Life Before Birth:
Impact of Prenatal Environment

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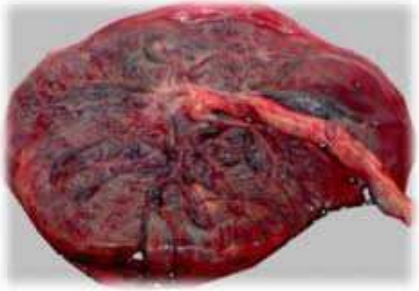
Disclosures

Conflicts: None

Off-label Use: None



The placenta is one of the least understood of human organs and arguably one of the most important, not only for the health of a woman and her fetus during pregnancy, but also for the lifelong health of both.

Functionally, the placenta is the interface between mother and fetus during the earliest period of human development, and thus plays a critical role influencing the fundamental processes of organogenesis.

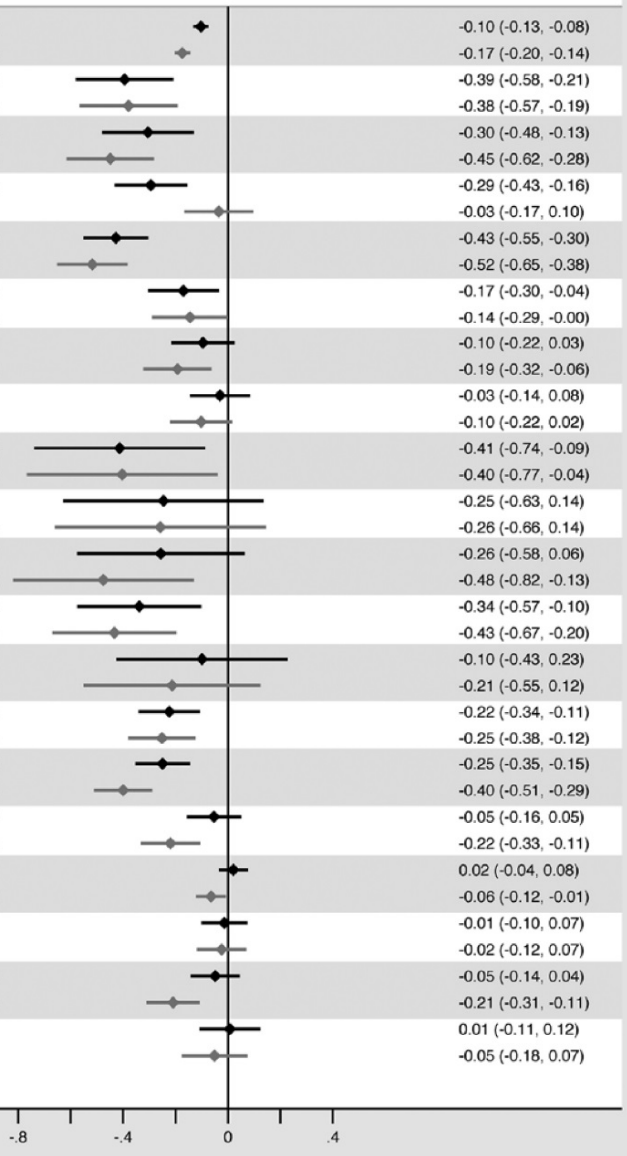
It is the only human organ than can be grown as new, discarded, then de novo grown again.

The placenta also has a critical role in “programming” of human health, well beyond the fetal and neonatal periods of life, a phenomenon now recognized as the fetal origins or “Barker” hypothesis.

Congenital Heart Defects and Indices of Fetal Cerebral Growth in a Nationwide Cohort of 924 422 Liveborn Infants

Niels B. Matthiesen, MD; Tine B. Henriksen, MD, PhD; J. William Gaynor, MD; Peter Agergaard, MD, PhD; Cathrine C. Bach, MD, PhD; Vibeke E. Hjortdal, MD, PhD; John R. Østergaard, MD, DMSc

Subtypes of Heart Defects	No.(%)	Z-score	Crude (95% CI)	Adjusted (95% CI)
All heart defects	5519 (100)	Head circumference	-0.15 (-0.18, -0.12)	-0.10 (-0.13, -0.08)
		Birth weight	-0.23 (-0.26, -0.20)	-0.17 (-0.20, -0.14)
Hypoplastic left heart syndrome	109 (2.0)	Head circumference	-0.34 (-0.54, -0.14)	-0.39 (-0.58, -0.21)
		Birth weight	-0.36 (-0.57, -0.16)	-0.38 (-0.57, -0.19)
Other single ventricle defects	151 (2.7)	Head circumference	-0.23 (-0.41, -0.05)	-0.30 (-0.48, -0.13)
		Birth weight	-0.41 (-0.58, -0.24)	-0.45 (-0.62, -0.28)
Transposition of the great arteries	221 (4.0)	Head circumference	-0.21 (-0.36, -0.07)	-0.29 (-0.43, -0.16)
		Birth weight	0.02 (-0.12, 0.16)	-0.03 (-0.17, 0.10)
Tetralogy of Fallot	257 (4.7)	Head circumference	-0.47 (-0.60, -0.35)	-0.43 (-0.55, -0.30)
		Birth weight	-0.62 (-0.76, -0.49)	-0.52 (-0.65, -0.38)
Atrioventricular septal defects	265 (4.8)	Head circumference	-0.54 (-0.68, -0.40)	-0.17 (-0.30, -0.04)
		Birth weight	-0.38 (-0.52, -0.23)	-0.14 (-0.29, -0.00)
Aortic stenosis	282 (5.1)	Head circumference	-0.01 (-0.13, 0.12)	-0.10 (-0.22, 0.03)
		Birth weight	-0.14 (-0.29, 0.00)	-0.19 (-0.32, -0.06)
Coarctation of the aorta	340 (6.2)	Head circumference	0.01 (-0.11, 0.12)	-0.03 (-0.14, 0.08)
		Birth weight	-0.07 (-0.20, 0.05)	-0.10 (-0.22, 0.02)
Common arterial trunk	38 (0.7)	Head circumference	-0.45 (-0.78, -0.13)	-0.41 (-0.74, -0.09)
		Birth weight	-0.56 (-0.93, -0.18)	-0.40 (-0.77, -0.04)
Interrupted aortic arch	37 (0.7)	Head circumference	-0.19 (-0.61, 0.23)	-0.25 (-0.63, 0.14)
		Birth weight	-0.27 (-0.70, -0.15)	-0.26 (-0.66, 0.14)
Double outlet right ventricle	41 (0.7)	Head circumference	-0.35 (-0.70, -0.00)	-0.26 (-0.58, 0.06)
		Birth weight	-0.57 (-0.96, -0.19)	-0.48 (-0.82, -0.13)
Anomalous Pulmonary Venous Return	79 (1.4)	Head circumference	-0.35 (-0.60, -0.09)	-0.34 (-0.57, -0.10)
		Birth weight	-0.46 (-0.70, -0.21)	-0.43 (-0.67, -0.20)
Pulmonary atresia	33 (0.6)	Head circumference	-0.15 (-0.50, 0.21)	-0.10 (-0.43, 0.23)
		Birth weight	-0.24 (-0.59, 0.11)	-0.21 (-0.55, 0.12)
Other severe defects	276 (5)	Head circumference	-0.25 (-0.37, -0.13)	-0.22 (-0.34, -0.11)
		Birth weight	-0.31 (-0.44, -0.17)	-0.25 (-0.38, -0.12)
Major ventricular septal defects	332 (6.0	Head circumference	-0.36 (-0.47, -0.25)	-0.25 (-0.35, -0.15)
		Birth weight	-0.54 (-0.66, -0.42)	-0.40 (-0.51, -0.29)
Major atrial septal defects	364 (6.6)	Head circumference	-0.19 (-0.30, -0.08)	-0.05 (-0.16, 0.05)
		Birth weight	-0.37 (-0.49, -0.25)	-0.22 (-0.33, -0.11)
Minor ventricular septal defects	1350 (24.5)	Head circumference	-0.01 (-0.06, 0.05)	0.02 (-0.04, 0.08)
		Birth weight	-0.10 (-0.16, -0.04)	-0.06 (-0.12, -0.01)
Pulmonary stenosis	500 (9.1)	Head circumference	-0.05 (-0.14, 0.04)	-0.01 (-0.10, 0.07)
		Birth weight	-0.07 (-0.17, 0.03)	-0.02 (-0.12, 0.07)
Combined septal defect and pulmonary stenosis	514 (9.3)	Head circumference	-0.15 (-0.24, -0.05)	-0.05 (-0.14, 0.04)
		Birth weight	-0.30 (-0.41, -0.19)	-0.21 (-0.31, -0.11)
Other mild defects	330 (6.0)	Head circumference	-0.01 (-0.13, 0.11)	0.01 (-0.11, 0.12)
		Birth weight	-0.11 (-0.24, 0.02)	-0.05 (-0.18, 0.07)



