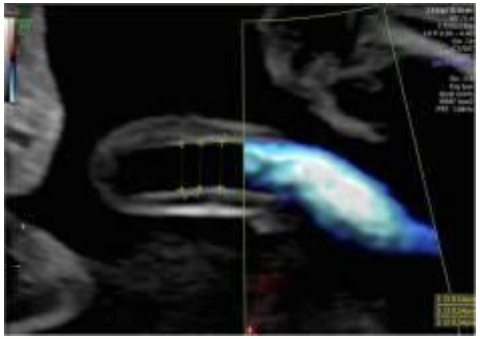
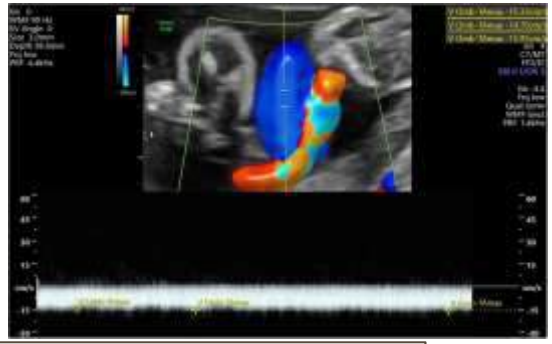
ASSESSING THE PLACENTA IN UTERO

UMBILICAL VENOUS VOLUME FLOW



Umbilical vein blood flow





Umbilical vein flow = cross sectional area x mean velocity x 60

Barbieri M, et al. *J Clin Ultrasound.* 2023

TABLE 2 Placental Blood Flow Characteristics

	Controls (n = 36)	All CHD (n = 31)	*P* Value[a]	Single Ventricle (n = 24)	*P* Value[b]
Fetal weight (g)	437 (340-546)	629 (530-756)	**<0.001**	646 (528-830)	**<0.001**
CCO (mL/min/kg)	394 (345-472)[c]	442 (321-542)	0.574	371 (321-471)	0.555
UVVF (mL/min)	51 (38-68)	61 (47-84)	0.147	59 (44-80)	0.333
UVVF/Wt (mL/min/kg)	113 (98-145)	96 (79-115)	**0.007**	87 (74-108)	**0.001**
UVVF/CCO (%)	30 (24-39)[c]	22 (18-30)	**0.006**	23 (20-31)	**0.045**

