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MATERNAL-FETAL EXCHANGE:
PLACENTA AS EMISSARY

Hilary S. Gammill, MD

March 24, 2016

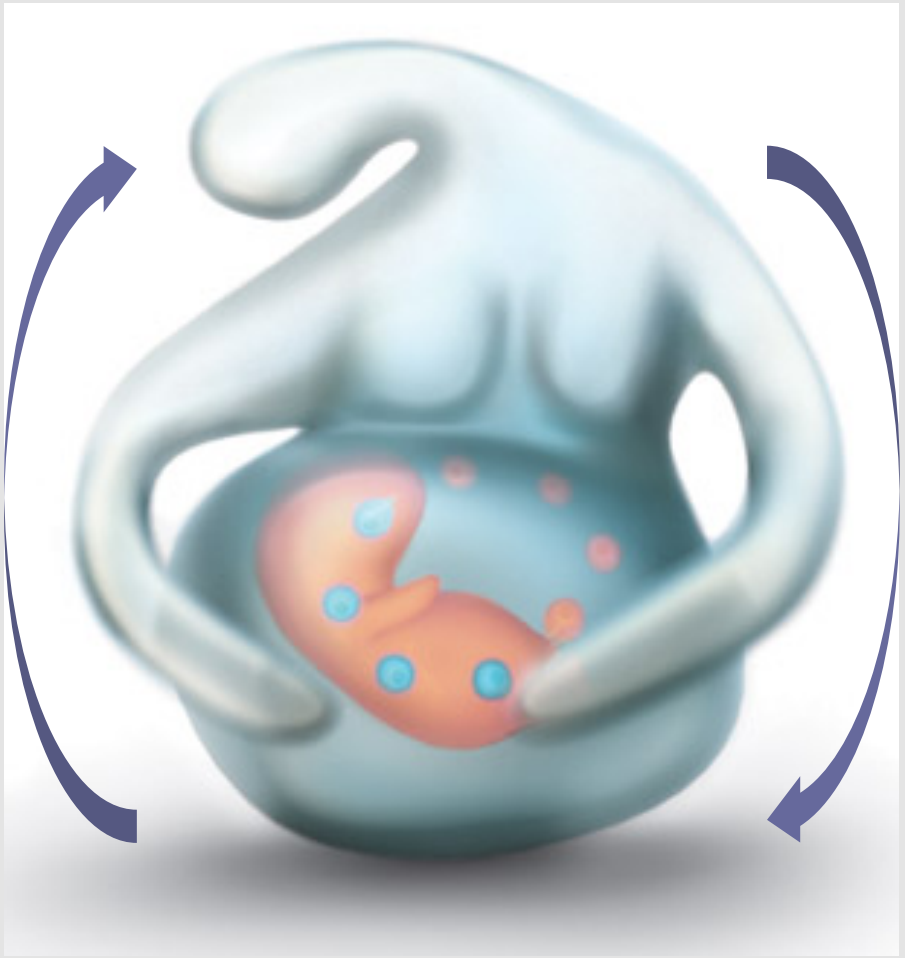
DISCLOSURES:

- Research funding from Faraday Pharmaceuticals (sulfide metabolism in preeclampsia)

PLACENTA AS BARRIER

From Williams classic OB text, 1907: "The foetal blood in the vessels of the chorionic villi at no time gains access to the maternal blood in the intervillous spaces…"