Fetal congenital heart disease and intrauterine growth restriction: a retrospective cohort study

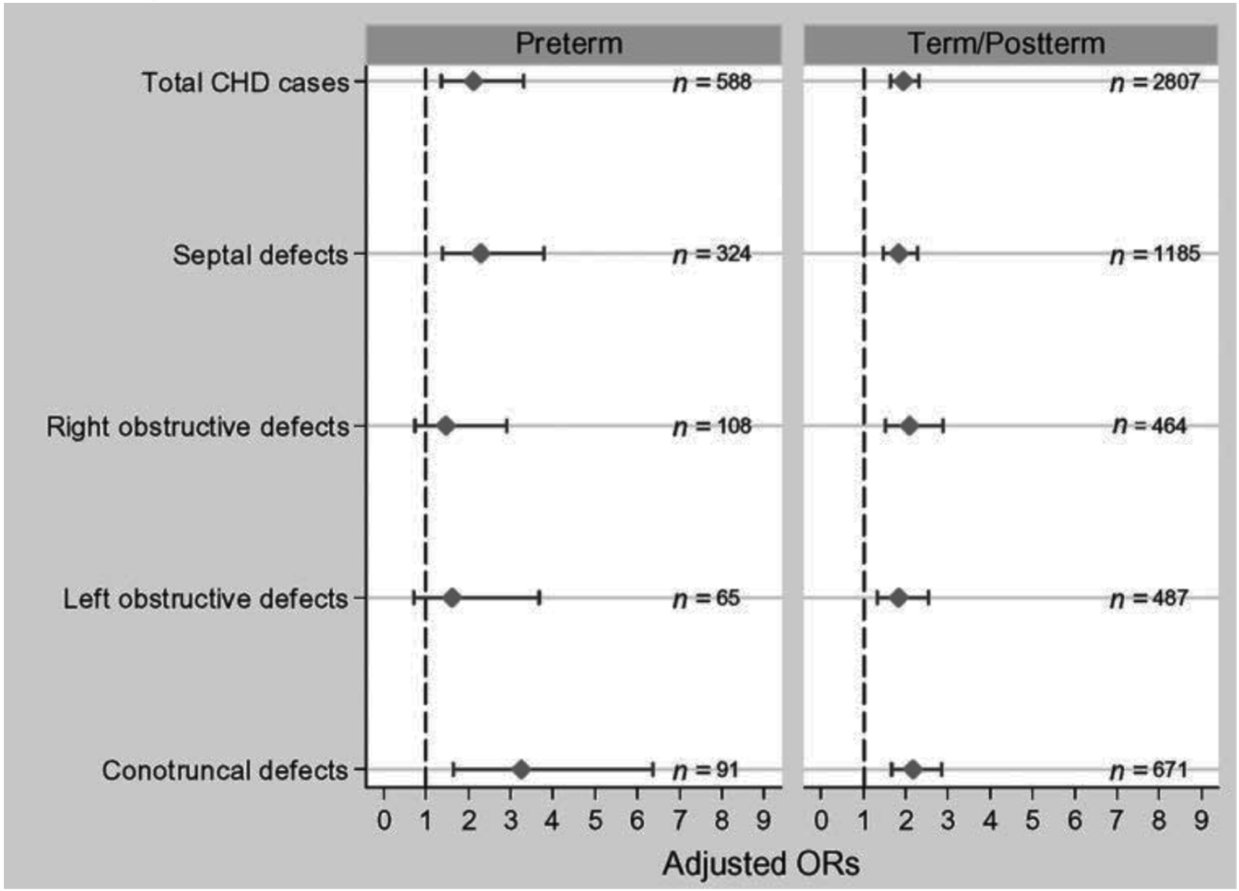
Matthew B. Wallenstein, Lorie M. Harper, Anthony O. Odibo, Kimberly A. Roehl, Ryan E. Longman, George A. Macones & Alison G. Cahill

Table II. Unadjusted and adjusted risk estimates for intrauterine growth restriction in congenital heart disease

Birth weight <10th Percentile	CHD	Controls ($n=67,630$)	Unadjusted RR (95% CI)	Adjusted OR (95% CI)	p Value
All CHD ($n=193$)	23.8% ($n=46$)	8.4% ($n=5,669$)	2.8 (2.2–3.6)	3.3 (2.4–4.6)*	*<.01*
Major CHD ($n=139$)	16.5% ($n=23$)	8.4% ($n=5,692$)	1.9 (1.3–2.8)	2.1 (1.3–3.2)**	*<.01*
Minor CHD ($n=36$)	13.9% ($n=5$)	8.4% ($n=5,710$)	1.6 (0.7–3.7)	1.7 (0.7–4.5)***	*0.25*
Isolated CHD ($n=129$)	17.8% ($n=19$)	8.5% ($n=3,914$)	2.1 (1.4–3.1)	2.2 (1.4–3.7)**	*0.01*

Association Between Congenital Heart Defects and Small for Gestational Age

Sadia Malik, MD, MPH[a,b,c], Mario A. Cleves, PhD[a,b,c], Weizhi Zhao, MS[a,b,c], Adolfo Correa, MD, MPH, PhD[d], Charlotte A. Hobbs, MD, PhD[a,b,c], and the National Birth Defects Prevention Study



Increased risk of FGR

Small for gestational age was observed among 15.2% of case subjects and among only 7.8% of control subjects.

Preterm Birth and Congenital Heart Defects: A Population-based Study

AUTHORS: Enora Laas, MD, MSc,[a] Nathalie Lelong, MSc,[a] Anne-Claire Thieulin, MSc,[a] Lucile Houyel, MD,[b] Damien Bonnet, MD, PhD,[c] Pierre-Yves Ancel, MD, PhD,[a] Gilles Kayem, MD, PhD,[a] François Goffinet, MD, PhD,[a,d] and Babak Khoshnood, MD, PhD,[a] on behalf of the EPICARD Study Group

TABLE 2 Proportion of PTBs for Newborns With CHD (Excluding Isolated ASD), Compared With the General Population[a]

CHD	*n*	Gestational Age (wk)							
		<32		32–36			<37		
		%	95% CI[a]	%	95% CI[a]	*P*[b]	%	95% CI[a]	*P*[c]
All cases	2189	2.4	1.8–3.1	11.1	9.8–12.5	<.001	13.5	12.1–15.0	<.001
Cases without chromosomal anomalies	2055	2.3	1.7–3.0	10.2	8.9–11.6	<.001	12.5	11.1–14.0	<.001
Cases without chromosomal and/or anomalies of other systems[d]	1770	2.1	1.5–2.9	9.4	8.1–10.8	<.001	11.5	10.1–13.1	<.001
Cases without chromosomal and/or anomalies of other systems, excluding isolated VSD	667	3.9	2.6–5.6	13.6	11.1–16.5	<.001	17.5	14.7–20.6	<.001
French NPS 2003[e]	1815	1.3	0.8–2.0	5.9	4.8–7.1		7.2	6.1–8.5	

There was a higher risk of spontaneous PTB for newborns with CHD.

Associations of CHD with chromosomal or other congenital anomalies explained only a small part of the higher risk of PTB for newborns with CHD.

Original Investigation

Association Between Preeclampsia and Congenital Heart Defects

Nathalie Auger, MD, MSc, FRCPC; William D. Fraser, MD, MSc, FRCSC; Jessica Healy-Profitós, MPH; Laura Arbour, MD, MSc, FRCPC, FCCMG

Table 3. Prevalence Ratio of Congenital Heart Defects for Preeclampsia vs No Preeclampsia