Josowitz R, et al. *JACC:Adv.* 2025

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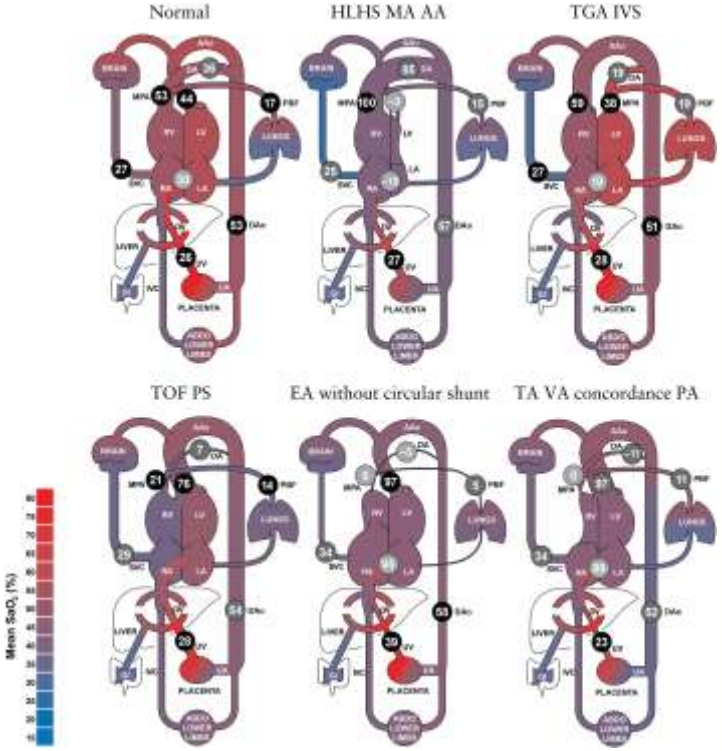
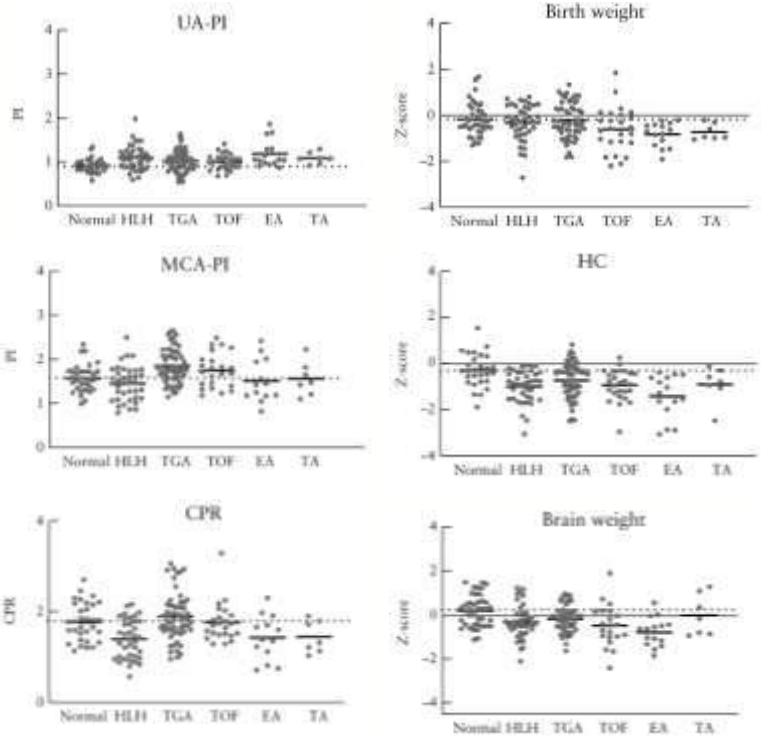
ASSESSING THE PLACENTA IN UTERO

FETAL MRI





Sun L, et al. *Ultrasound Obstet Gynecol.* 2021

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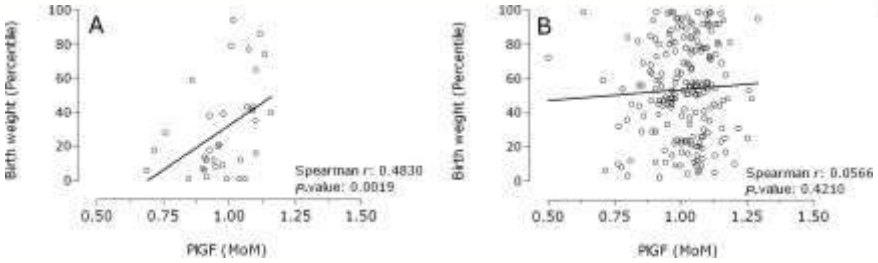
IMPAIRED GROWTH IN CHD

A role for abnormal placental development?

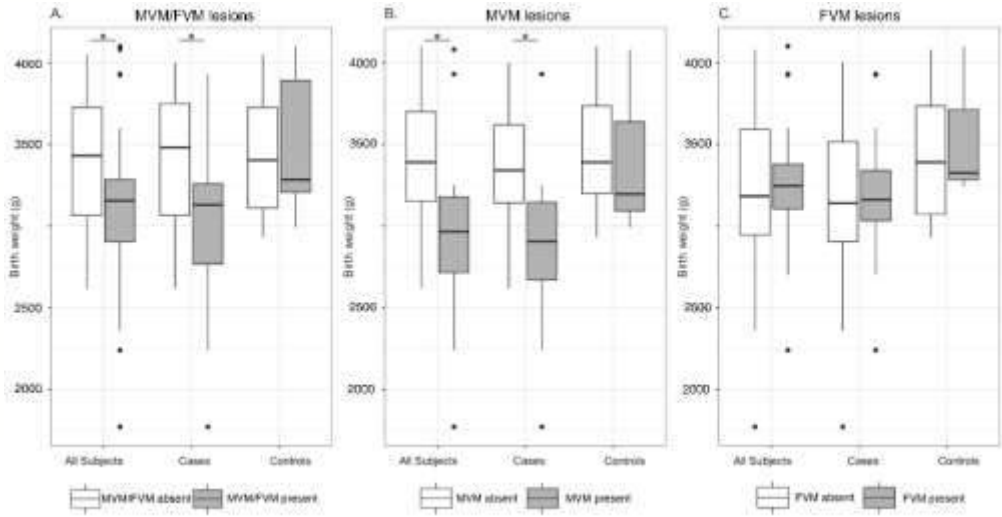
Table 2
Effect size of placental volume and neonatal clinical characteristics in CHD fetuses.

