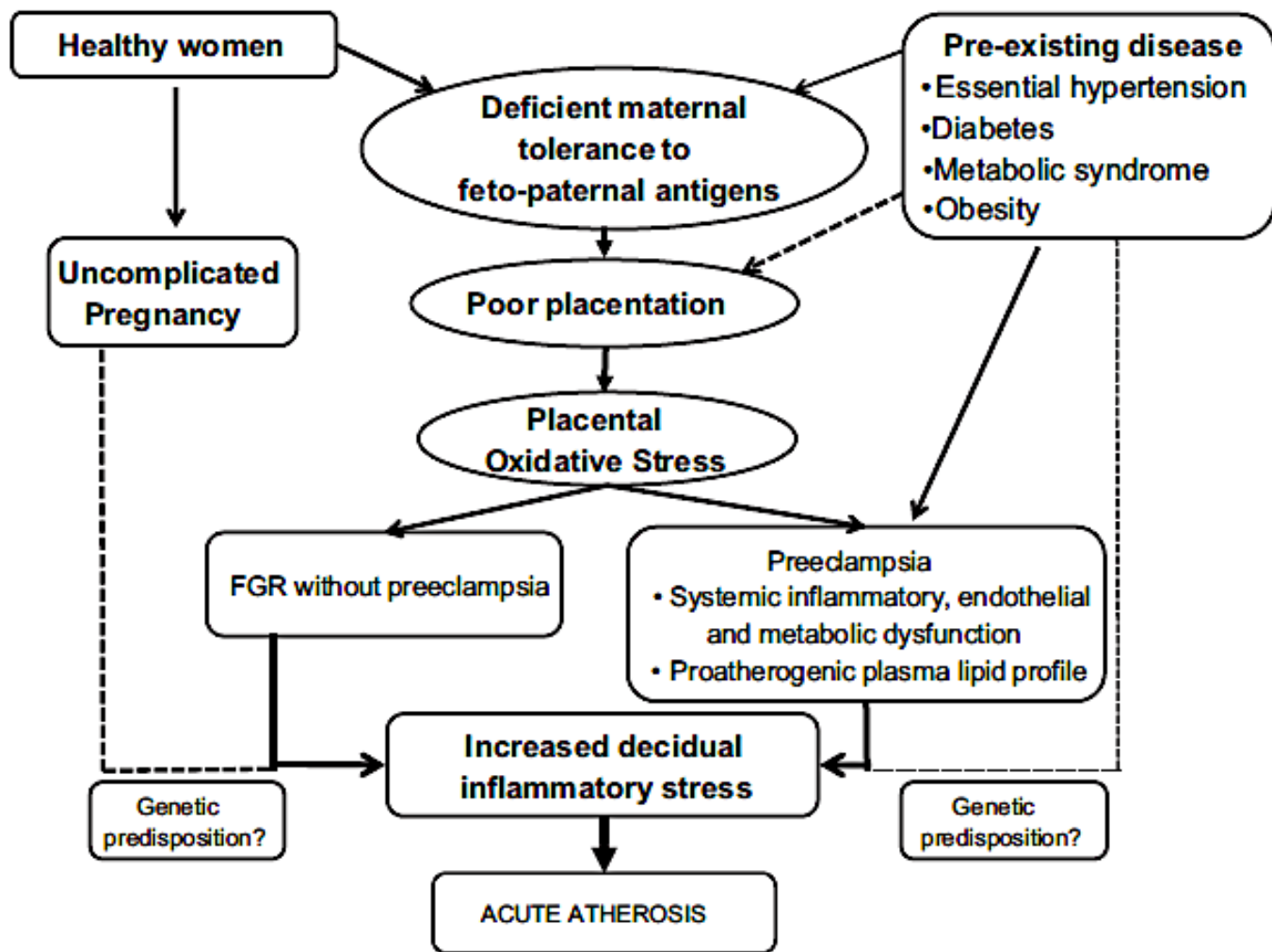


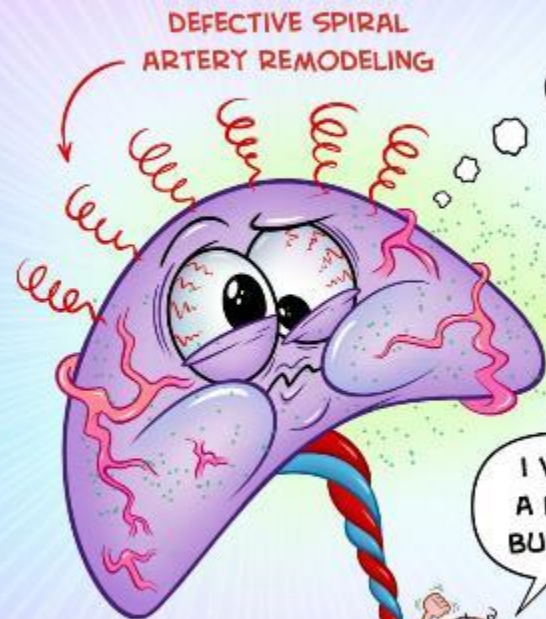


**Preeclampsia is a placental disorder:
lies, damn lies and medical science**





PREECLAMPSIA: PATHOPHYSIOLOGY



CURATIVE TREATMENT IS DELIVERY

SYSTEMIC VASOCONSTRICTION AND ENDOTHELIAL DYSFUNCTION

DISEASED PLACENTA RELEASES PROINFLAMMATORY PROTEINS INTO MATERNAL CIRCULATION



HYPERTENSION AND END-ORGAN DAMAGE



HEMOLYSIS
ELEVATED LIVER ENZYMES
LOW PLATELETS



PROTEINURIA

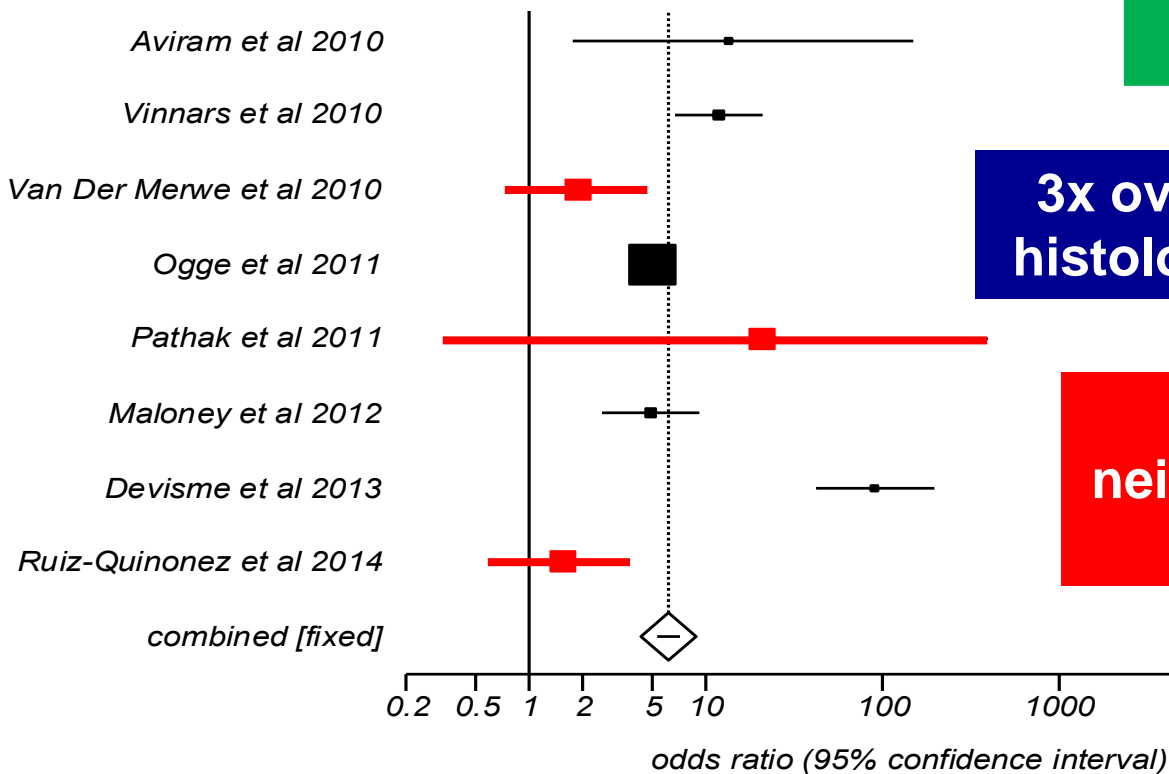
Placental histology

Late-onset preeclampsia

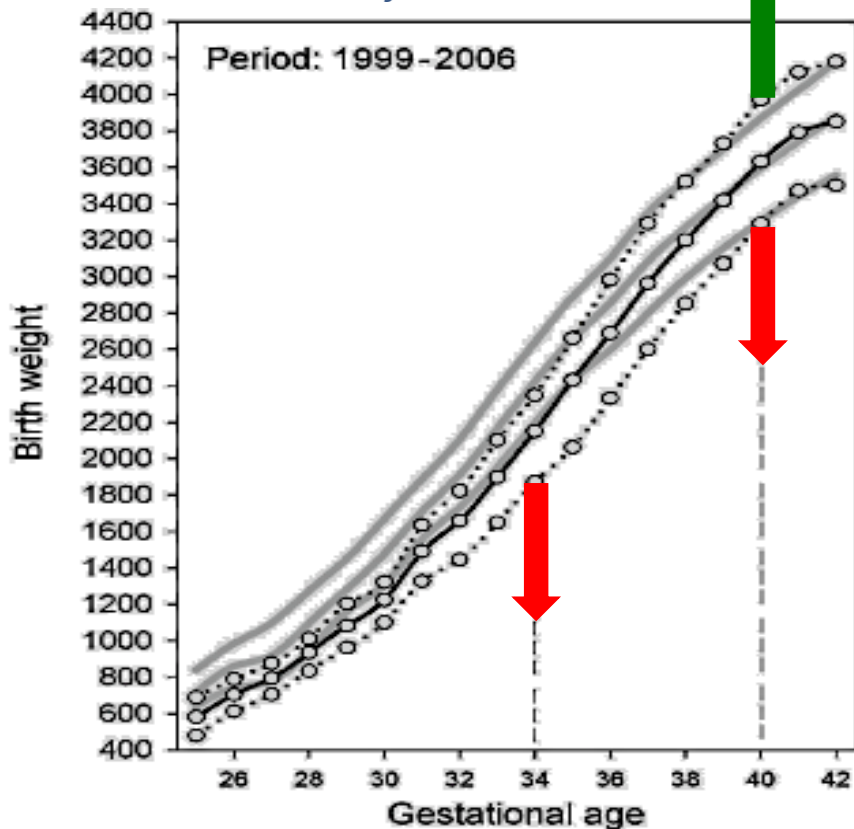
Prevalence of vascular and villous lesions in PE

3x over-reporting of abnormal histology in PE when unblinded

Placental histology is neither sensitive nor specific for preeclampsia



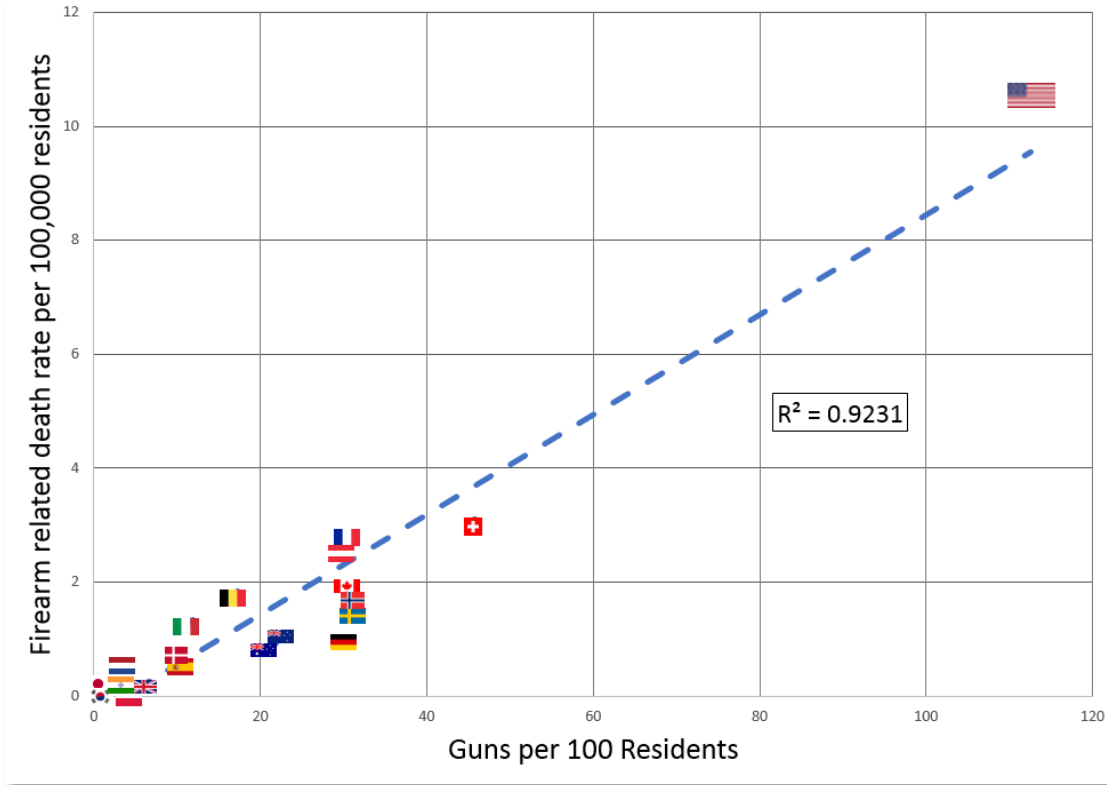
SGA in preeclampsia



Most (80%) of preeclampsia are late-onset

Term PE associated with both LGA and SGA birth (after exclusion of diabetes)