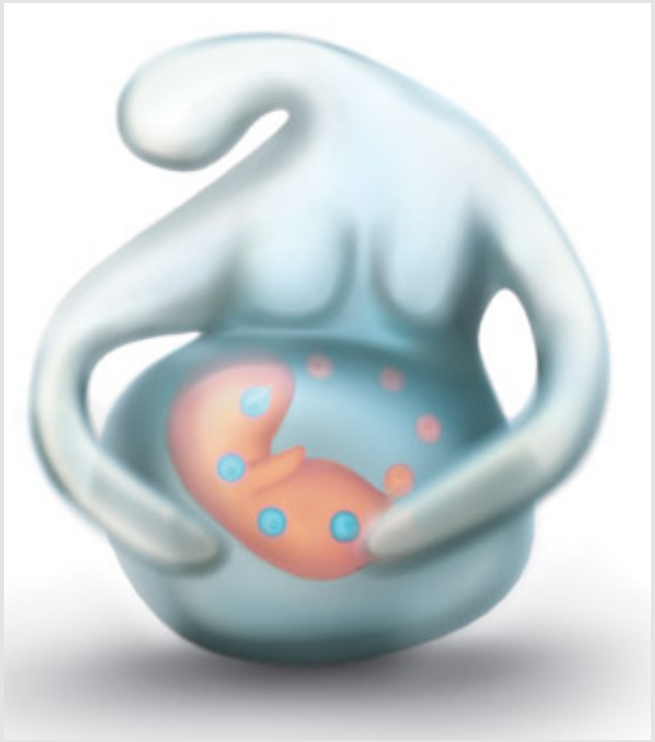
PLACENTA AS EMISSARY



Nelson, Scientific American, 2008

Maternal-Fetal Exchange:

- **DNA**
- **RNA**
- **Extracellular vesicles**
- **Cells**



Reproductive origins of disease:

- Mother (placental disorders and later life health)
- Offspring (and cord blood transplant)

Cells

DNA
RNA
Extracellular vesicles

Immediate reflection of obstetric condition:

- Fetal/placental genetics
- Placental function
- Adverse pregnancy outcomes

CELLULAR MICROCHIMERISM

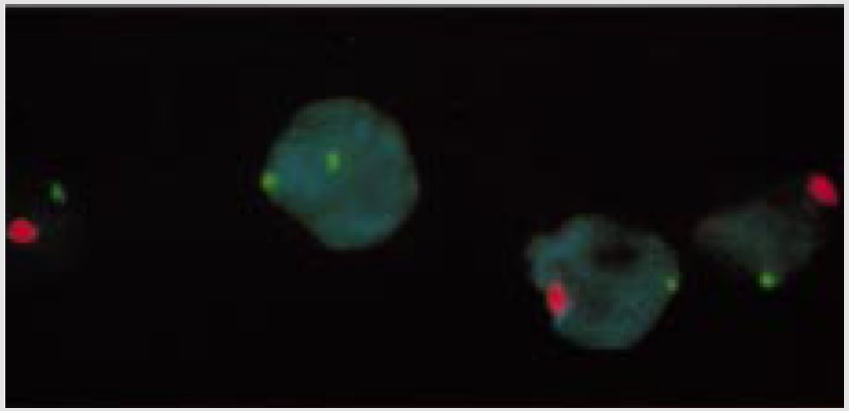
Bidirectional maternal-fetal transfer
Long-term persistence

Fetal

	Clinical history				
Patient	No. of pregnancies	Male infants	Female infants	Tab/Sab	Interval between sampling and most recent male
1	4	3	1	0	1 year
2	3	1	2	0	7 years
3	2	2	0	0	2 years
4	3	2	1	0	3 years
5	10	6	3	1	27 years
6	3	2	0	1	6 years
7	4	2	1	1	10 months
8	1	1	0	0	6 months