Clinical factor	CHD	Control	Effect size[a]	P-value
GA age at birth in weeks, mean (±SD)	37.8 (±1.5)	39.0 (±1.5)	2.11	P = 0.041
Birth weight in kg, mean (±SD)	3.141 (±0.70)	3.345 (±0.46)	5.01	P < 0.001
Fenton z-score for birth weight, mean (±SD)	−0.05 (±1.00)	−0.02 (±0.07)	4.85	P < 0.001

Andescavage N, et al. *Placenta*. 2015



Llurba E, et al. *Eur Heart J*. 2014



Josowitz R, et al. *JACC:Adv*. 2025

Impaired placental development acts in synergy with CHD to impair fetal growth

CARDIOLOGY 2025

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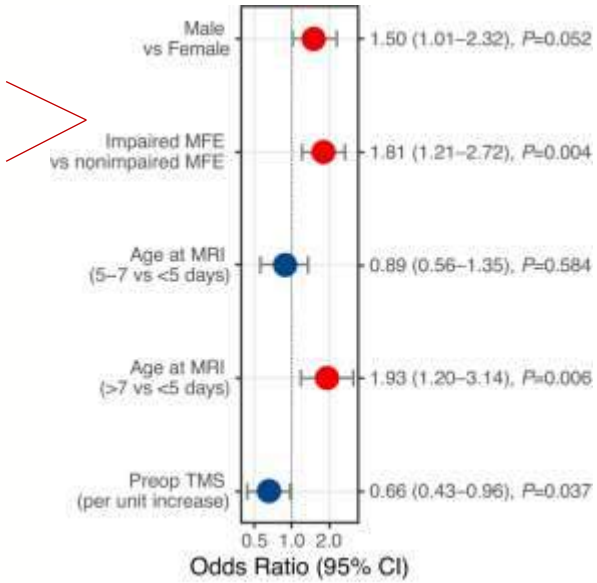
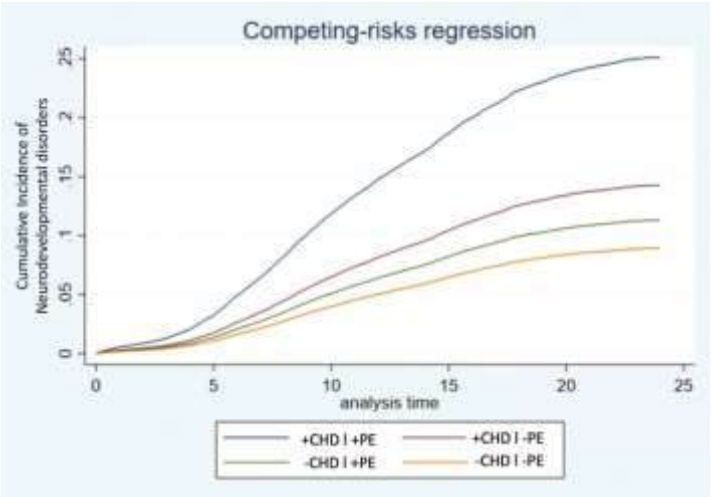
IMPAIRED BRAIN GROWTH AND INCREASED WHITE MATTER INJURY IN CHD

A role for abnormal placental development?