	Prevalence Ratio (95% CI)		Adjusted Prevalence Difference per 100 000 Infants (95% CI)[b]
	Unadjusted	Adjusted[a]	
Critical defect			
Tetralogy of Fallot	2.23 (1.52 to 3.28)	1.67 (1.12 to 2.50)	16.6 (2.0 to 31.1)
Transposition of great vessels	0.76 (0.39 to 1.47)	0.63 (0.33 to 1.23)	−6.5 (−14.6 to 1.6)
Truncus arteriosus	1.66 (0.67 to 4.09)	1.91 (0.80 to 4.59)	2.8 (−3.2 to 8.8)
Hypoplastic left heart	1.36 (0.74 to 2.49)	1.07 (0.58 to 1.95)	0.7 (−7.7 to 9.2)
Common ventricle	2.96 (1.42 to 6.15)	2.41 (1.09 to 5.33)	6.4 (−1.5 to 14.2)
Coarctation of aorta	1.82 (1.17 to 2.83)	1.34 (0.85 to 2.10)	4.5 (−7.1 to 16.1)
Other[c]	0.72 (0.27 to 1.95)	0.58 (0.22 to 1.58)	−3.0 (−8.6 to 2.6)
Any	1.66 (1.34 to 2.06)	1.25 (1.00 to 1.57)	23.6 (−1.0 to 48.2)
Noncritical defect			
Endocardial cushion	2.82 (1.86 to 4.29)	2.23 (1.44 to 3.45)	21.2 (6.7 to 35.6)
Ventricular septum	1.44 (1.28 to 1.62)	1.24 (1.10 to 1.40)	79.1 (32.2 to 126.0)
Atrial septum	2.69 (2.45 to 2.95)	1.91 (1.73 to 2.10)	327.5 (265.4 to 389.7)
Valve	2.77 (2.13 to 3.61)	1.75 (1.33 to 2.29)	26.0 (6.3 to 45.6)
Aorta	1.51 (0.90 to 2.55)	1.05 (0.61 to 1.80)	7.0 (−3.9 to 18.0)
Pulmonary artery	2.82 (2.36 to 3.36)	2.00 (1.66 to 2.41)	96.2 (64.3 to 128.2)
Heterotaxy	1.38 (0.71 to 2.70)	1.06 (0.54 to 2.09)	2.1 (−6.2 to 10.4)
Other[c]	1.49 (1.31 to 1.69)	1.42 (1.25 to 1.62)	86.5 (45.0 to 128.0)
Any	1.92 (1.81 to 2.05)	1.56 (1.47 to 1.67)	521.1 (431.1 to 611.0)
Site of defect			
Aorta or pulmonary artery	2.47 (2.11 to 2.90)	1.76 (1.49 to 2.07)	103.6 (68.3 to 138.9)
Valve	2.51 (2.03 to 3.10)	1.75 (1.41 to 2.18)	54.6 (28.3 to 80.8)
Septum	2.10 (1.95 to 2.26)	1.63 (1.51 to 1.76)	397.3 (321.7 to 472.9)
Patent ductus, ≥37 wk	1.72 (1.43 to 2.08)	1.55 (1.28 to 1.88)	76.7 (38.2 to 115.1)
Multiple defects[d]			
1	1.88 (1.76 to 2.01)	1.56 (1.46 to 1.67)	468.7 (383.2 to 554.2)
≥2	2.26 (1.96 to 2.61)	1.68 (1.45 to 1.94)	109.7 (70.7 to 148.6)
Any[c]	1.93 (1.82 to 2.05)	1.57 (1.48 to 1.67)	577.1 (483.0 to 671.1)

Population-level analysis of live births, 1989-2012, for the entire province of Quebec. All women who delivered an infant with or without heart defects in any Quebec hospital were included (N = 1,942,072 neonates).

The absolute prevalence of congenital heart defects was higher for infants of women with preeclampsia than those without it.

Possible Common Aetiology behind Maternal Preeclampsia and Congenital Heart Defects in the Child: a Cardiovascular Diseases in Norway Project Study

Kristoffer Brodwall,[a,c] Elisabeth Leirgul,[a,d] Gottfried Greve,[c,b] Stein Emil Vollset,[a,g] Henrik Holmstrøm,[h] Grethe S. Tell,[a,f] Nina Øyen[a,e]

Information on all births registered in the Medical Birth Registry of Norway, 1994–2009.

Among 914,703 singleton births without chromosomal abnormalities, 32,864 (3.6%) were born after a pregnancy with preeclampsia.

When adjusting for year of birth, maternal age, parity, and gestational diabetes, *the risk ratio (RR) for severe CHD in offspring of mothers with any preeclampsia was **1.3** [95% (CI) 1.1, 1.5], and in pregnancies with early-onset preeclampsia, the RR was **2.8** (95% CI 1.8, 4.4).*

Congenital Heart Defects and Indices of Placental and Fetal Growth in a Nationwide Study of 924 422 Liveborn Infants

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John R. Østergaard, MD, DMSc

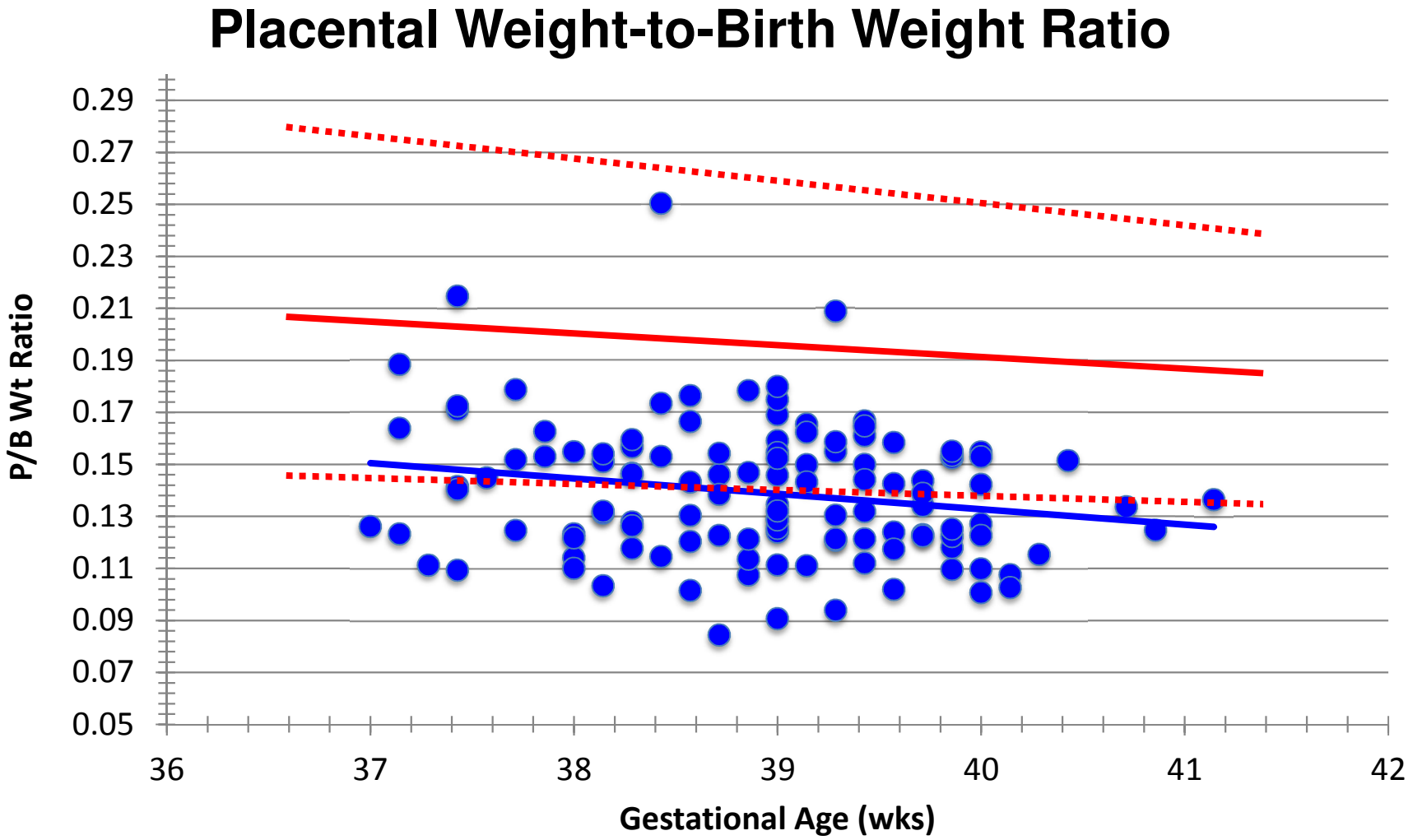
Placental weight was lower for a given gestational age in newborns with CHD.

Some types of CHD were associated with markedly smaller placental weights, including TOF, DORV, and major VSDs.

Lower placental weight was associated with a decrease in both overall growth and cerebral growth in fetuses with all types of CHD.

Characterization of the Placenta in Congenital Heart Disease: Are There Distinctions Based on Type of Cardiac Anomaly?