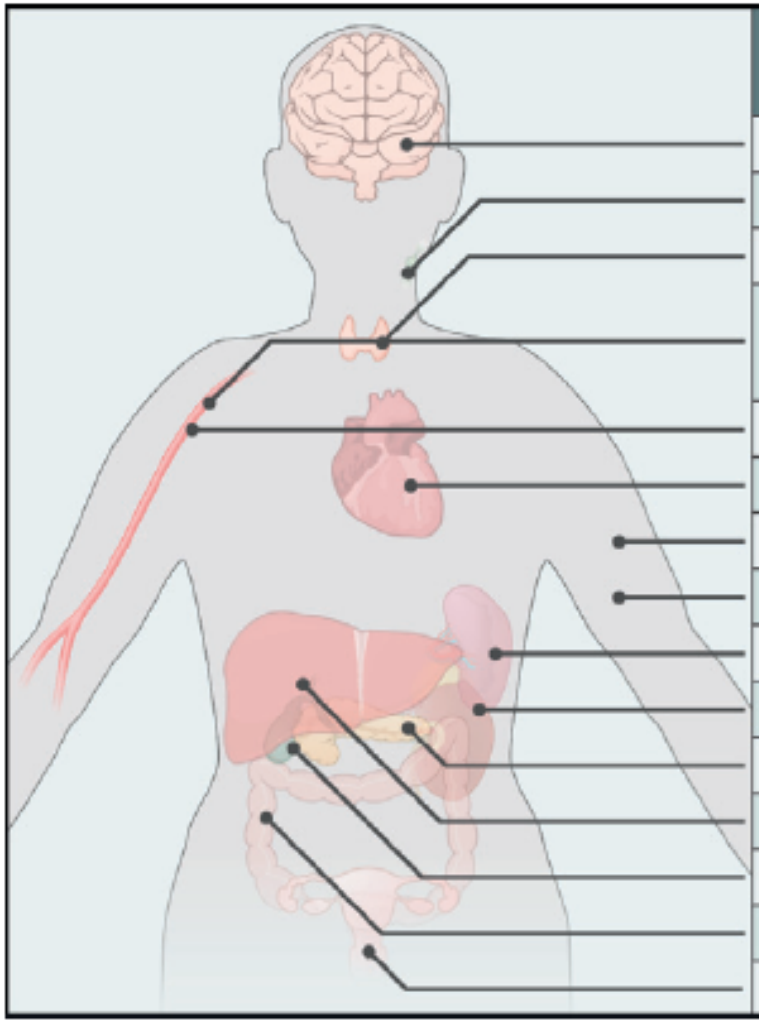
Bianchi, PNAS, 1996

Maternal



Maloney, JCI, 1999

MICROCHIMERISM: CELL AND TISSUE TYPES



Organ	Presumed cell type	Maternal origin Mc	Fetal origin Mc
Brain	Neurons(murine)		X
Lymph node	Hematopoietic cells		X
Thyroid	Epithelial cells, thyrocytes		X
Blood	T cells, B cells, monocytes/ macrophages, NK cells, granulocytes	X	X
Blood	Lymphoid progenitor cells		X
Heart	Cardiac myocytes	X	X
Skin	Endothelial cells		X
Skin	Keratinocytes	X	
Spleen	Hematopoietic cells		X
Kidney	Renal tubular cells	X	
Pancreas	Islet beta cells	X	
Liver	Hepatocytes	X	X
Gallbladder	Epithelial cells		X
Intestine	Epithelial cells		X
Cervix	Epithelial cells		X