Gestational diabetes
Gestational hypertension
Preeclampsia
Exposure to tobacco
Hypothyroidism
"Other" complications of pregnancy



Licht DJ, et al. *J Am Heart Assoc*. 2023



Omann C, et al. *Eur Heart J Open*. 2022

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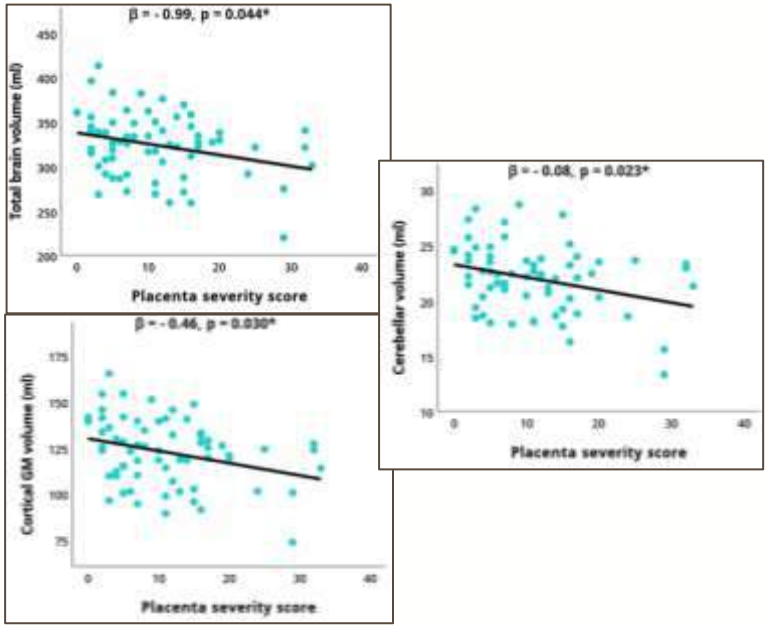
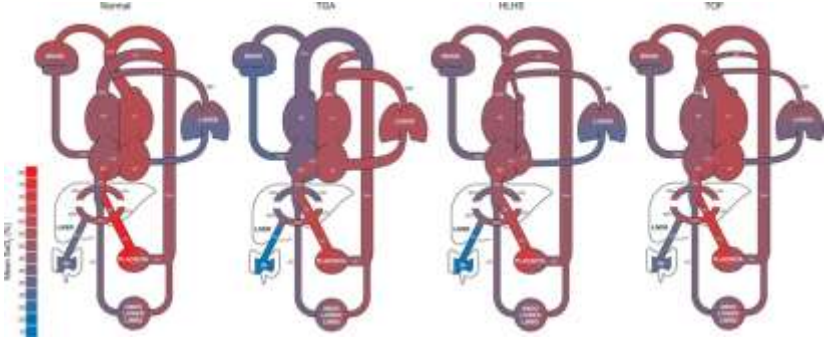
IMPAIRED BRAIN GROWTH AND INCREASED WHITE MATTER INJURY IN CHD

A role for abnormal placental development?



Nijman, et al. *J Am Heart Assoc.* 2024



Sun L, et al. *Circulation.* 2015

Decreased umbilical vein saturation

+

Abnormal streaming of fetal oxygenated blood

- **15% decrease in cerebral DO2**
- **32% decrease in cerebral VO2**

↔ 13% reduction in fetal brain volume

Impaired placental development acts in synergy with CHD to impair brain growth and neurodevelopmental outcomes