Jack Rychik, MD, Donna Goff, MD, Eileen McKay, MD, Antonio Mott, MD, Zhiyun Tian, MD, RDM, Daniel J. Licht, MD, J. William Gaynor, MD

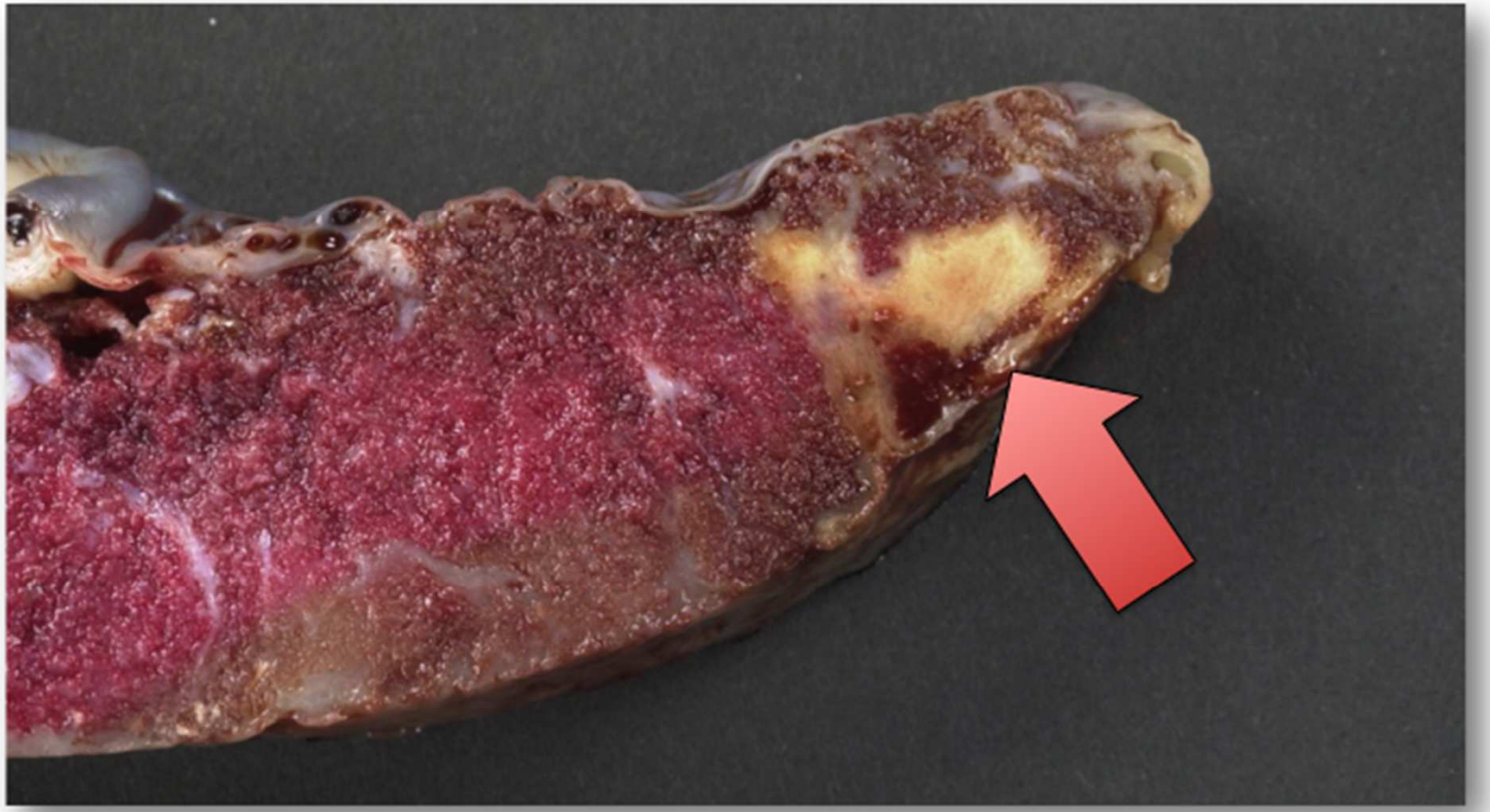


Normal data derived from: Almog, et al. *Placenta* 2011;32:58-62

Characterization of the Placenta in Congenital Heart Disease: Are There Distinctions Based on Type of Cardiac Anomaly?

Jack Rychik, MD, Donna Goff, MD, Eileen McKay, MD, Antonio Mott, MD, Zhiyun Tian, MD, RDM[1], Daniel J. Licht, MD, J. William Gaynor, MD

Placental Thrombosis and Infarction



Placental thrombosis was evident in 41% of cases, with placental infarction seen in 17%.

Is the imbalance between pro-angiogenic and anti-angiogenic factors associated with preeclampsia?

Letícia Lemos Jardim [a], Danyelle Romana Alves Rios [b], Luíza Oliveira Perucci [c], Lirlândia Pires de Sousa [c], Karina Braga Gomes [c], Luci Maria S. Dusse [c,*]

Possible joint pathways of early pre-eclampsia and congenital heart defects via angiogenic imbalance and potential evidence for cardio-placental syndrome

Karen Sliwa[1]* and Alexandre Mebazaa[2]

Maternal and foetal angiogenic imbalance in congenital heart defects

Elisa Llurba[1,2,3†]*, Olga Sánchez[2,3†], Queralt Ferrer[4], Kypros H. Nicolaides[5,6], Aina Ruíz[1,2], Camen Domínguez[3,7], Joan Sánchez-de-Toledo[8], Belén García-García[1,2], Gemma Soro[1,2], Silvia Arévalo[1], Maria Goya[1,2], Anna Suy[1,2], Santiago Pérez-Hoyos[9], Jaume Alijotas-Reig[10], Elena Carreras[1,2], and Lluís Cabero[1,2]

OBSTETRICS

Allelic variations in angiogenic pathway genes are associated with preeclampsia

Sindhu K. Srinivas, MD, MSCE; Alanna C. Morrison, PhD; Christina M. Andrela, MS; Michal A. Elovitz, MD

Maternal/newborn *VEGF-C936T* interaction and its influence on the risk, severity and prognosis of preeclampsia, as well as on the maternal angiogenic profile

Lucia Maria Procopciuc[1], Gabriela Caracostea[2], Gabriela Zaharie[3], and Florin Stamatian[2]

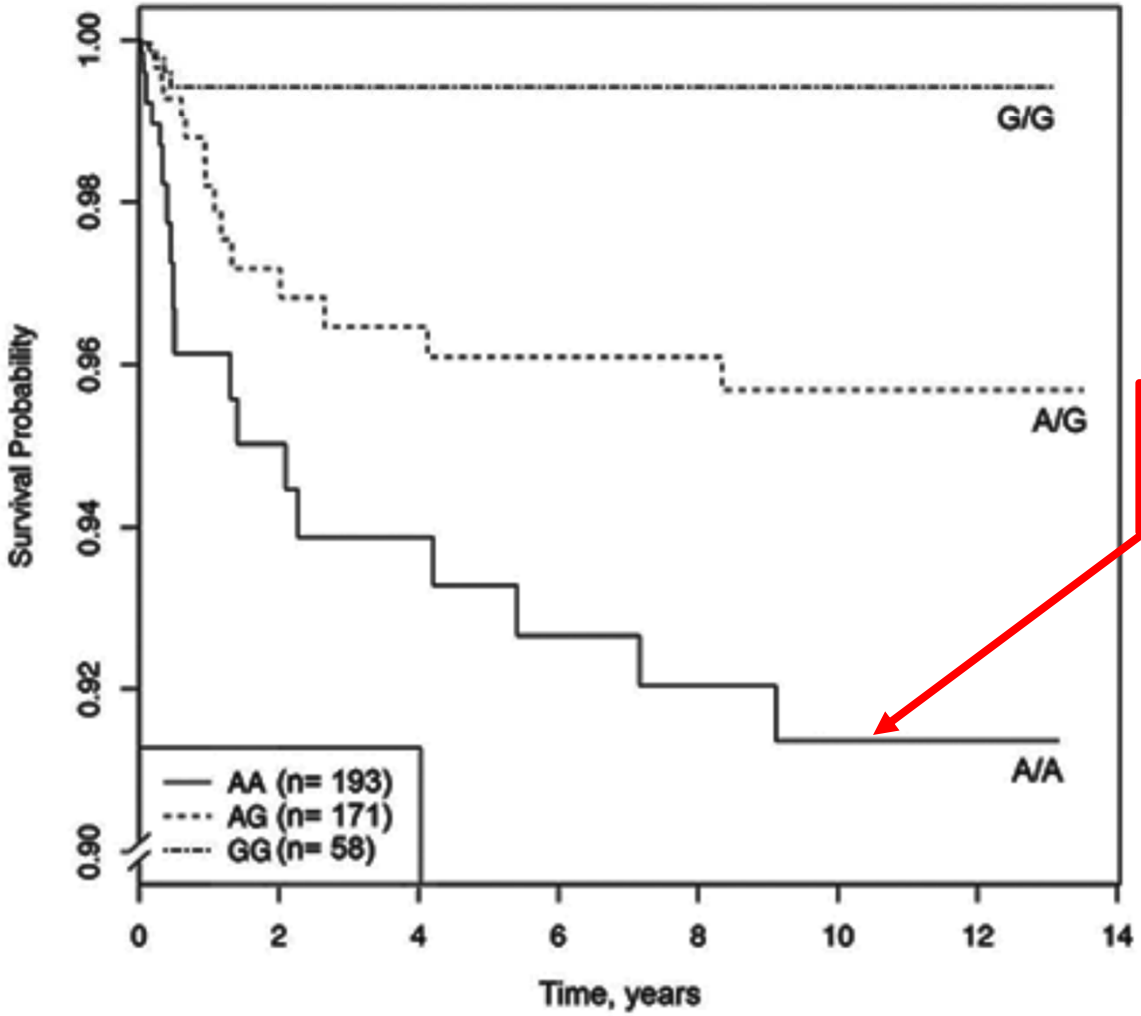
Association of *VEGFA* gene polymorphisms and VEGFA plasma levels with spontaneous preterm birth