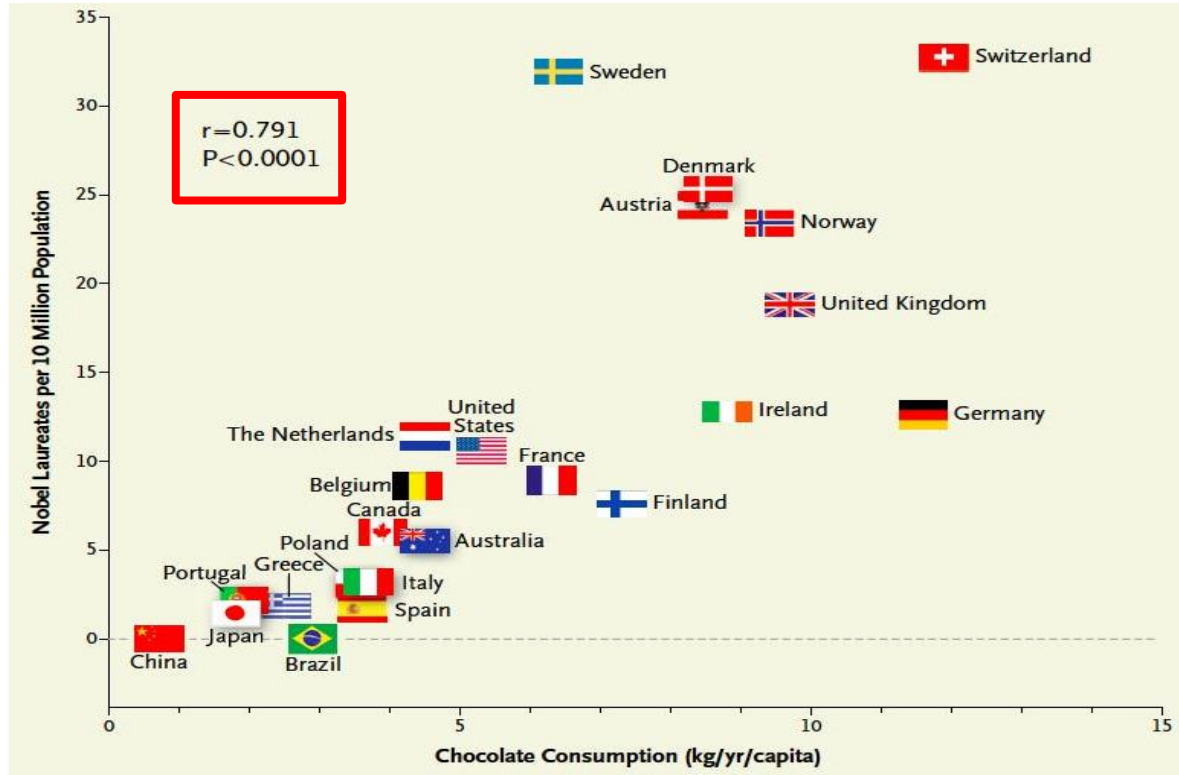
Important correlations





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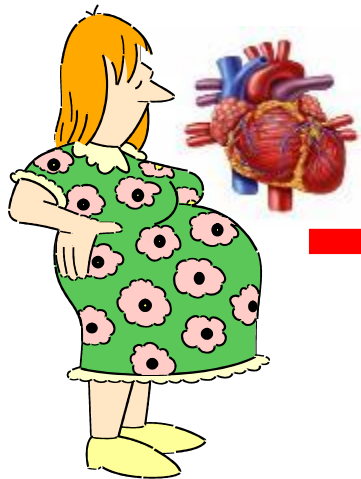
Spurious correlations



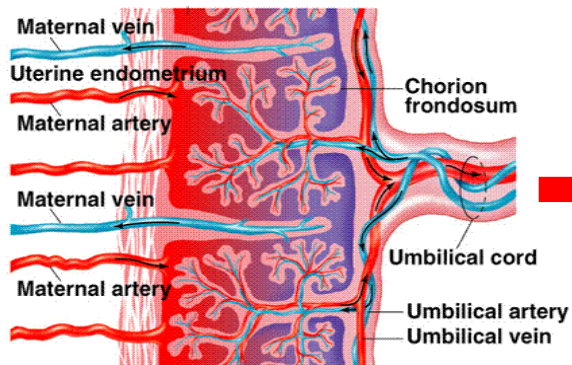
PLEXIT



The placenta Villain or victim?



Cardiac
performance



Placental
function



Fetal
demands



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University of London

Pre-pregnancy

Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction

Fung L. Foo, Amita A. Mahendru, Giulia Masini, Abigail Fraser, Stefano Cacciatore, David A. MacIntyre, Carmel M. McEniery, Ian B. Wilkinson, Phillip R. Bennett, Christoph C. Lees

Preconception Parameter	Normal pregnancy	FGR and preeclampsia	p-value
CO, L/min	5.8 (1.0)	4.9 (0.9)	0.002
CI, L/min per meter ²	3.3 (0.6)	2.9 (0.6)	0.031
HR, bpm	67.3 (10.3)	66.2 (10.4)	0.685
SV, mL	82.2 (14.5)	73.9 (14.6)	0.047
TPR,* dynes-sec-cm ⁻⁵	1156.1 (776.2–1819.7)	1396.4 (891.3–1737.8)	<0.001
Systolic BP, mm Hg	113.6 (10.5)	119.2 (10.5)	0.05
Diastolic BP, mm Hg	66.2 (7.3)	67.0 (7.3)	0.158
MAP, mm Hg	82.3 (7.3)	87.1 (7.3)	0.04

THE ASSOCIATION BETWEEN BIRTHPLACE AND MORTALITY FROM CARDIOVASCULAR CAUSES AMONG BLACK AND WHITE RESIDENTS OF NEW YORK CITY

JING FANG, M.D., SHANTHA MADHAVAN, DR.P.H., AND MICHAEL H. ALDERMAN, M.D.

Lifetime Risks of Cardiovascular Disease

Jarett D. Berry, M.D., Alan Dyer, Ph.D., Xuan Cai, M.S., Daniel B. Garside, B.S.,

C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction

The Emerging Risk Factors Collaboration*

Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors

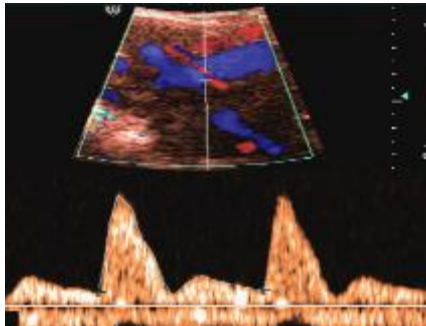
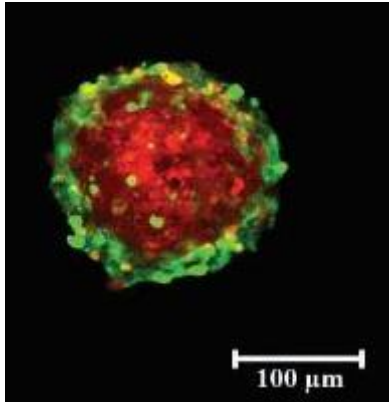
Markus Juonala, M.D., Ph.D., Costan G. Magnussen, Ph.D.,



St George's
University of London

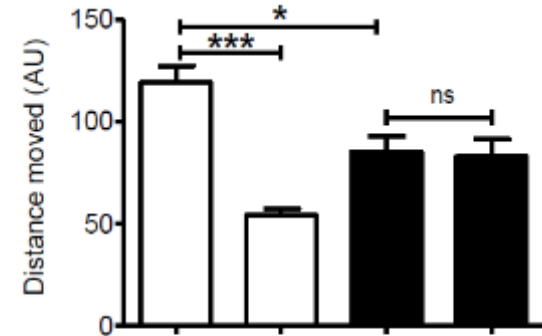
Early pregnancy

Uterine Doppler and Trophoblast Function



Lab Invest. 2018 Oct 5.
 J Leukoc Biol. 2015;97:79-86
 Hum Reprod. 2014 Apr;29(4):652-60
 Am J Pathol. 2013;183:1853-61
 Arterio Thromb Vasc Biol. 2013;33:93-101
 J Pathol. 2012;228:322-32
 Am J Pathol. 2007;170:1903-9

Endothelial cell behaviour and apoptosis



Normal RI CS	+	+	-	-
High RI CS	-	-	+	+
HGF block	-	+	-	+
IgG ₁ control	+	-	+	-

Table II. Histological findings in products of conception from pregnancies with high- and low-resistance uterine artery blood flow examined in the late first trimester

	High-resistance (<i>n</i> = 17)	Low-resistance (<i>n</i> = 14)	<i>P</i> -value
Implantation site identified	13/17 (76%)	12/14 (86%)	0.52
Endovascular trophoblast invasion present	8/13 (62%)	8/12 (67%)	0.79
No. of implantation site vessels per case	9 (3-17)	7 (3-22)	0.44
No. of implantation site vessels with endovascular trophoblast invasion	39/114 (34%)	70/143 (49%)	0.02

Increased Apoptosis, Altered Oxygen Signaling, and Antioxidant Defenses in First-Trimester Pregnancies with High-Resistance Uterine Artery Blood Flow

Karin Leslie,[†] Guy St.J. Whitley,^{*} Florian Herse,[‡] Ralf Dechend,[‡] Sandra V. Ashton,^{*} Ken Laing,[§] Baskaran Thilaganathan,[†] and Judith E. Cartwright^{*}

Elevated glucocorticoid metabolism in placental tissue from first trimester pregnancies at increased risk of pre-eclampsia

S. Mukherjee^{a,b,*}, J.L. James^c, B. Thilaganathan^{a,b}, G.St.J. Whitley^c, A.E. Michael^c, J.E. Cartwright^c

Cell Injury, Repair, Aging and Apoptosis

Increased Apoptosis in First Trimester Extravillous Trophoblasts from Pregnancies at Higher Risk of Developing Preeclampsia

Decidual Natural Killer Cell Interactions with Trophoblasts Are Impaired in Pregnancies at Increased Risk of Preeclampsia

Alison E. Wallace, Amanda J. Host, Guy S. Whitley, and Judith E. Cartwright

Decidual cell regulation of trophoblast is altered in pregnancies at risk of pre-eclampsia

Alison E. Wallace,¹ K. Leslie^{1,2}, A. E. Wallace¹ and J. E. Cartwright¹

Impaired decidual natural killer cell regulation of vascular endothelial cells in early human pregnancies with high uterine artery blood flow

Krupna Fraser,¹ Guy St. J. Whitley,¹ Alan P. Johnstone,¹ Amanda J. Host,¹ Neil J. Sebire,² Baskaran Thilaganathan,³ and Judith E. Cartwright^{1*}

Placental endothelial cells from pregnancies with high uterine artery Doppler are more sensitive to apoptotic stimuli

A. J. Host^{1,2} · Sandra Ashton¹ · Zoe Tryfonos¹ · Karin Leslie³ · Baskaran Thilaganathan^{1,3} · Guy St. J. Whitley^{1*}