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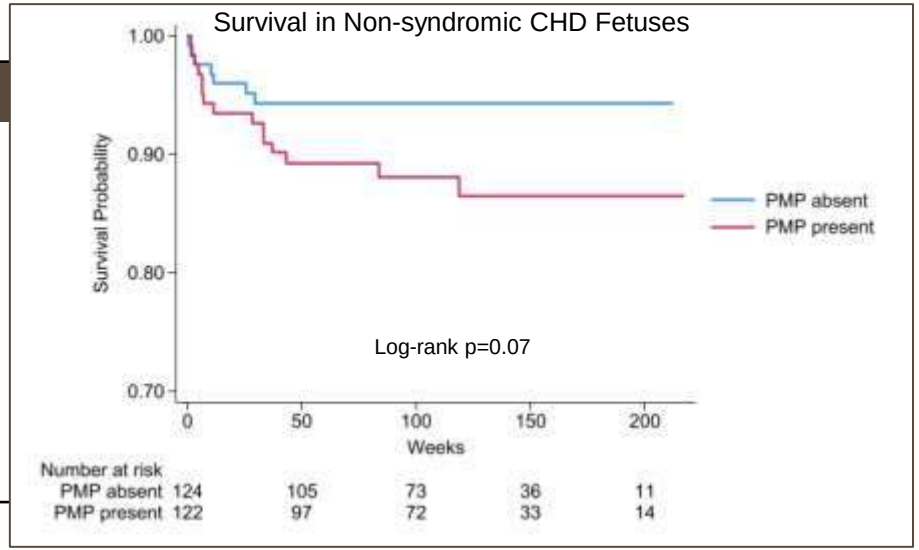
INCREASED MORBIDITY AND MORTALITY IN CHD

A role for abnormal placental development?

	PMP Present (n= 122)	PMP Absent (n= 124)	p
Extracardiac anomalies	39 (31.9%)	32 (25.8%)	0.286
Birth gestational age (weeks)	38.8 (37.4, 39.3)	38.9 (38.1, 39.3)	0.253
Birth weight (g)	2985.5 (2654.9, 3400)	3329.9 (3100, 3674.9)	**<.001**
Birth length (cm)	48 (45, 50)	48.9 (47.5, 51)	**<.001**
Birth head circumference (cm)	33 (31.5, 34)	34 (33, 35)	**<.001**
Index hospitalization LOS (days)	20.5 (9, 47)	15 (8, 28.5)	**0.041**
ECMO	12(9.8%)	5 (4%)	0.073
Mortality	15 (12.3%)	7 (5.6%)	0.068

Josowitz R, unpublished data



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INCREASED MORBIDITY AND MORTALITY IN CHD

A role for abnormal placental development?

SYNDROMIC CHD	PMP Present (n= 30)	PMP Absent (n= 22)	p
Birth Gestational Age (weeks)	38.1 (37.3, 39.0)	37.9 (37.3, 39.0)	0.60
Extracardiac anomalies	22 (70.1%)	9 (40.1%)	**0.03**
Birth weight (g)	2944.9 (2265.1, 3299.9)	3144.9 (2599.9, 3400)	0.27
Birth length (cm)	46.2 (43, 47.2)	48 (44.5, 50.1)	0.07
Birth head circumference (cm)	32.4 (31, 34)	33 (31.8, 33.8)	0.84
Index Hospitalization LOS (days)	44 (23, 84)	26 (7, 62)	0.06
ECMO	4 (12.9%)	3 (12.6%)	0.94
Mortality	8 (25.8%)	3 (13.6%)	0.28

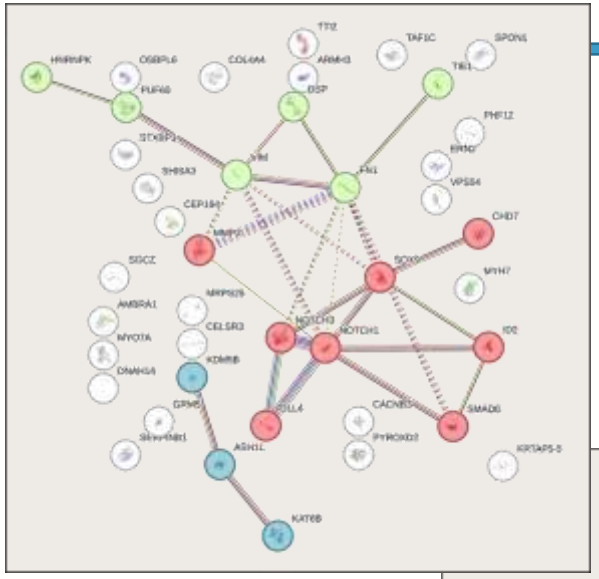
Josowitz R, unpublished data

Impaired placental development acts in synergy with CHD & genetics to increase morbidity and mortality