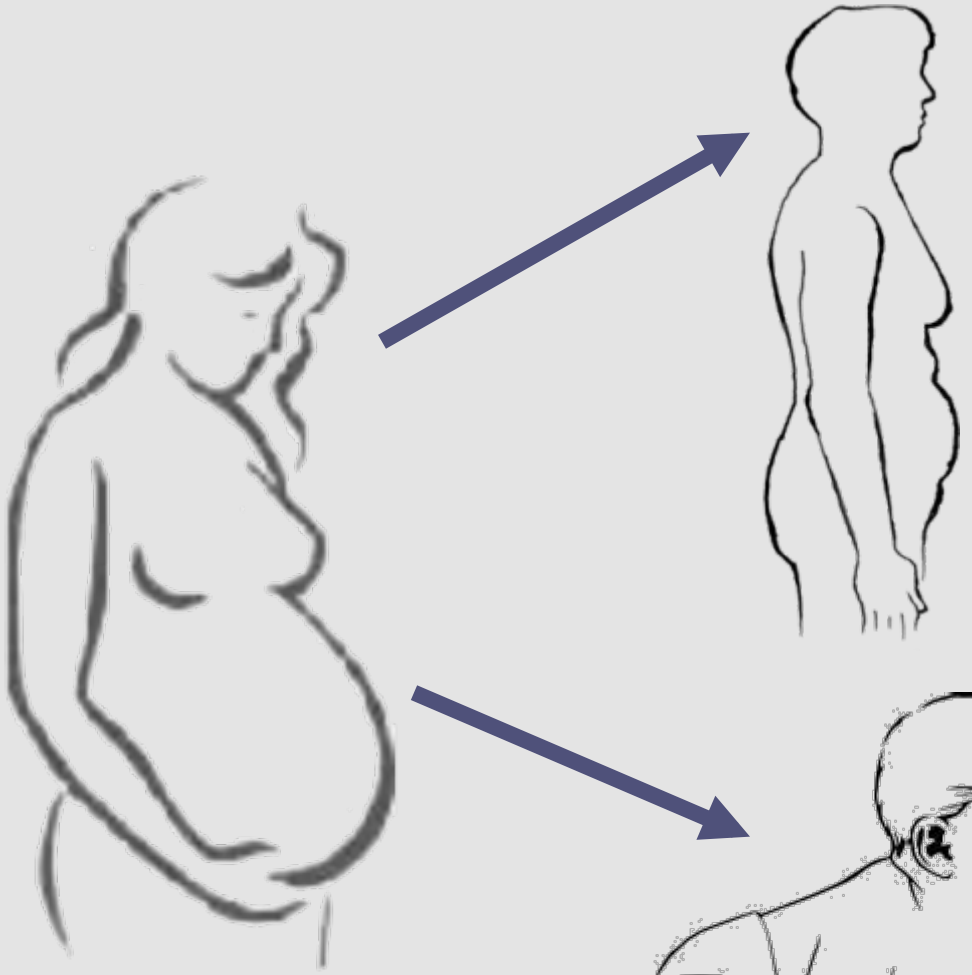
Nelson, Trends Immunol, 2012

CELLULAR MICROCHIMERISM

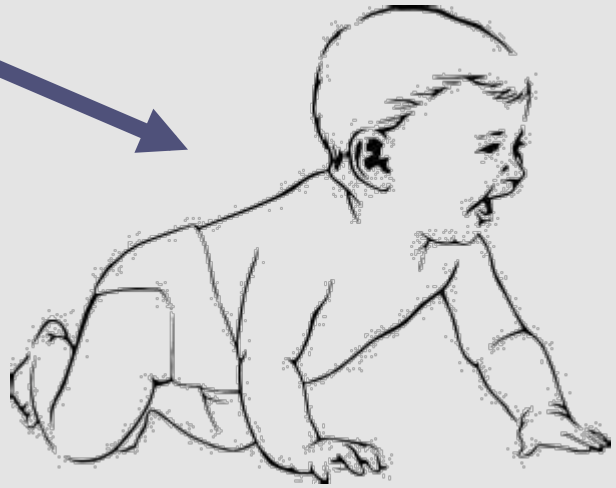
Cells exchanged during pregnancy can lead to persistent microchimerism:

- Among healthy adults,
  - 78% had detectable fetal microchimerism
  - 39% had detectable maternal microchimerism

Loubiere, Lab Investigation, 2006



Maternal later-life health:
Autoimmune disease
Cardiovascular disease
Cancer



Fetal origins of adult disease

Placental disorders:
Preeclampsia

*Naturally acquired cellular microchimerism may contribute to **reproductive origins of disease***

FETAL CELLULAR MICROCHIMERISM IN NORMAL PREGNANCY

- Longitudinal study of normal pregnancies:
  - 7/35 (20%) of women had detectable fetal microchimerism in PBMC in at least one time point
  - Detection and concentration increased with gestational age and was highest around delivery
  - Fetal microchimerism was detectable in CD4+ and CD8+ cell subsets in ~10%