Decidual natural killer cells regulate vessel stability: implications for impaired spiral artery remodelling in pregnancies at risk of pre-eclampsia

Alison E. Wallace,¹ Guy St.J. Whitley^a, Baskaran Thilaganathan^b, and Judith E. Cartwright^{a,*}

^aDepartment of Cell Sciences, St. George's, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom
^bDepartment of Obstetrics and Gynaecology, St. George's Hospital, Blackshaw Road, London SW17 0QT, United Kingdom





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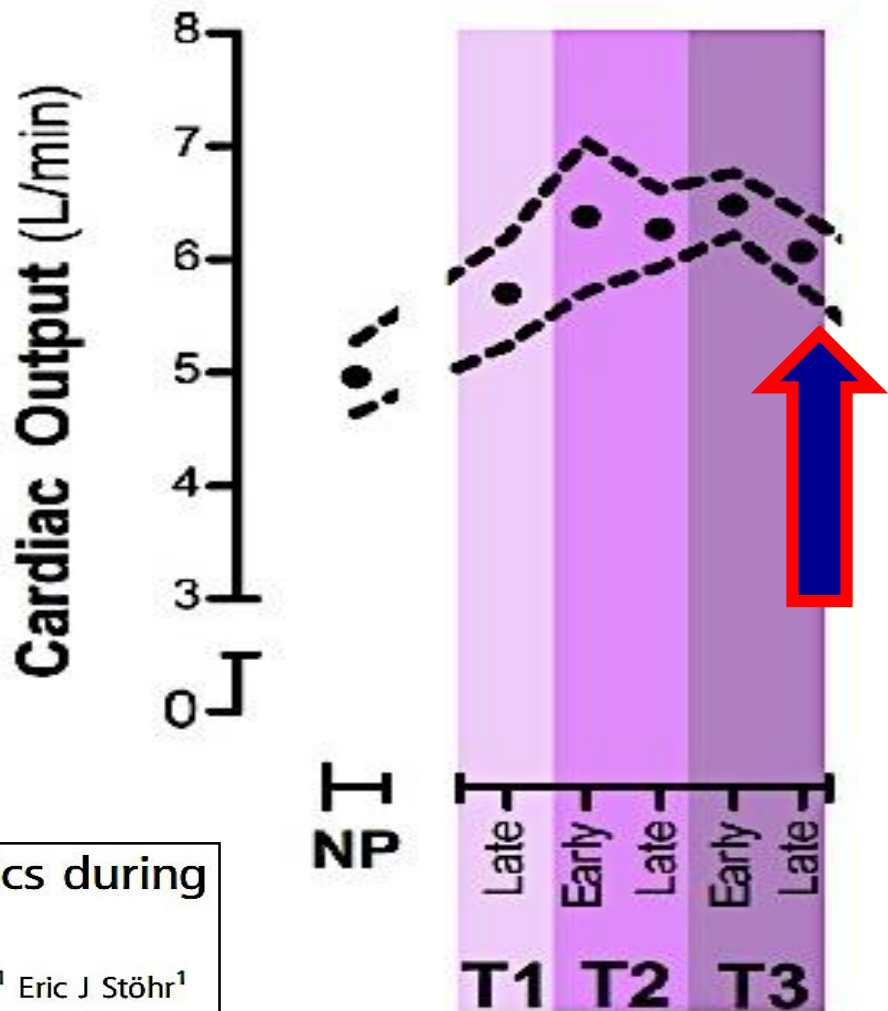
Late pregnancy

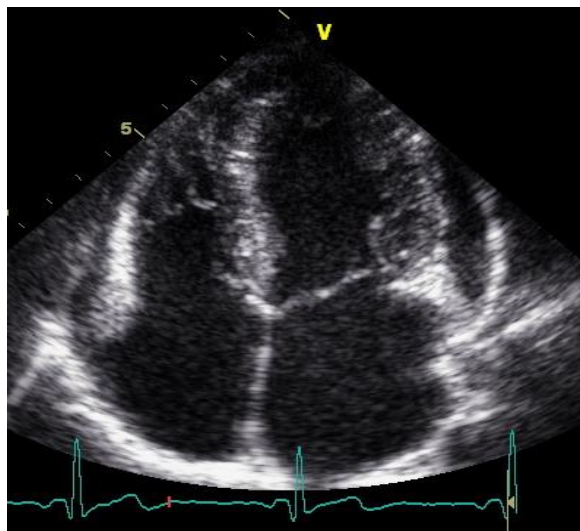
39 studies
3082 patients

Paradoxical drop in
cardiac output at term

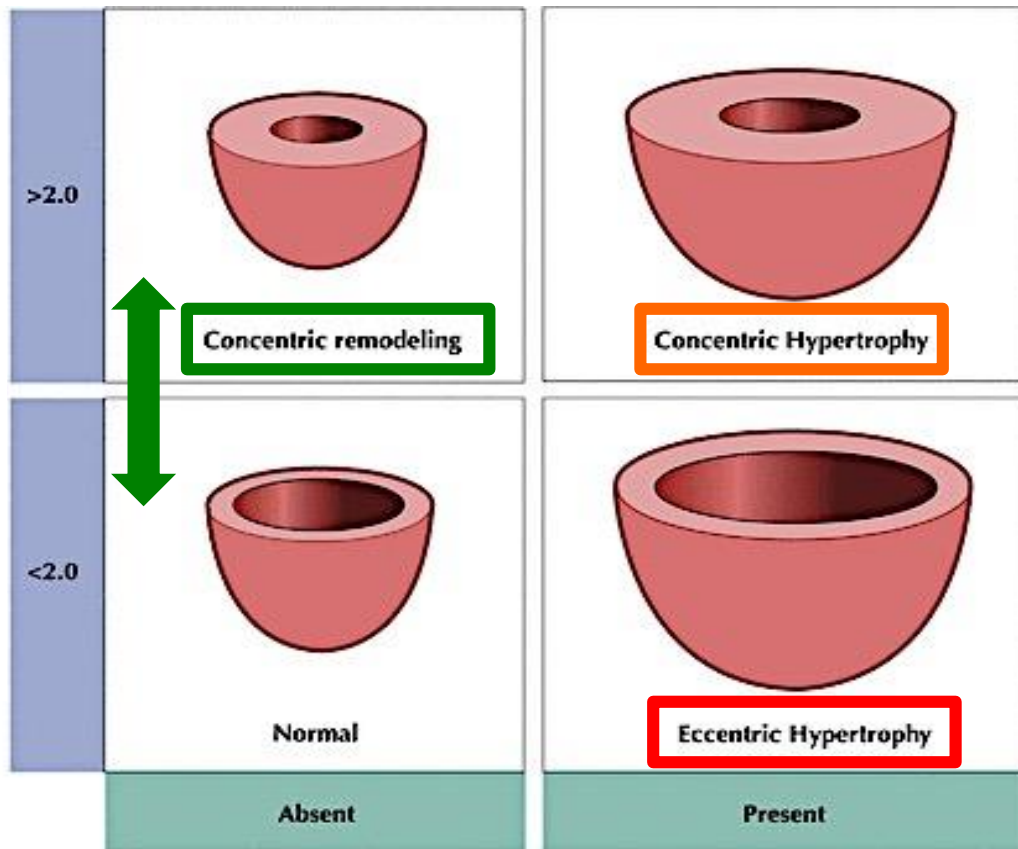
Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses

Victoria L Meah,¹ John R Cockcroft,² Karianne Backx,¹ Rob Shave,¹ Eric J Stöhr¹



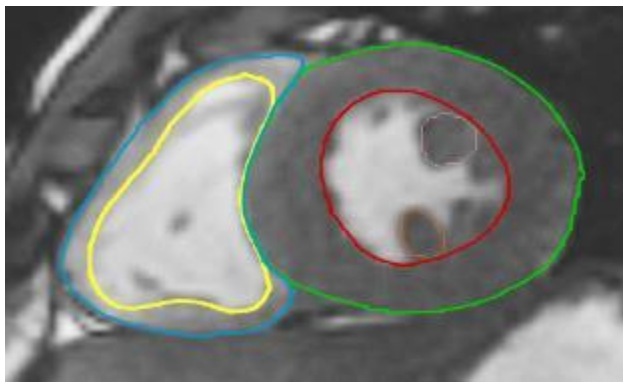


Relative wall thickness



Left ventricular mass

Hypertension. 2016;67:754-762.



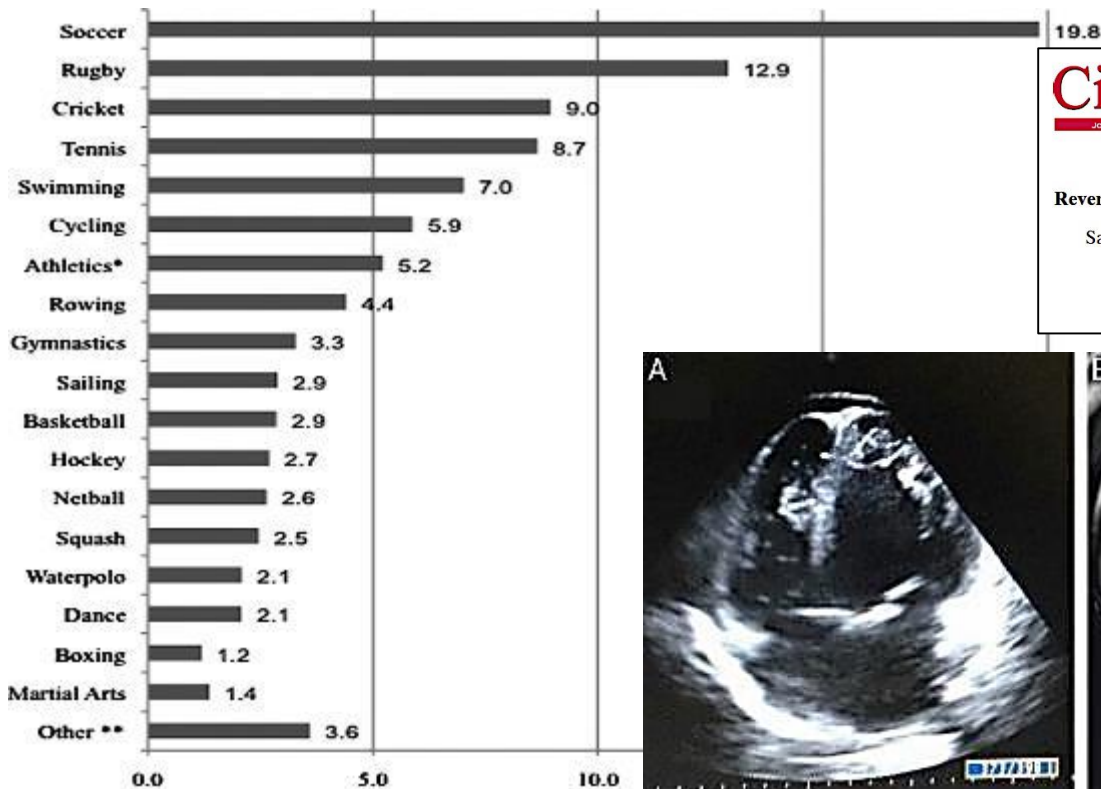
LV mass increase
40% in pregnancy (9 months)
25% in elite athletes (24 months)

Table 1. Hemodynamic, Geometric Indices, and Indices Describing Global Pump Performance (Chamber Function) of Study Groups

Parameter	NPC	T1	T2	T3	Term	PPC	PValue
LVM, g	88 (71–110)	103 (83–127)*	106 (92–127)*	110 (88–130)*	123 (104–143)*†‡§	105 (84–117)*†§	<0.001
LVMI, g/m ²	60 (57–78)	70 (59–85)*	71 (61–82)*	70 (54–80)	69 (55–77)	63 (56–76)†‡	0.006
RWT	0.32 (0.27–0.36)	0.33 (0.30–0.37)*	0.33 (0.29–0.37)	0.36 (0.31–0.43)*†‡	0.37 (0.31–0.38)*	0.33 (0.26–0.38)§	0.001