Univariate Cox Regression for Mortality Unadjusted			
Covariate	**HR**	**95% CI**	**p**
Impaired MFE	1.32	0.61-2.85	0.48
Fetal sex	0.82	0.42-1.64	0.59
ART	0.83	0.20-3.50	0.81
Genetic syndrome	**2.45**	**1.19-5.06**	**0.02**
De novo SNV	1.59	0.77-3.31	0.21
Severe CHD	1.45	0.60-3.51	0.41
Single ventricle	**2.07**	**1.03-4.16**	**0.04**
TGA	0.22	0.03-1.62	0.14
Other CHD	0.78	0.34-1.79	0.56
PMP	**1.49**	**1.03-2.17**	**0.03**
Multivariable Cox Regression for Mortality			
Covariate	**Adjusted HR**	**95% CI**	**p**
PMP	1.44	1.00-2.09	0.05
Genetic syndrome	2.79	1.32-5.92	<0.01
Single ventricle	2.47	1.20-5.09	0.01

MECHANISMS OF PLACENTAL MALDEVELOPMENT IN CHD

PMP Present

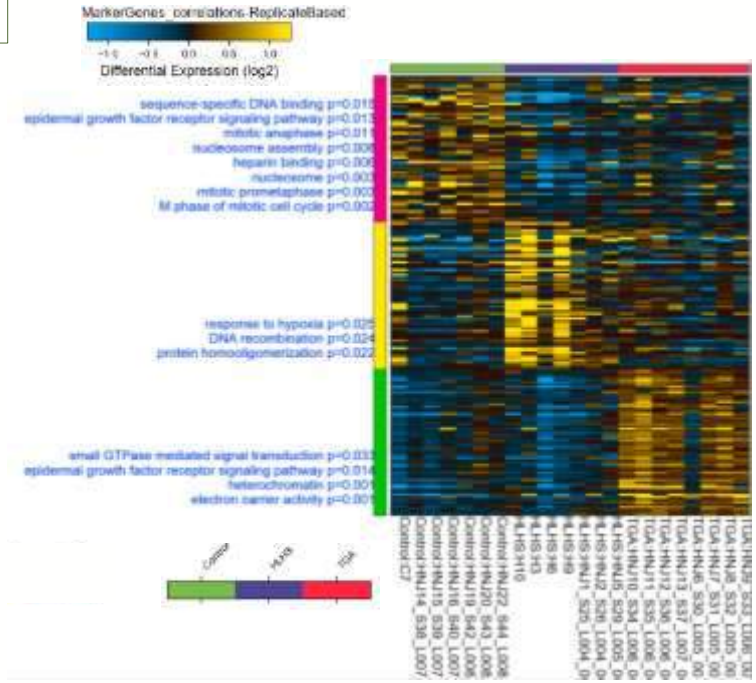


Epithelial to Mesenchymal Transition & Collagen Regulation

Notch signaling

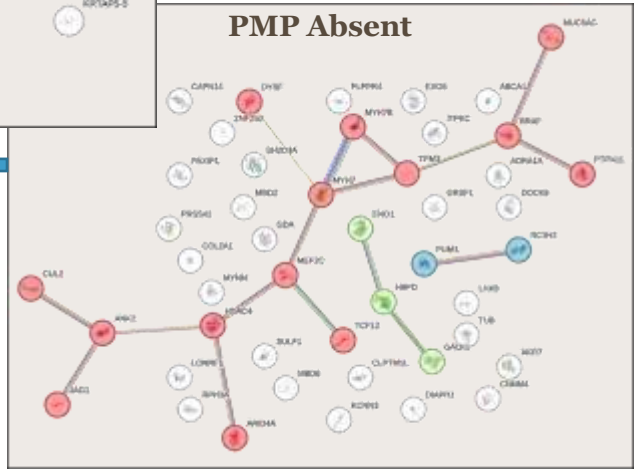
Chromatin remodeling

COL4A4
FN1
MMP2
NOTCH1
NOTCH3
DLL4
SMAD6
VIM
TIE1



Courtney et al. *Placenta*. 2020

PMP Absent



Growth factor signaling

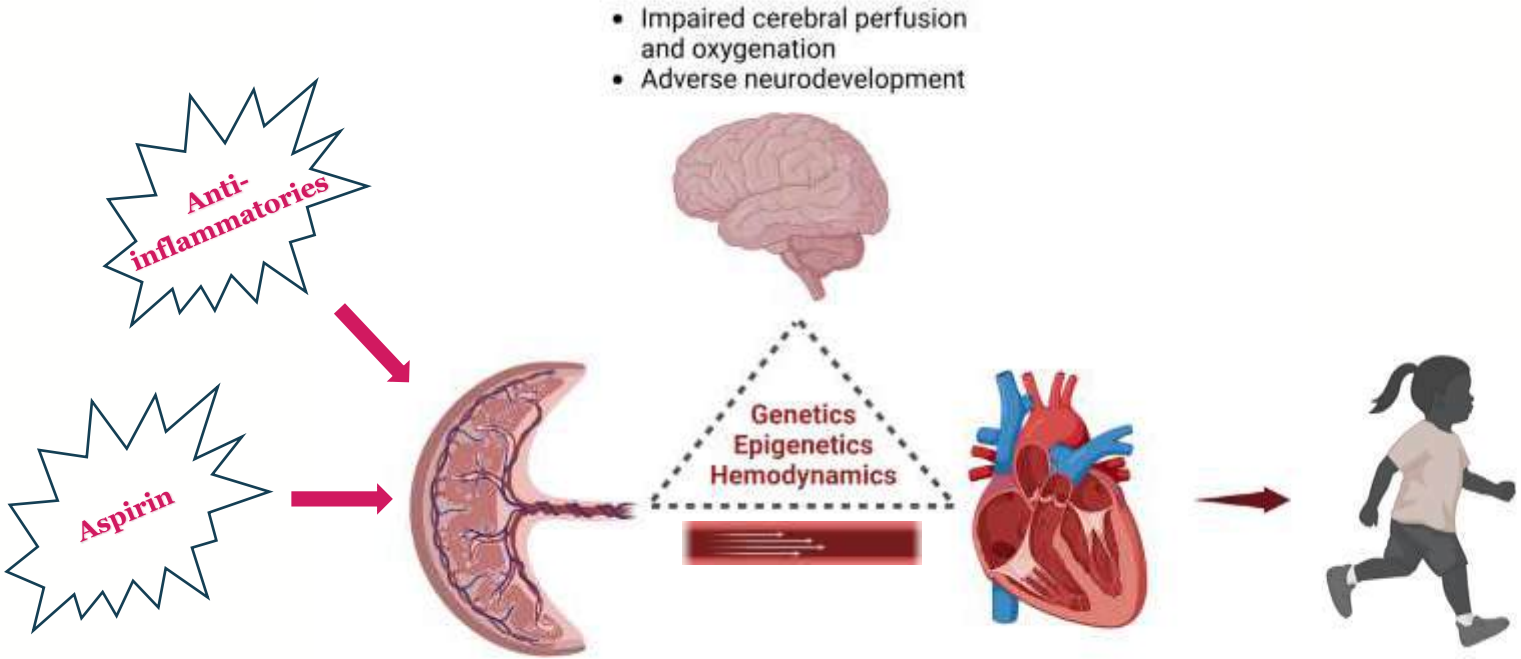
Glycolysis, carbohydrate metabolism

CARDIOLOGY 2025

Josowitz R, unpublished data

Children's Hospital of Philadelphia Cardiac Center

IS THE PLACENTA THE NEXT FRONTIER IN CHD?



THANK YOU

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