Immaculate Mbongo Langmia[a], Yamunah D. Apalasamy[a], Siti Z. Omar[b] and Zahurin Mohamed[a]

J. MAXWELL CHAMBERLAIN MEMORIAL PAPER FOR CONGENITAL HEART SURGERY

Patient Genotypes Impact Survival After Surgery for Isolated Congenital Heart Disease

Daniel Seung Kim, BS, Jerry H. Kim, MD, Amber A. Burt, MS, David R. Crosslin, PhD, Nancy Burnham, MSN, Donna M. McDonald-McGinn, MS, Elaine H. Zackai, MD, Susan C. Nicolson, MD, Thomas L. Spray, MD, Ian B. Stanaway, BS, Deborah A. Nickerson, PhD, Mark W. Russell, MD, Hakon Hakonarson, MD, PhD, J. William Gaynor, MD, and Gail P. Jarvik, MD, PhD



Decreased VEGF Expression

An international network (PlaNet) to evaluate a human placental testing platform for chemicals safety testing in pregnancy

Paul Brownbill[a,b,*], Igor Chernyavsky[c], Barbara Bottalico[d], Gernot Desoye[e], Stefan Hansson[d], Gerry Kenna[f], Lisbeth E. Knudsen[g], Udo R. Markert[h], Nicola Powles-Glover[i], Henning Schneider[j], Lopa Leach[k]

Xenobiotics are chemicals to which an organism is exposed that are extrinsic to the normal metabolism of that organism.

The fetus is potentially vulnerable to xenobiotics that cross the placental barrier, which either cause direct damage to the fetus, or indirectly affect embryo development by interfering with normal placental function.

The New York Times

The Womb Is No Protection From Toxic Chemicals

By FREDERICA PERERA JUNE 1, 2017

Until a few decades ago, the popular but falsely reassuring belief was that babies in the womb were perfectly protected by the placenta and that children were just “little adults,” requiring no special protections from environmental threats. We now know that a host of chemicals, pollutants and viruses readily travel across the placenta from mother to fetus, pre-polluting or pre-infecting a baby even before birth.

Toxic chemicals like lead, certain air pollutants, pesticides, synthetic chemicals and infectious agents like Zika can derail the intricate molecular processes involved in a fetus’s healthy brain development. So can physical and social stress experienced by the mother.

Studying Toxicants as Single Chemicals: Does this Strategy Adequately Identify Neurotoxic Risk?

Deborah A. Cory-Slechta *

The multi-hit hypothesis: the brain may readily compensate for the effects of an individual chemical itself acting on a particular target system, …

… but when multiple target or functional sites are attacked by different mechanisms (i.e., multiple chemical exposures or chemical exposures combined with other risk factors), homeostatic capabilities may be restricted, thereby leading to sustained or cumulative damage.

The New York Times

SundayReview | OPINION

Protect Our Children's Brains

By SHARON LERNER FEB. 3, 2017

The revised risk assessment relied on evidence of "neurodevelopmental effects in fetuses and children resulting from chlorpyrifos exposure" and drew on studies showing increased risk of ***delays in mental development, intelligence loss, attention problems and autism spectrum disorder*** in children who were exposed to organophosphates, the class of pesticides to which chlorpyrifos belongs.

Brain anomalies in children exposed prenatally to a common organophosphate pesticide

Virginia A. Rauh[a,b,1], Frederica P. Perera[b,c], Megan K. Horton[b,d], Robin M. Whyatt[b,c], Ravi Bansal[e], Xuejun Hao[e], Jun Liu[e], Dana Boyd Barr[f], Theodore A. Slotkin[g], and Bradley S. Peterson[e,h]

…. found significant abnormalities in morphological measures of the cerebral surface associated with higher prenatal chlorpyrifos exposure, after adjusting for possible confounders.

Our findings indicate that ***prenatal*** chlorpyrifos exposure, at levels observed with routine (non-occupational) use and ***below the threshold for any signs of acute exposure***, has a measureable effect on brain structure in a sample of 40 children 5.9–11.2 y of age.

Effect of Synthetic Pyrethroid Pesticide Exposure During Pregnancy on the Growth and Development of Infants

Zhanyou Xue, MD[1], Xiaoqiong Li, BSMed[2], Qian Su, MMedSc[1], Li Xu, MD[1], Peng Zhang, MD[1], Zhenyu Kong, BSMed[1], Jianhui Xu, MMedSc[1], and Junfang Teng, MMedSc[3]

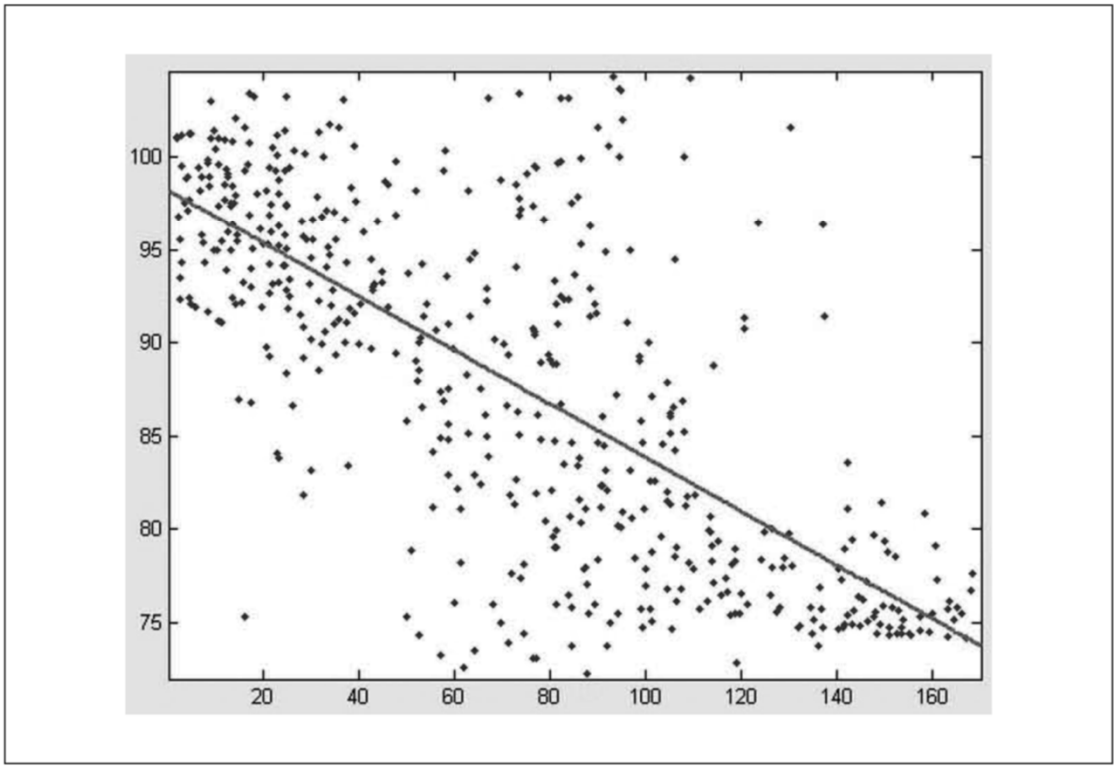


Figure 1. Changes of the DQ of infants with the level of exposure of pregnant women.

Table 4. Comparison of the DQ and MI of Infants Among Different Levels of SP Exposure.

	DQ			MI		
Group	n	Mean ± SD	Range	n	Mean ± SD	Range
Low exposure group	125	91.12 ± 10.23	57-125	125	89.25 ± 11.47	71-117
Middle exposure group	250	88.36 ± 12.64	52-128	250	85.69 ± 14.75	59-200
High exposure group	122	84.58 ± 10.22	52-112	122	82.86 ± 10.61	64-115
		$F = 3.545$	$P = .018$		$F = 2.682$	$P = .087$
		$Z = 4.102$	$P = .047$		$Z = 3.924$	$P = .061$

Review

The Effects of Nicotine on Human Fetal Development

Bradley D. Holbrook

Nicotine is extremely harmful to the developing fetus through many different mechanisms, and the harms increase with later gestational age at exposure.

Pregnancies complicated by maternal nicotine use are more likely to have significant adverse outcomes.

Nicotine-exposed children tend to have several health problems throughout their lives, including impaired function of the endocrine, reproductive, respiratory, cardiovascular, and neurologic systems.