Term Pregnancy

25% trabeculations



Circulation

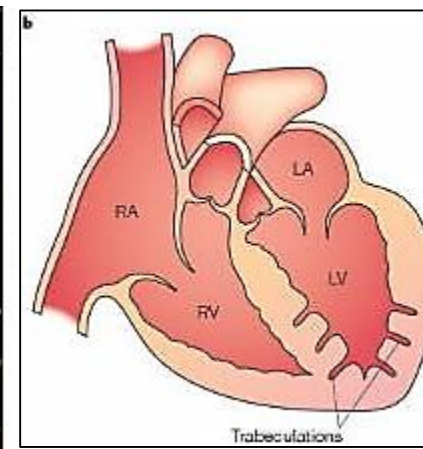
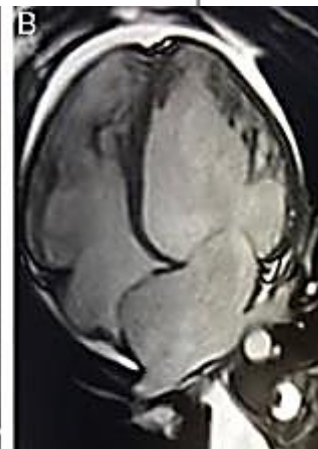
JOURNAL OF THE AMERICAN HEART ASSOCIATION



Reversible De Novo Left Ventricular Trabeculations in Pregnant Women: Implications for the Diagnosis of Left Ventricular Noncompaction in Low-Risk Populations

Sabiha Gati, Michael Papadakis, Nikolaos D. Papamichael, Abbas Zaidi, Nabeel Sheikh, Matthew Reed, Rajan Sharma, Baskaran Thilaganathan and Sanjay Sharma

Circulation. 2014;130:475-483; originally published online July 8, 2014;





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Myocardial vs chamber function

Impaired myocardial relaxation

Impaired myocardial contraction
(+relaxation)

Chamber diastolic dysfunction

Chamber systolic (+diastolic)
dysfunction

Melchiorre K *et al.*
Hypertension 2016

Asymptomatic diastolic
dysfunction in 10-15%
of women at term



Shortness
of breath



Swelling of
feet & legs



Chronic lack
of energy



Difficulty sleeping
at night due to
breathing problems



Increased
urination
at night



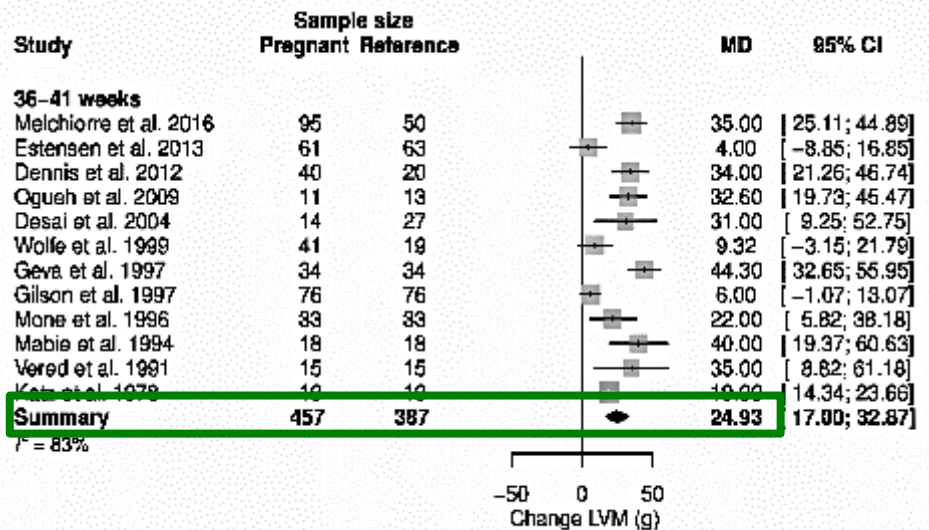
Confusion and/or
impaired memory



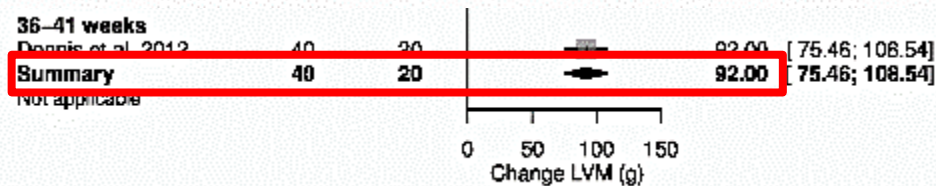
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Cardiac function in preeclampsia

Remodelling in preeclampsia

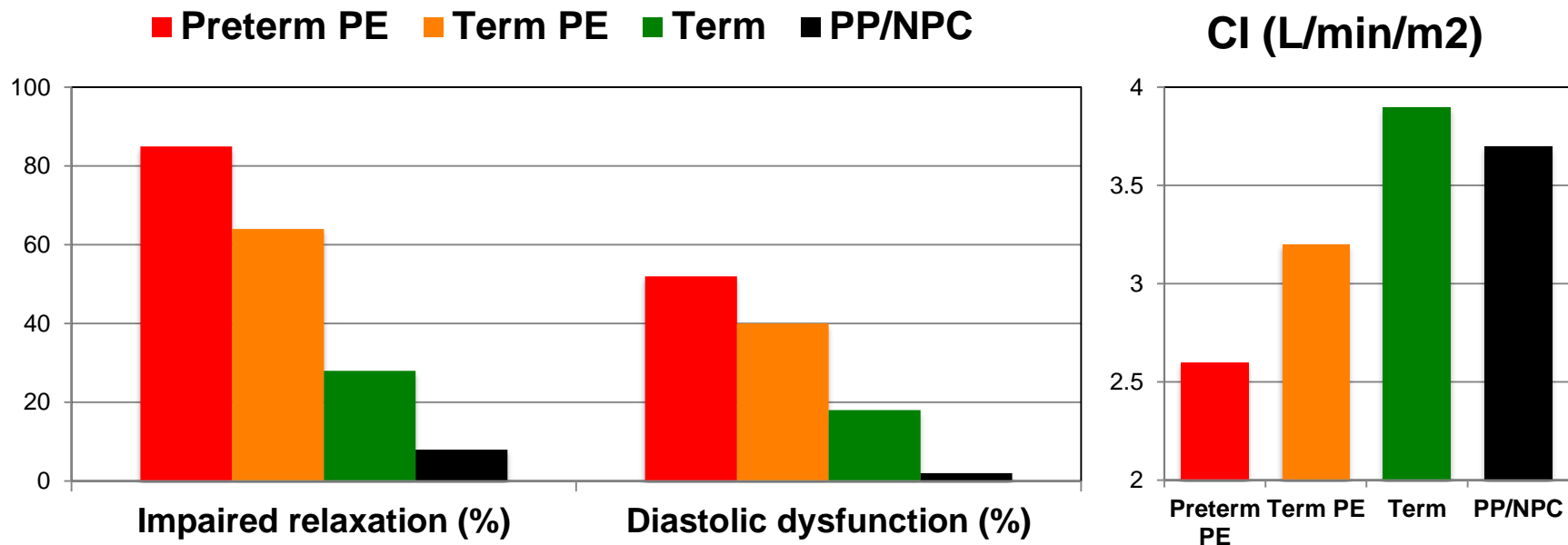


LVM increases by 71% and RWT by 46% more in preeclampsia than during a normotensive pregnancy



**De Haas et al. UOG 2018
Meta-analysis of 48 studies**

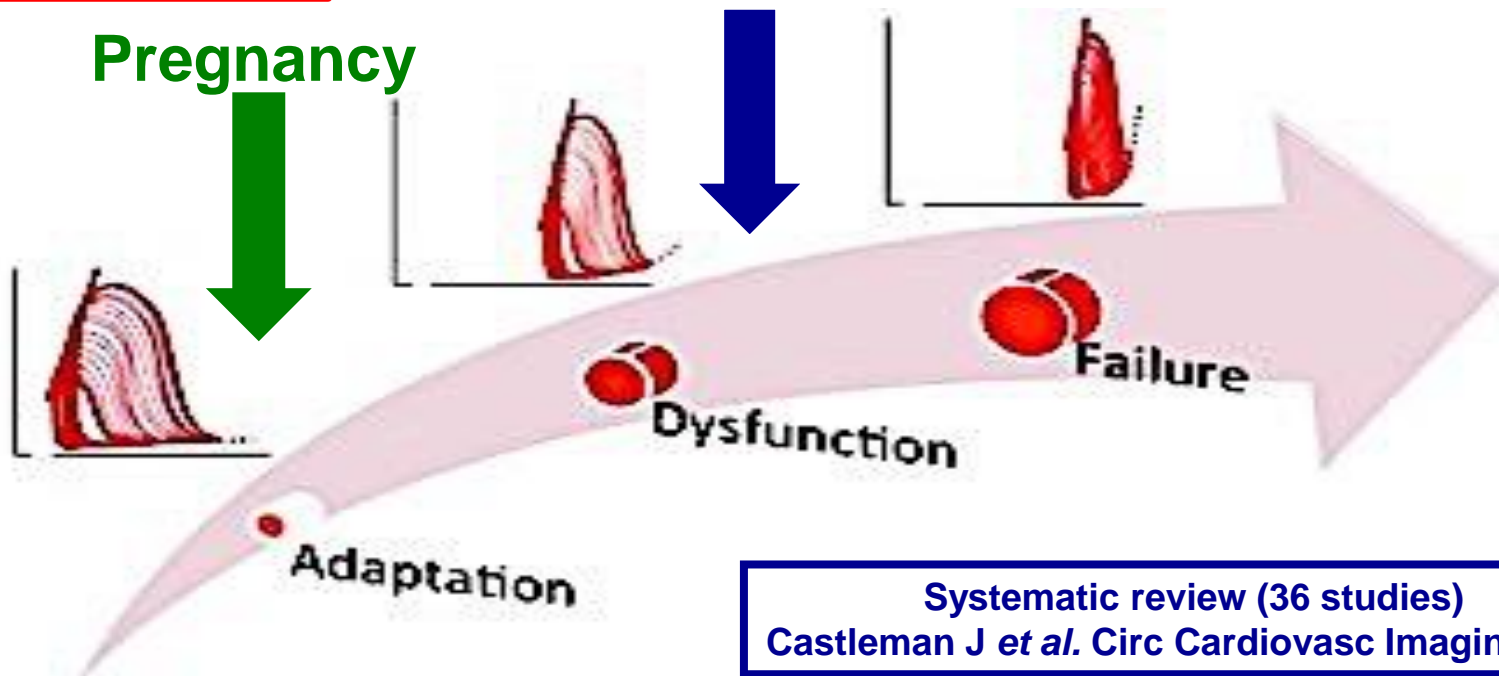
Myocardial function in preeclampsia



Maternal cardiac dysfunction

De Haas *et al.* UOG 2018
Meta-analysis (48 studies)

FGR and
Preeclampsia



Systematic review (36 studies)
Castleman J *et al.* Circ Cardiovasc Imaging 2016

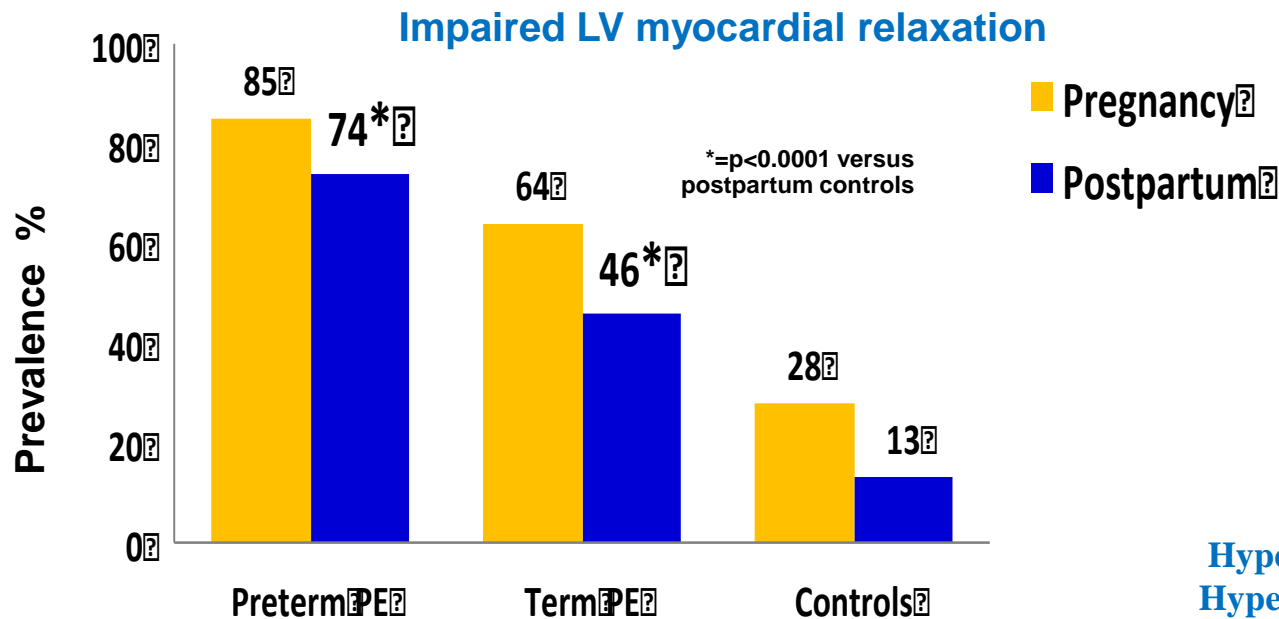


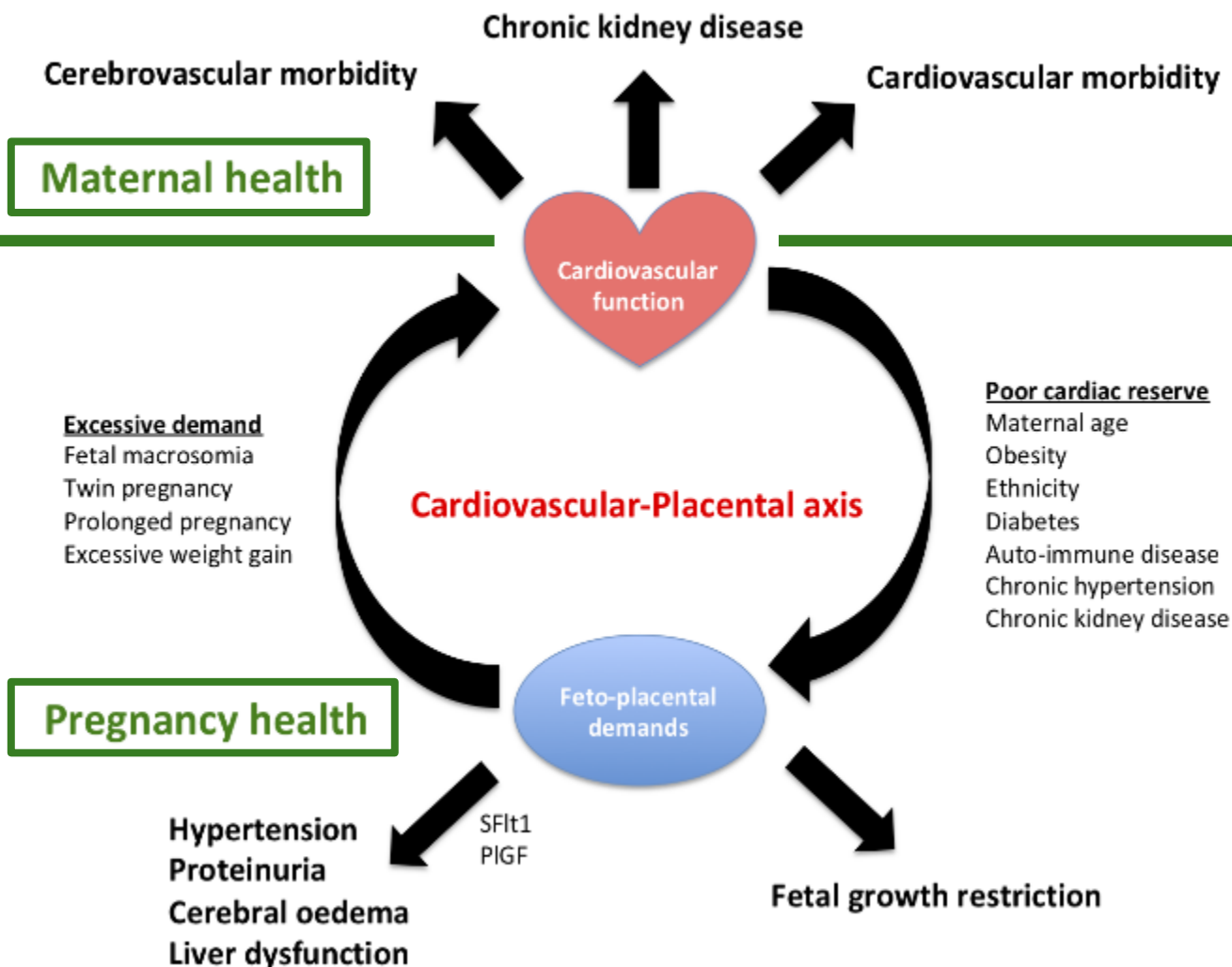
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Post-partum

Cardiac function one year after preeclampsia

- Impaired myocardial relaxation persisted in term and preterm PE
- Impaired myocardial contractility persisted in preterm PE





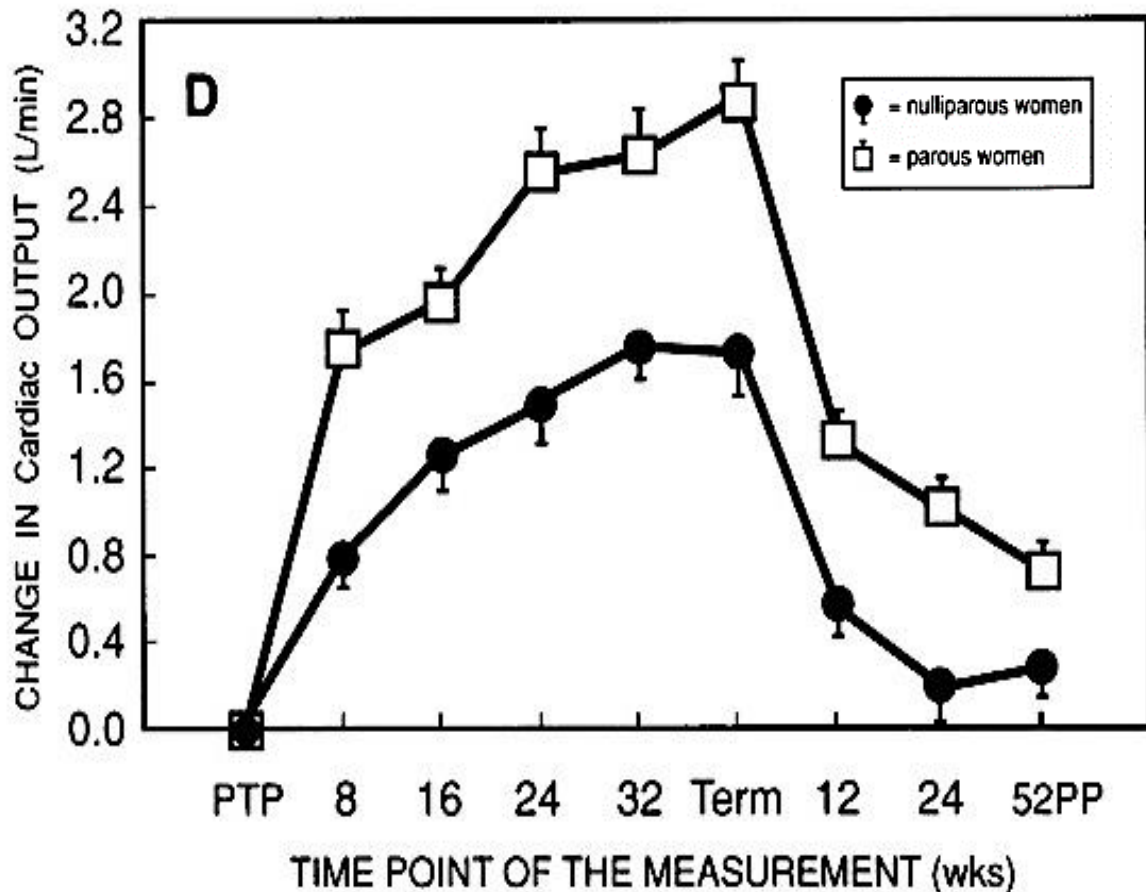
'Placental' disorders

	GDM	HDP
Definition	New onset abnormal glucose >20wks	New onset abnormal BP >20wks
Predisposing factors	Same as for type 2 diabetes mellitus	Same as for cardiovascular disease
Screening test	GTT (measures pancreatic function)	BP and Uterine Doppler (measures cardiac function)
Diagnosis	High glucose levels	High BP levels
Pre-pregnancy disease	More severe pregnancy phenotype	More severe pregnancy phenotype
'Cure'	Birth	Birth
Maternal Long-term	50% risk of diabetes in 10 years	30% risk of hypertension in 10 years

Longitudinal study
15 nullips, 15 multips
Started pre-pregnancy
9 time points
270 echocardiograms
“Pre-conditioning”

Clapp AF. *Am J Cardiol.* 1997 (n=30)
Turan OM *et al.* *UOG.* 2008 (n=4689)
Ling HZ *et al.* *AmJOG.* 2109 (n=1574)

Nulliparity

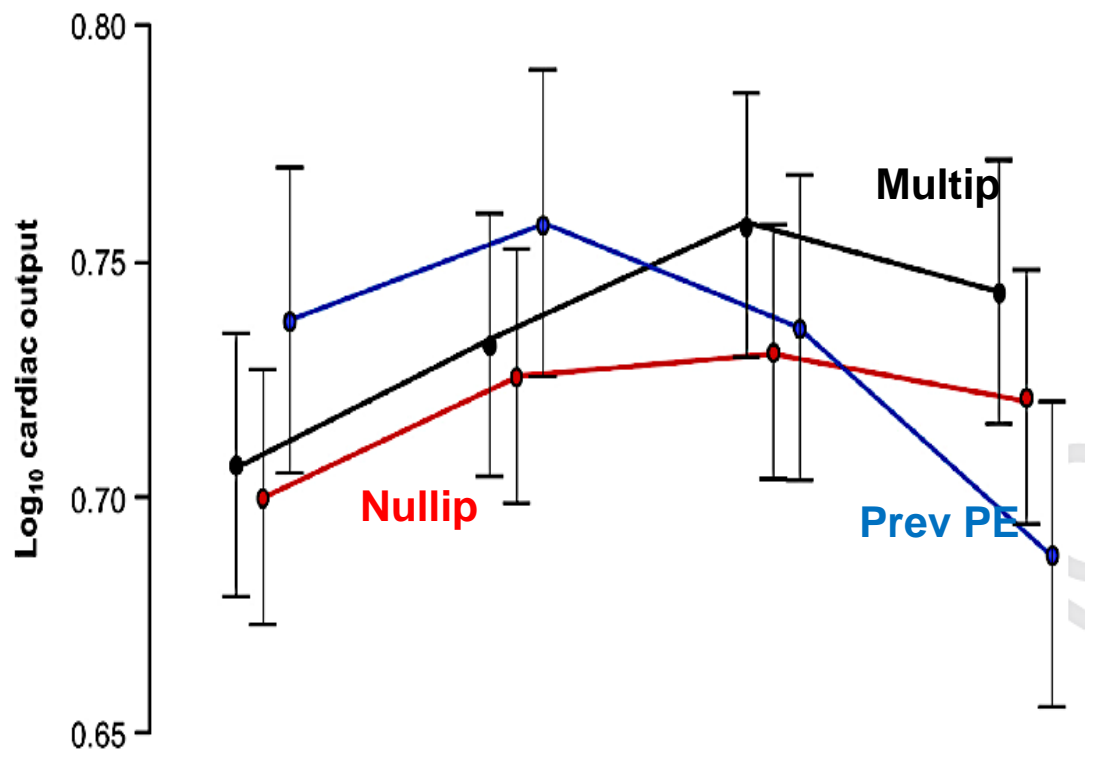


Longitudinal study
829 nullips, 632 multips
113 prev PE+/-SGA

“Multipara have the optimal haemodynamic response to pregnancy”

Ling HZ et al. AmJOG. 2109 (n=1574)

FIGURE 1
Model for Log₁₀ cardiac output and Log₁₀ peripheral vascular resistance



Partner specificity

THE INTERVAL BETWEEN PREGNANCIES AND THE RISK OF PREECLAMPSIA
(N Engl J Med 2002;346:33-8.)

ROLV SKJÆRVEN, PH.D., ALLEN J. WILCOX, M.D., PH.D., AND ROLV T. LIE, PH.D.