Poor academic performance and significant behavioral disruptions are also common, including ADHD, aggressive behaviors, and future substance abuse.

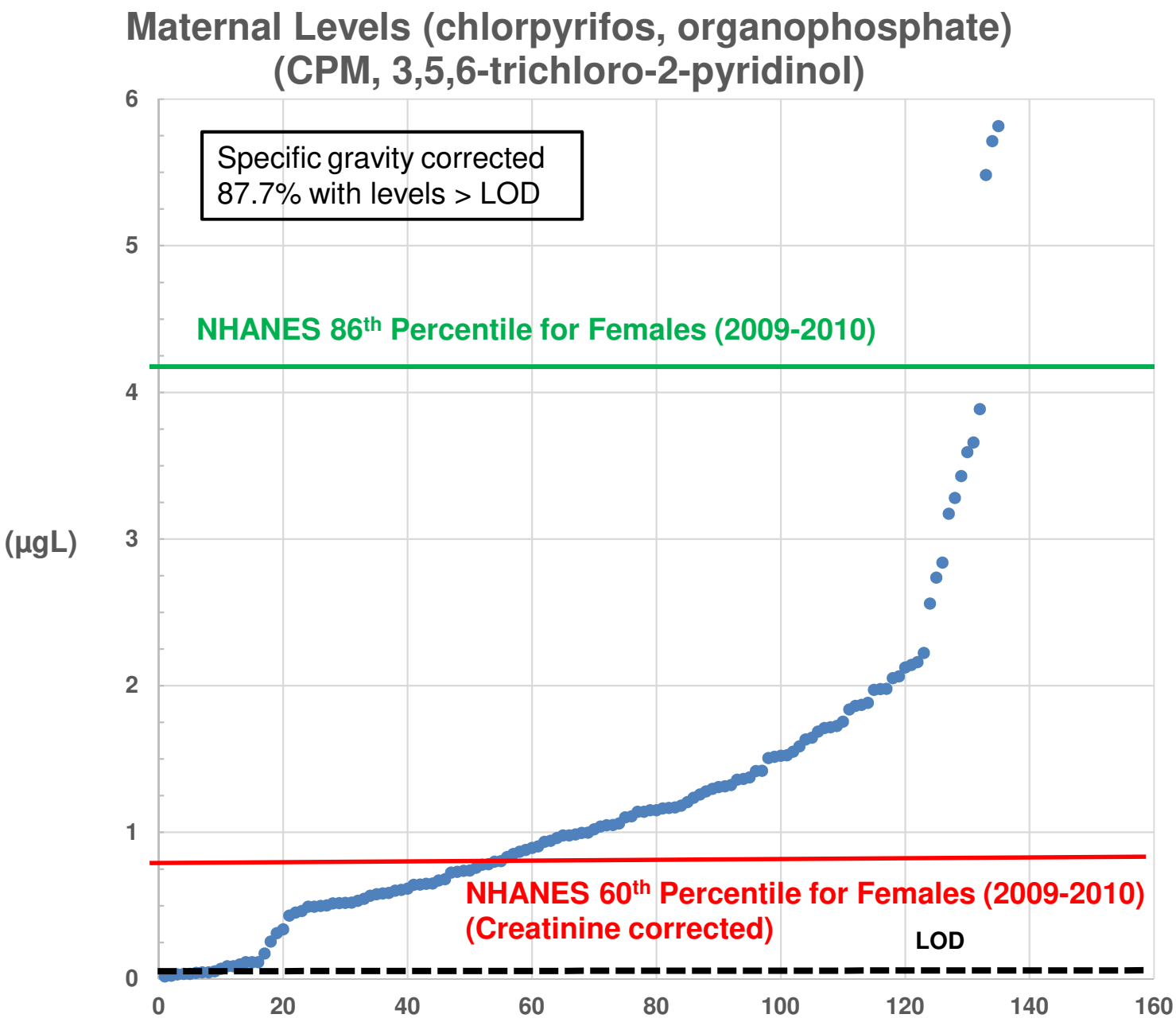
Prenatal Exposure to Environmental Contaminants and Neurobehavioral Outcomes in Newborns with CHD

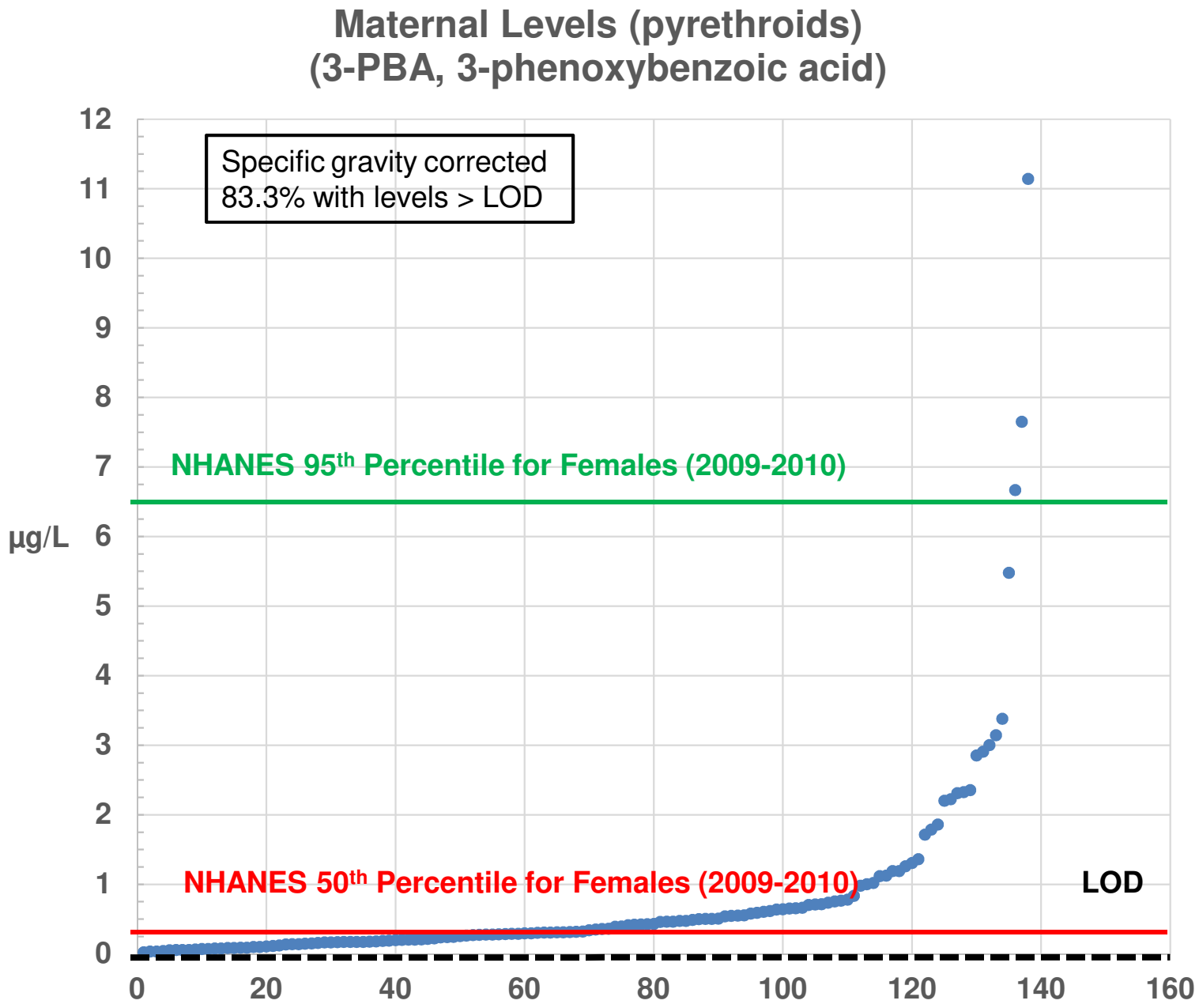
Objective:
To determine if prenatal exposure to environmental contaminants (tobacco smoke, lead, mercury, phthalates, phenols, and pesticides), is associated with worse neurobehavioral outcomes after cardiac surgery.

Study Interventions and Measures:
In-utero environmental exposures (tobacco, lead, mercury, phthalates, phenols, and pesticides) assessed by maternal and infant blood and urine, exposure questionnaire

Neurodevelopmental evaluation at 18 months of age using the BSID-III [Cognitive Composite, Language Composite, Motor Composite] at 18 months of age.

Study Status:
Enrollment began in September, 2011 and was closed in July, 2015. 140 mothers and newborns enrolled. The 18 month evaluation was completed in 110 infants.