**Increase in PE risk explained
by inter-pregnancy interval**



VARIABLE	MEDIAN TIME BETWEEN PREGNANCIES (YR)	PREECLAMPSIA IN LATER PREGNANCY		
		NO. OF CASES OF PREECLAMPSIA	NO. OF DELIVERIES	RISK OF PREECLAMPSIA (%)
From 1st to 2nd pregnancy				
Same partner	2.9	6237	490,845	1.3
Different partners	5.9	443	30,526	1.5

IVF and ovum donation

26,696 IVF/ICSI

999,804 controls

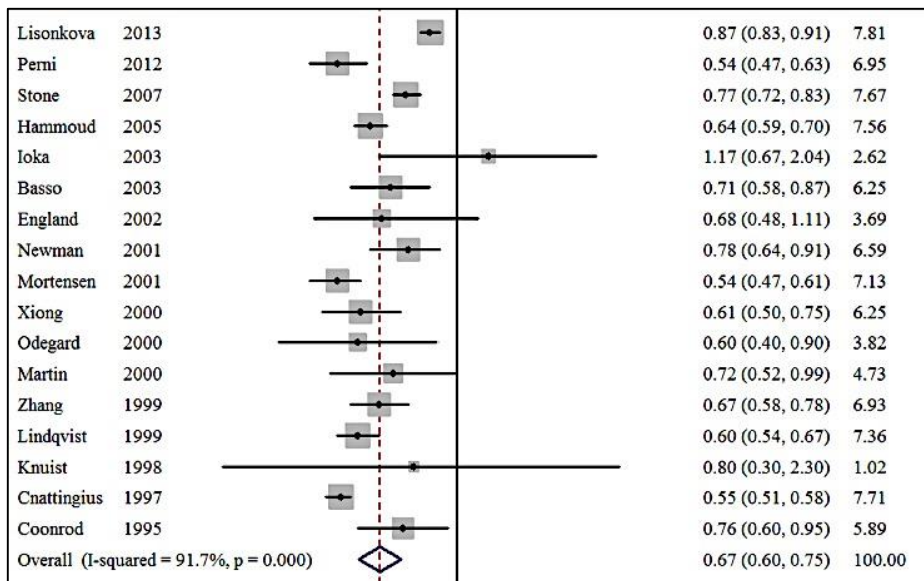
PE risk conferred by
ovum donation, not IVF

Outcome	OD vs. IVF/ICSI Adjusted OR (95% CI)	OD vs. spontaneous conception Adjusted OR (95% CI)
Caesarean section	2.37 (1.93–2.92)	2.37 (1.93–2.91)
Preeclampsia	3.05 (2.23–4.16)	2.84 (2.10–3.84)
Gestational diabetes	1.04 (0.46–2.38)	0.96 (0.43–2.18)

High risks of maternal and perinatal complications in singletons born after oocyte donation

SARAH NEJDET¹, CHRISTINA BERGH¹, KARIN KÄLLÉN², ULLA-BRITT WENNERHOLM³ & ANN THURIN-KJELLBERG¹

33% reduction in PE



Leffler CW *et al.* Am J Physiol Heart 2011
Wei J *et al.* Oncotarget 2015



Immediate effects (minutes)

Vasconstriction – nicotine

Short-term effects (hours/days)

Hypotension – carbon monoxide



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**Placenta or heart:
Does it really matter?**

Conventional risk assessment

Low Risk

- No known risk factors

Increased Risk: one or more of the following:

Maternal Risk Factors

- Maternal age >40 years
- Ongoing smoker (at booking)
- Drug misuse

Previous Pregnancy History

- Previous SGA baby (<10th centile)
- Previous stillbirth

Maternal Medical History

- Chronic hypertension
- Diabetes
- Renal impairment
- Antiphospholipid syndrome

Unsuitable for monitoring by fundal height- e.g.

- Large fibroids
- BMI >35

Current Pregnancy Complications

Early Pregnancy

- PAPP-A <0.415 MoM
- Fetal echogenic bowel

Late Pregnancy

- Severe pregnancy induced hypertension or pre-eclampsia (=PIH and proteinuria)
- Unexplained antepartum haemorrhage



Royal College of
Obstetricians &
Gynaecologists

Royal College
of OBSTETRICIANS
and GYNAECOLOGISTS



Hypertension in pregnancy:
the management of hypertensive
disorders during pregnancy

August 2010 (revised reprint January 2011)

NICE Clinical Guideline

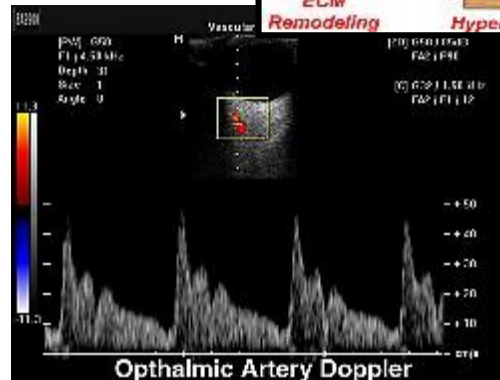
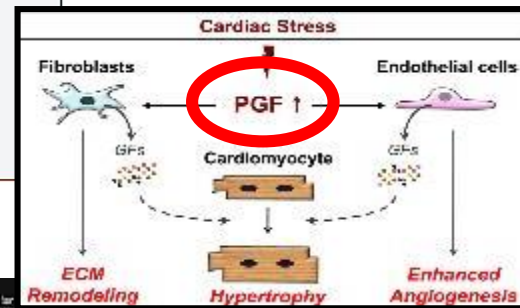
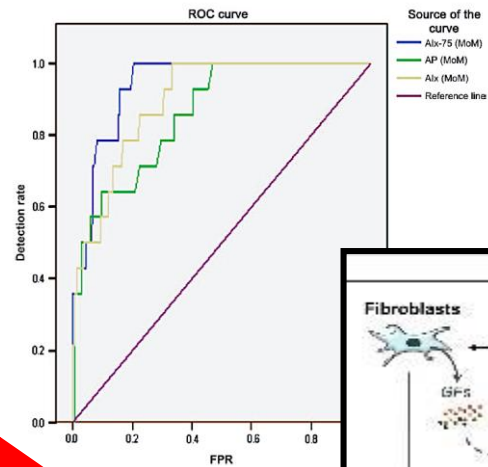
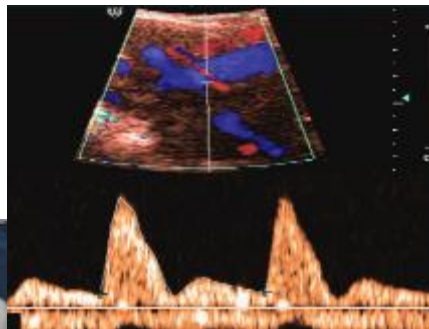
Risks treated as equal
Modest risk elevation
Interaction of factors
Risk elevation only

High false +ve rate (60%)
Low detection (40%)
Aspirin prescription (15%)
Aspirin compliance (?)



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ASPRE screening



Rolnik D *et al.* NEJM 2018
Kalafat E *et al.* UOG 2018
Khalil A *et al.* BJOG 2008

Radial and Ophthalmic Arteries

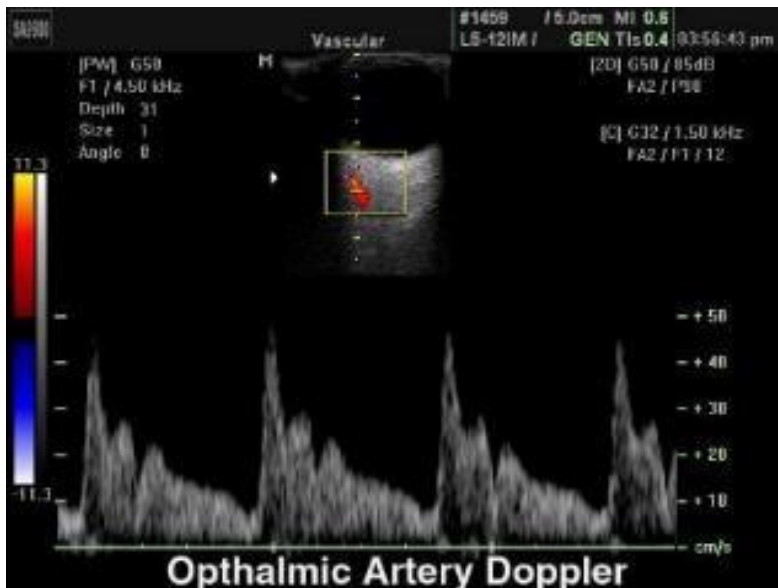
Maternal ophthalmic and radial artery Doppler at 11-13 weeks is as good as uterine Doppler in prediction of preeclampsia

Maternal hemodynamics at 11–13 weeks' gestation and risk of pre-eclampsia

A. KHALIL*, R. AKOLEKAR†, A. SYNGELAKI†, M. ELKHOULI† and K. H. NICOLAIDES*†

Ophthalmic artery Doppler for prediction of pre-eclampsia: systematic review and meta-analysis

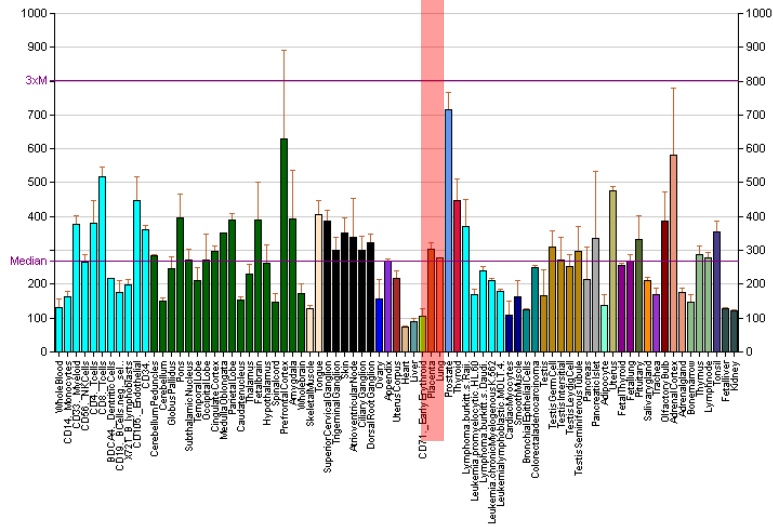
E. KALAFAT^{1,2,3}Ⓢ, A. LAORETTI^{1,2}, A. KHALIL^{1,4}Ⓢ, F. DA SILVA COSTA⁵ and B. THILAGANATHAN^{1,4}



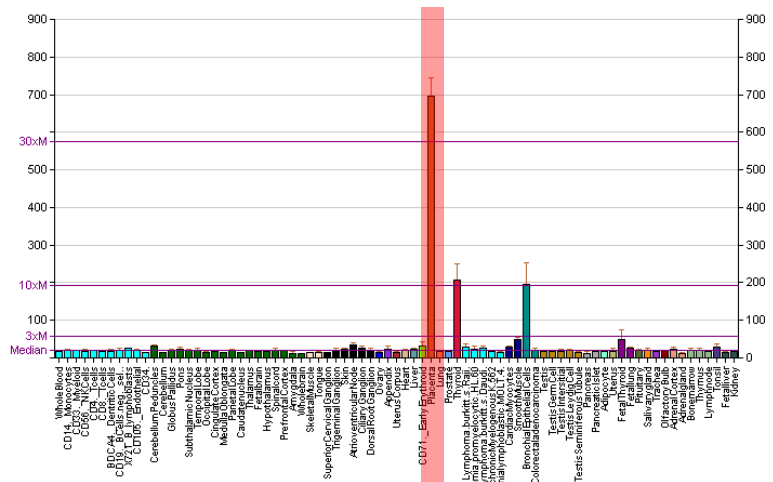
Placental surface 12-15m²
Capillary surface 6000-7000m²
(x500 higher surface area)

PIGF protein produced equally
by endothelium of most organs

PIGF protein expression



PIGF RNA expression



ASPREScreening

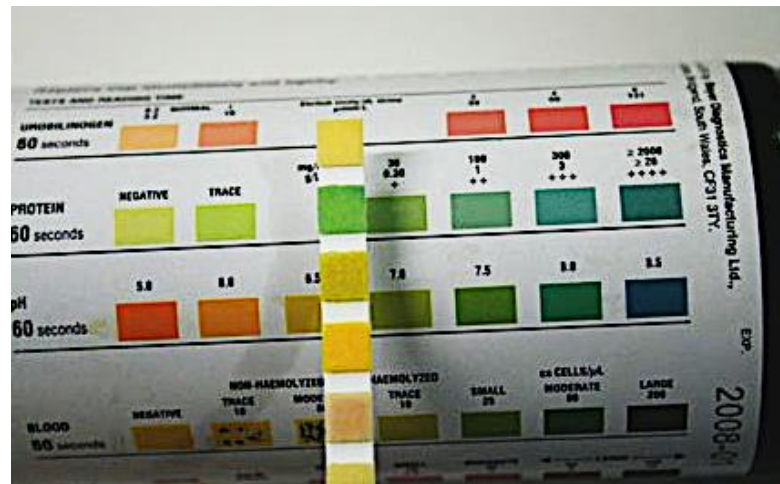
Implementation at StGeorges

11-14wk scan - FMF Algorithm (History, UtA Doppler, MAP, PAPP-A)

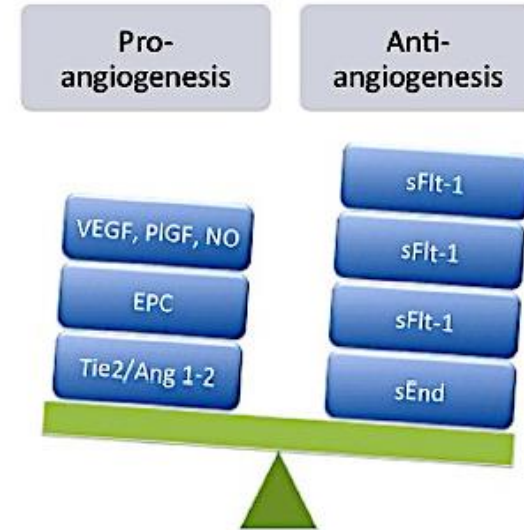
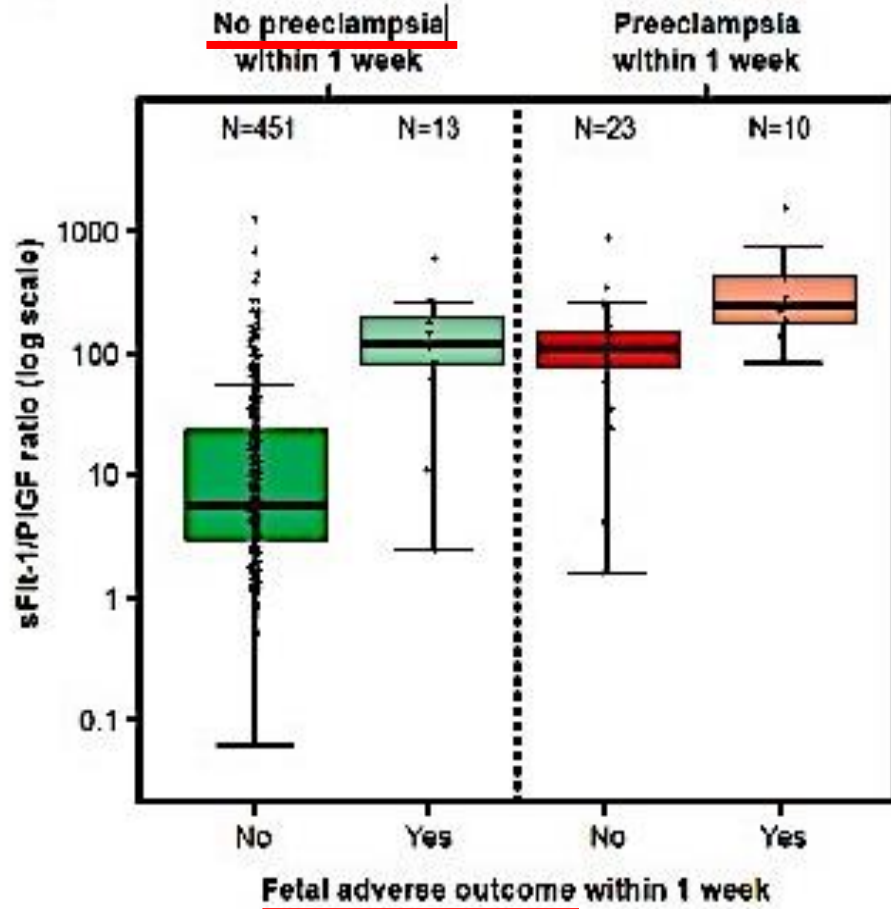
	2017-2018 Routine care	2019 ASPREScreen	
Pregnancies	8110	3260	
Preterm PE (<37wks)	61 (0.75%)	15 (0.46%)	↓ 40%
Term PE (>37wks)	167 (2.1%)	50 (1.5%)	↓ 30%

Potential therapies: Aspirin, Calcium, Statins, Metformin

Diagnosis and prognosis



Diagnosis



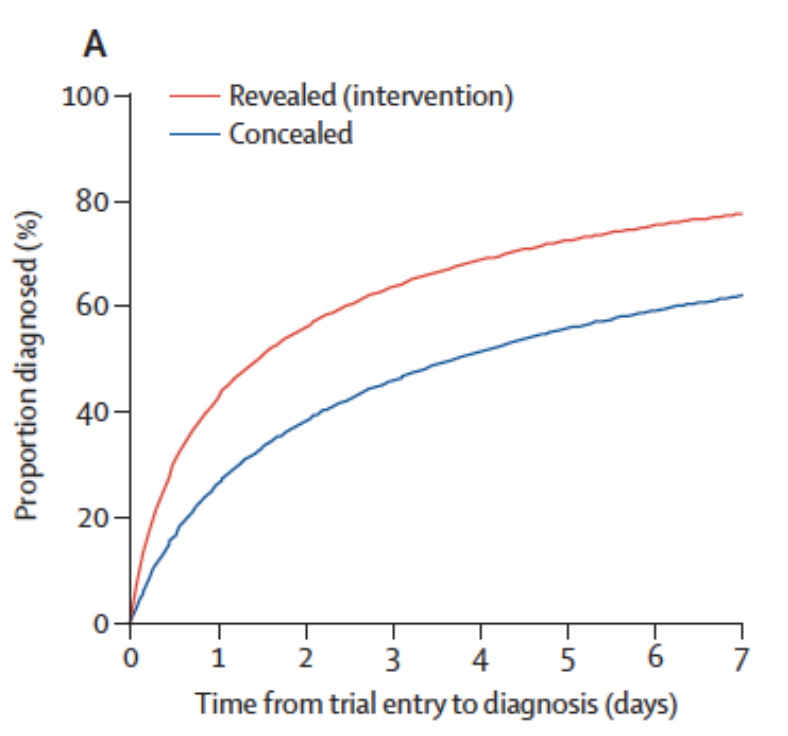
The **NEW ENGLAND**
JOURNAL *of* **MEDICINE**

ESTABLISHED IN 1812

JANUARY 7, 2016

VOL. 374 NO. 1

Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia

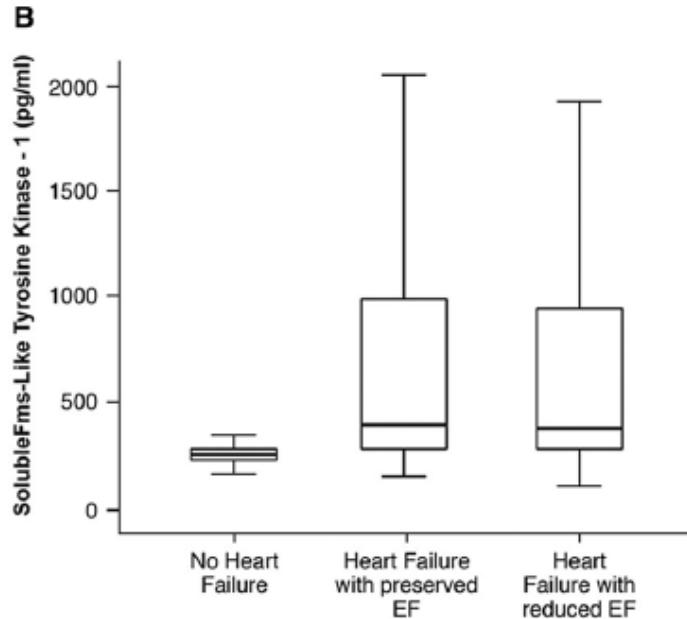
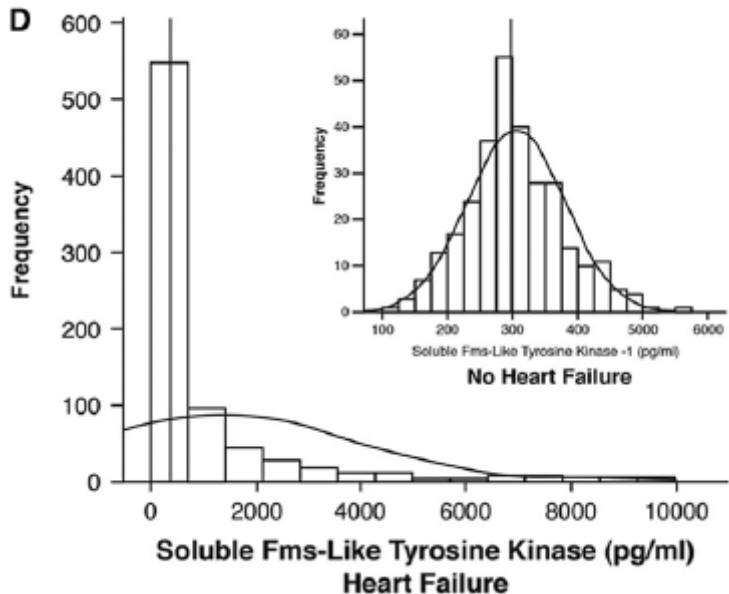


	Revealed PIGF (intervention; n=573)	Concealed PIGF (n=446)
Number of women with maternal adverse events	0	4 (1%)
Maternal death	0	0
Maternal stroke	0	2 (<1%)
Maternal cardiac arrest	0	1 (<1%)*
Eclampsia	0	2 (<1%)
Number of babies with perinatal serious adverse events	10 (2%)	7 (2%)

Use of PIGF permitted earlier delivery and improved maternal outcomes

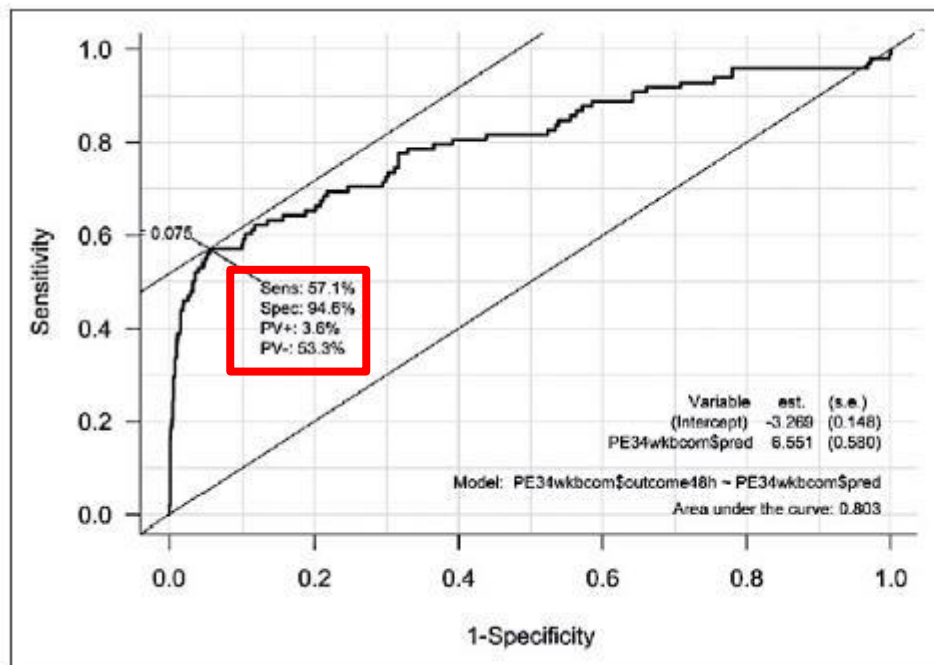
Elevated Soluble Fms-Like Tyrosine Kinase-1 and Placental-Like Growth Factor Levels Are Associated With Development and Mortality Risk in Heart Failure

Muhammad Hammadah, MD; Vasiliki V. Georgiopoulou, MD, MPH, PhD;



Assessment of the fullPIERS Risk Prediction Model in Women With Early-Onset Preeclampsia

U. Vivian Ukah, Beth Payne, Jennifer A. Hutcheon, J. Mark Ansermino, Wessel Ganzevoort, Shakila Thangaratnam, Laura A. Magee, Peter von Dadelszen