Maternal Levels (chlorpyrifos, organophosphate)
(CPM, 3,5,6-trichloro-2-pyridinol)
Specific gravity corrected
87.7% with levels > LOD
NHANES 86th Percentile for Females (2009-2010)
NHANES 60th Percentile for Females (2009-2010)
(Creatinine corrected)
LOD
(µgL)
0
1
2
3
4
5
6
0
20
40
60
80
100
120
140
160


Maternal Levels (pyrethroids)
(3-PBA, 3-phenoxybenzoic acid)
Specific gravity corrected
83.3% with levels > LOD
NHANES 95th Percentile for Females (2009-2010)
NHANES 50th Percentile for Females (2009-2010)
LOD
µg/L
0
1
2
3
4
5
6
7
8
9
10
11
12
0
20
40
60
80
100
120
140
160

Maternal Tobacco Exposure

Tobacco exposure was confirmed by levels of nicotine or cotinine > LOD in 13/140 (9.3%) of mothers.

An additional 6 mothers reported tobacco exposure during the pregnancy.

Overall, there was evidence of tobacco exposure during pregnancy in 19 mothers (13.6%).

Impact of Impaired MFE on Outcomes: CHOP Data (n=135)

An impaired MFE was considered to be present if one or more of the following occurred:

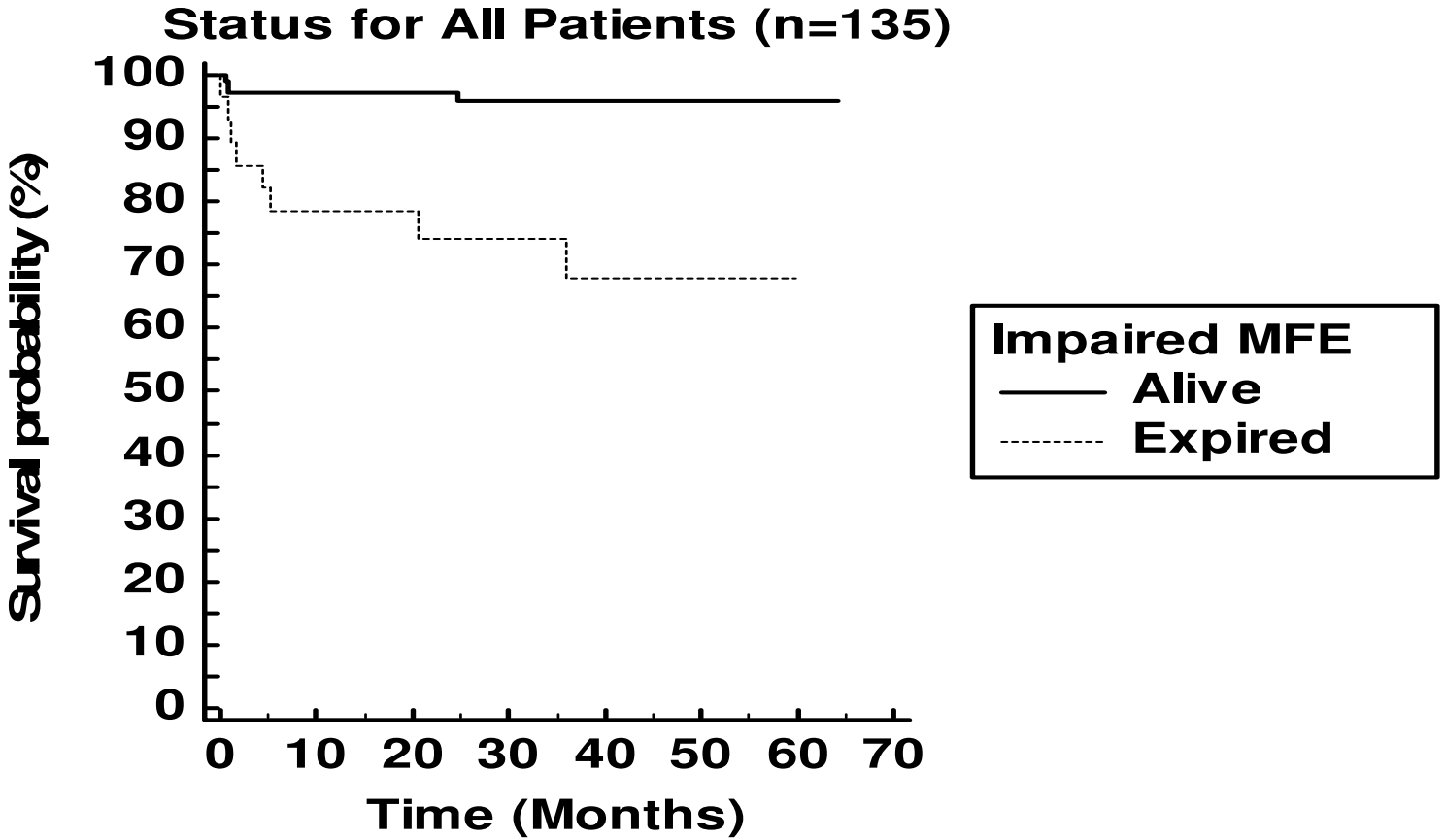
- ***Gestational hypertension*** *defined as 2 blood pressure measurements of > 140/90 mmHg at least 4 hours apart at > 20 weeks gestational age.*
- ***Preeclampsia (PE)*** *defined as gestational hypertension with proteinuria or end-organ injury (liver, kidney).*
- ***Fetal growth restriction (FGR)*** *defined as birthweight below the 10th percentile for gestational age.*
- ***Preterm birth (PTB)*** *defined as birth prior to 37 weeks gestational age.*

Placenta and Impaired MFE

Umbilical artery pulsatility index was higher for fetuses with an impaired MFE, (1.21 vs. 1.03, p=0.012) consistent with increased placental vascular resistance and possible altered perfusion.

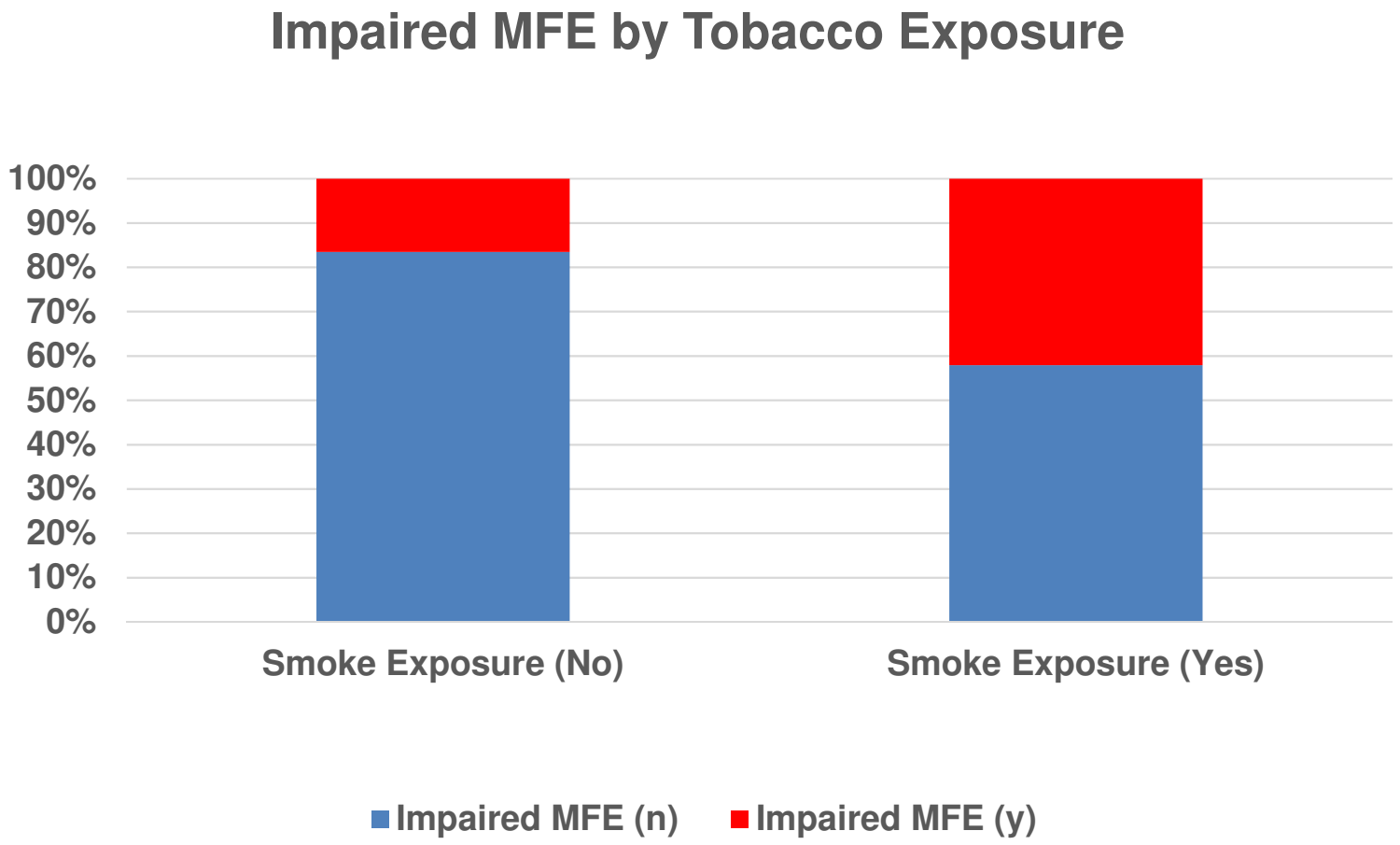
Placental weight was lower for babies with an impaired MFE compared to those without evidence of an impaired MFE, (425 vs. 460 gm, p=0.048).