1388 preeclampsia cases
7.3% adverse maternal outcome



Table 3. Schemes of Oral Antihypertensive Medication in Mild-to-Moderate Hypertension in Pregnancy (SBP between 140 and 159 mm Hg or DBP between 90 and 109 mm Hg)

Drug	Starting Oral Dose	Intervals	Maximum Total Dose/Die	Maternal Adverse Effects
Labetalol	100 to 400 mg	2 to 4 times daily	1200 mg/d	Headache
Alfametildopa	250 to 500 mg	2 to 4 times daily	2000 mg/d	Maternal sedation, elevated liver function enzymes, depression
Intermediate-acting nifedipine	10 to 20 mg	2 to 3 times daily	Maximum 120 mg/d	Headache
Long-acting Nifedipine	20 to 60 mg	1 time daily	Maximum 120 mg/d	Headache

In the absence of comorbidities, whether BP targets should be high normotension (85 mm Hg DBP) or nonsevere hypertension (105 mm Hg DBP) is not standardized. Data from the Cochrane Database Systematic Review on Antihypertensive drug therapy for mild-to-moderate hypertension during pregnancy (2007),⁷¹ unless otherwise stated. The illustrated schemes of treatments are recommended by the **Society of Obstetricians and Gynecologists of Canada (SOGC guidelines, 2008),⁶ American College of Obstetricians and Gynecologists (ACOG guidelines, 2012),⁷² and UK National Institute of Clinical Excellence (NICE guidelines, 2011)⁴ with minimal differences. In particular, for ACOG 2012, the maximum total dose/die for labetalol is 2000 mg and for alfametildopa is 3000 mg/die.⁷² BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.**

Cardiovascular Management in Pregnancy

Cardiovascular Implications in Preeclampsia

An Overview

Karen Melchiorre, MD, PhD; Rajan Sharma, MD, MRCP; Basky Thilaganathan, MD, PhD, FRCOG

(*Circulation*. 2014;130:703-714.)

Cardiovascular Management in Pregnancy

Cardiovascular Implications in Preeclampsia An Overview

Karen Melchiorre, MD, PhD; Rajan Sharma, MD, MRCP; Basky Thilaganathan, MD, PhD, FRCOG

(Circulation. 2014;130:703-714.)

Tissue oxygen delivery



$$\text{BP} = \text{CO} \times \text{SVR}$$

blood
pressure

cardiac output

SV x HR
stroke
volume heart
rate

systemic vascular
resistance

Treatment of BP

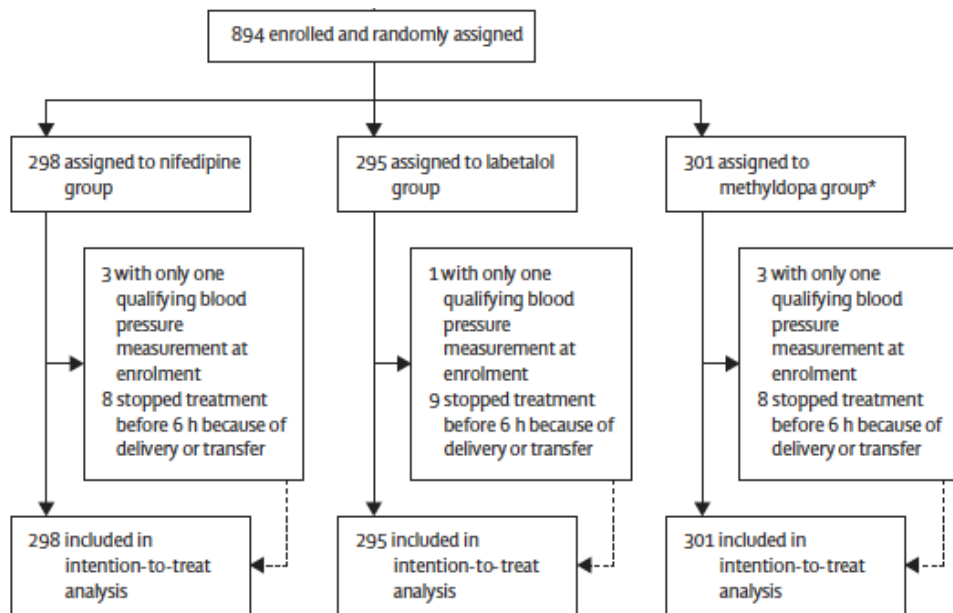
Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial

Thomas Easterling, Shuchita Mundle, Hillary Bracken, Seema Parvekar, Sulabha Mool, Laura A Magee, Peter von Dadelszen, Tara Shochet,

All three drugs achieved the primary outcome within 12hrs

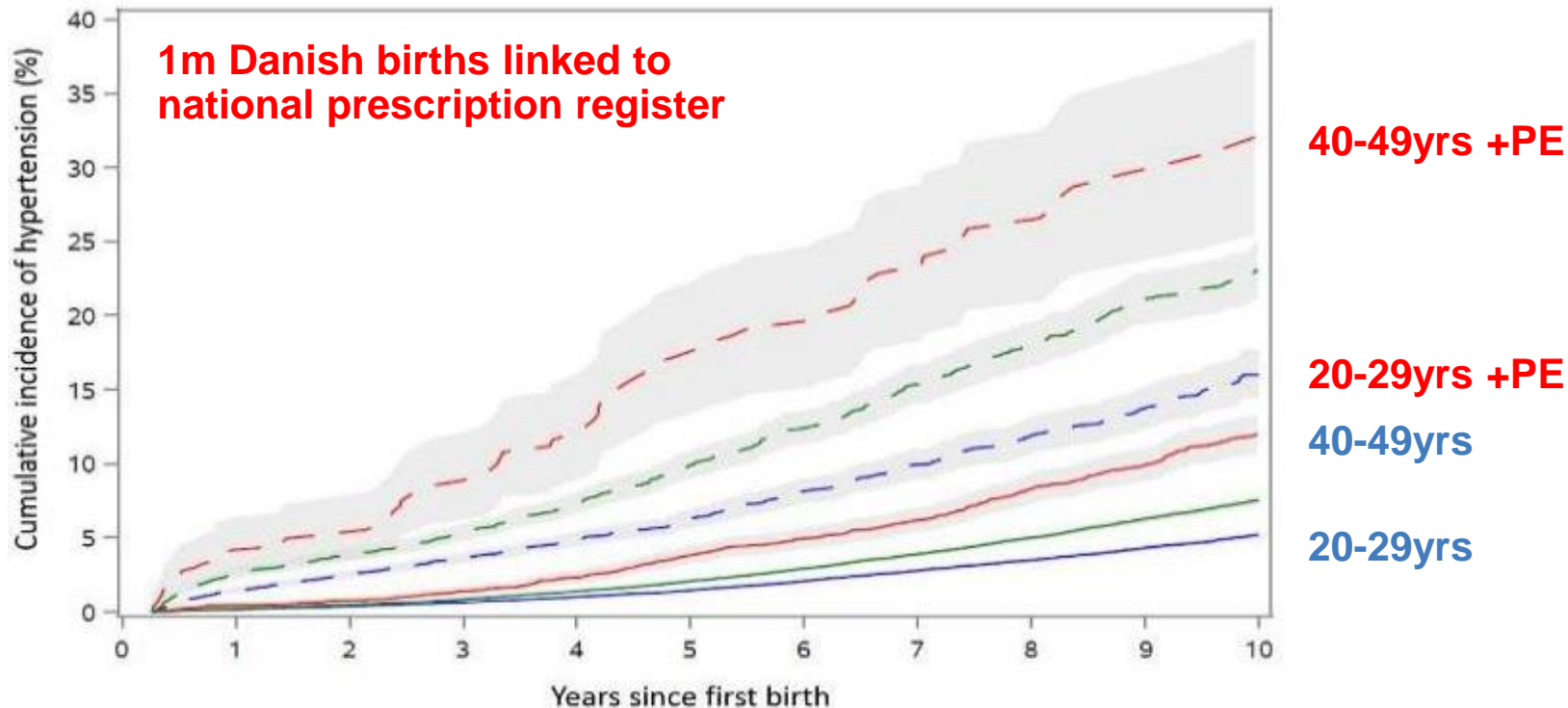
Nifedipine and labetalol achieved outcome within 3hrs

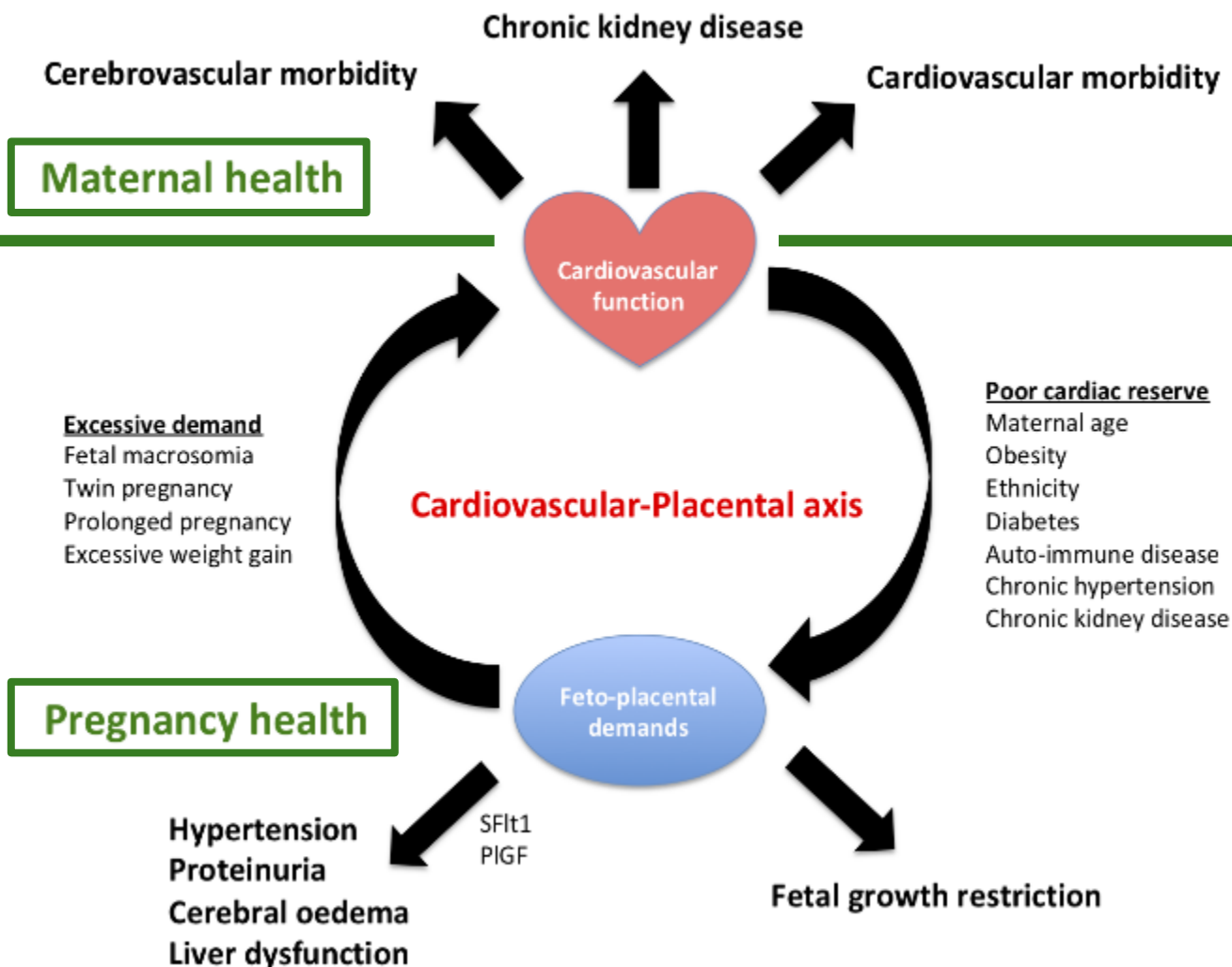
Nifedipine resulted in:
More maternal blood Tx
Increased NICU admissions x2
Increased RDS x4
Increased SGA x2



Cardiovascular legacy

Chronic hypertension after PE





First they ignore
you. Then they
laugh at you. Then
they fight you.
Then you win.

Mahatma Gandhi



Cardiovascular System in Preeclampsia and Beyond

Hypertension

March 2019

Basky Thilaganathan, Erkan Kalafat