Impact of Impaired MFE on Outcomes: CHOP Data



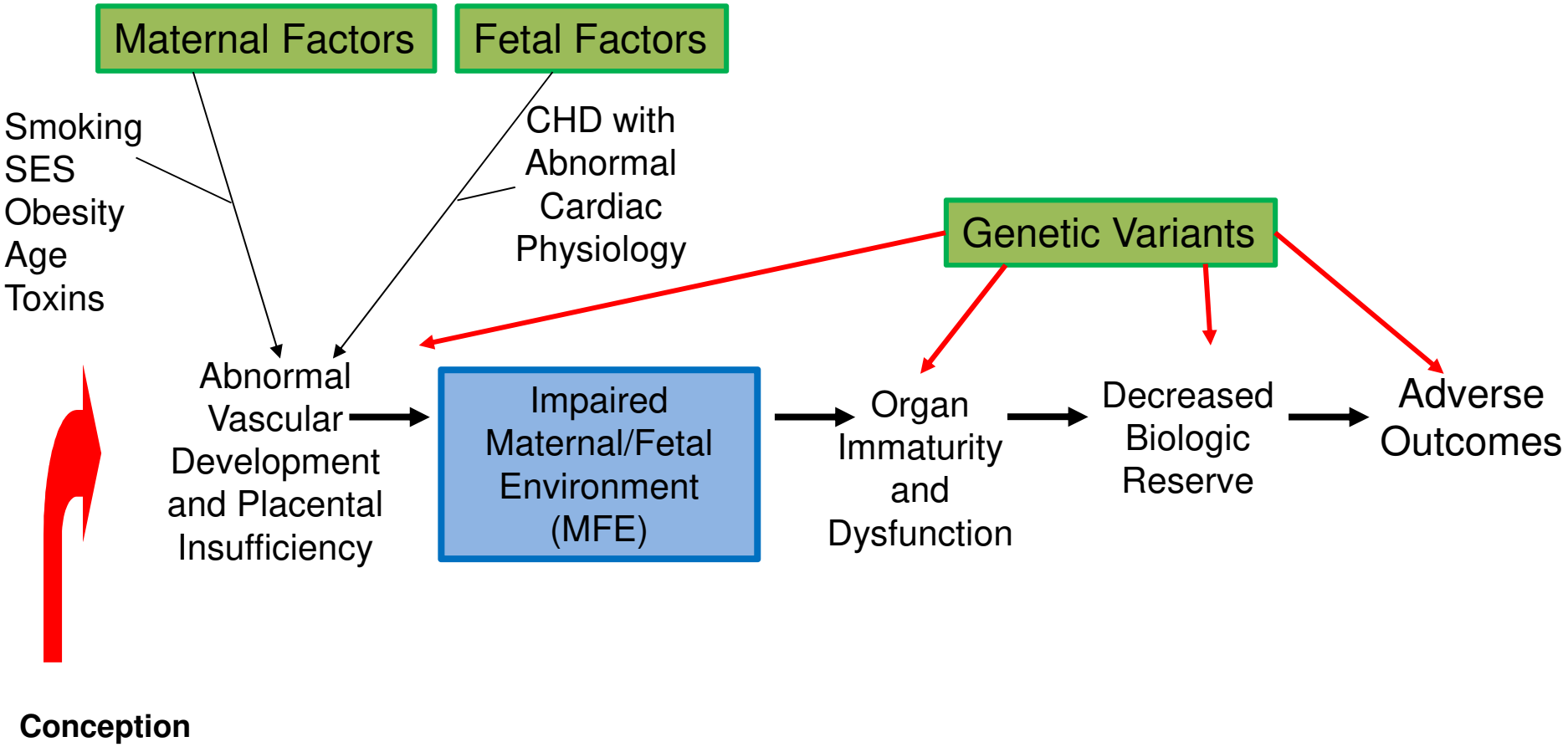
For the entire cohort, survival at 36 months was greater for those without an impaired MFE (96% vs. 68%, p=0.0002) by log-rank test.

Impact of Impact of Maternal Tobacco Exposure



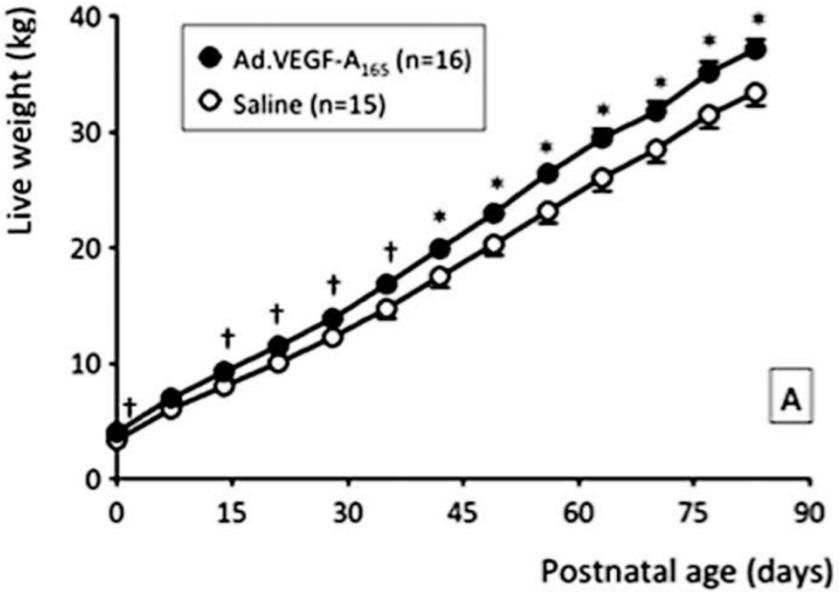
Maternal tobacco exposure (assessed by blood levels of nicotine and cotinine) was associated with an increased occurrence of impaired MFE, $p < 0.01$.

Impaired Maternal/Fetal Environment Leads to Adverse Outcomes



Peri- and Postnatal Effects of Prenatal Adenoviral VEGF Gene Therapy in Growth-Restricted Sheep[1]

David J. Carr,[2,3,4] Jacqueline M. Wallace,[4] Raymond P. Aitken,[4] John S. Milne,[4] John F. Martin,[5] Ian C. Zachary,[5] Donald M. Peebles,[3,6] and Anna L. David[3,6]



Singleton-bearing ewes were evenly allocated to receive Ad.VEGF-A165 (5 3 1010 particles/ml, 10 ml, n = 17) or saline (10 ml, n = 16) injected into each UtA at laparotomy (0.6 gestation).

At delivery, gestation length (P=0.07), lamb birthweight (P=0.08), umbilical girth (P=0.06), and plasma glucose (P=0.09) tended to be greater in Ad.VEGF-A165-treated lambs.

Absolute postnatal growth rate (P= 0.02), and weight at necropsy (P=0.04) were increased by Ad.VEGF-A165 treatment.

EVERREST Project - Clinical Trial

Scientific title: Does maternal growth factor gene therapy safely improve outcome in severe placental insufficiency?

An open label, dose-escalating phase I/II trial to determine the safety and efficacy of intra-uterine artery administration of Ad.VEGF-D^{DNDC} in women with pregnancies affected by severe early-onset placental insufficiency

The EVERREST Clinical Trial is currently in the set-up phase. It is a gene-therapy, first-in-man trial looking to develop an effective treatment for pregnant women diagnosed with severe early onset placental insufficiency.

The main aim of the EVERREST Clinical Trial is to see if using a replication deficient adenoviral vector expressing vascular endothelial growth factor (VEGF) can be used safely in pregnant women to treat severe early onset placental insufficiency. Some of the key secondary outcomes for trial are: increased uterine artery volume blood flow, fetal, neonatal and infant growth, andthe experience and psychological impact of trial participation.

The trial will investigate the maximum tolerated dose of the ATIMP using a 3 + 3 expansion dose escalation design. Up to 27 women will be recruited to the EVERREST Clinical Trial, the criteria to define the trial sample population is based on the data already collected as part of the EVERREST prospective study.

Funder: European Commission

Sponsor: University College London