Adams Waldorf, Placenta, 2010

FETAL CELLULAR MICROCHIMERISM IN PREECLAMPSIA

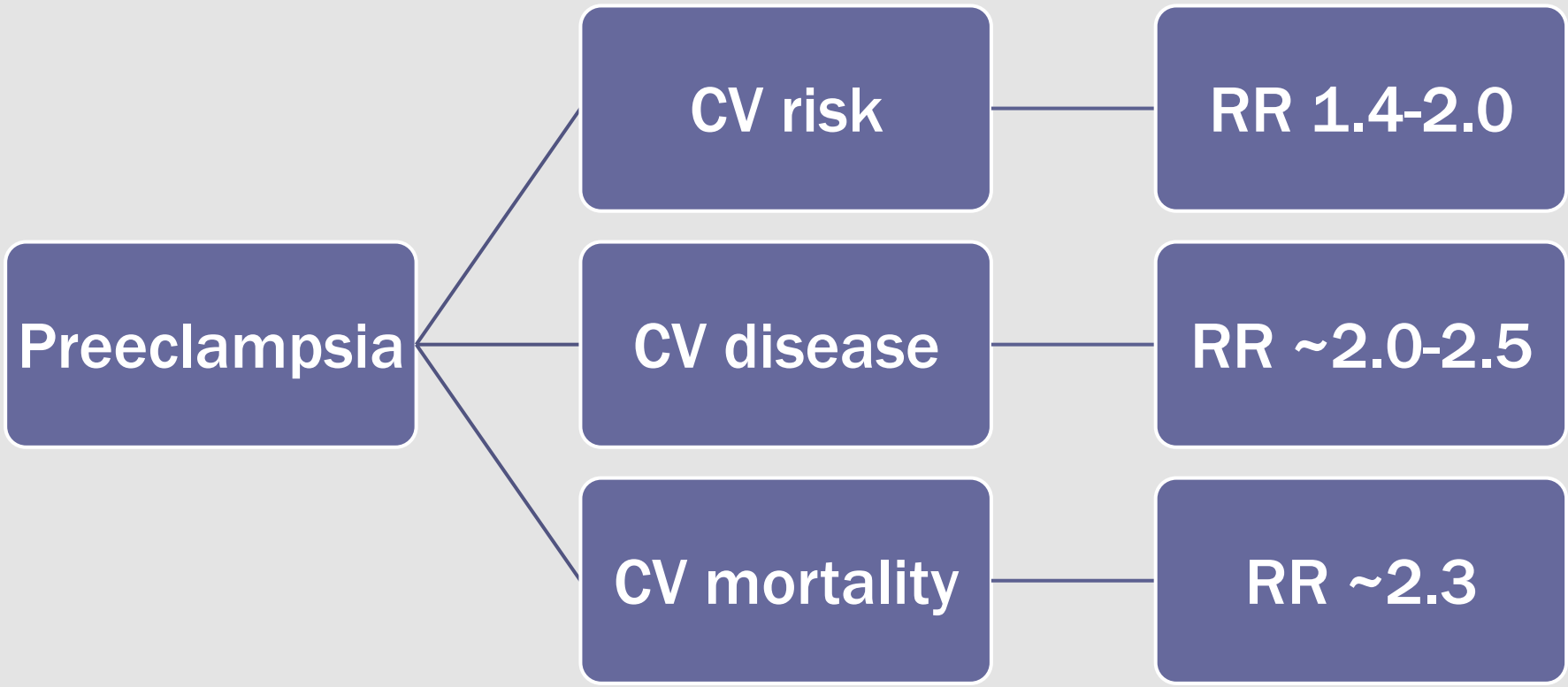
- 17/53 (32%) samples positive in preeclampsia
- 6/57 (10.5%) samples positive in normotensive pregnancies
- p=0.007

Concentration of Cellular Fetal Microchimerism Among Subjects With Preeclampsia and Subjects With Normal Pregnancy

	Detection Rate Ratio (95% CI; *P* Value)	
Group	Unadjusted	Adjusted*
Normal pregnancy, n=47 subjects (57 samples)	…	…
Preeclampsia, n=46 subjects (53 samples)	17.4 (2.7–110.4; *P*=0.002)	15.8 (3.2–77.8; *P*<0.001)

Gammill, Hypertension, 2013

PREECLAMPSIA IS ASSOCIATED WITH LATER CARDIOVASCULAR DISEASE



Bellamy, BMJ, 2007; Fraser, Circulation, 2012; McDonald, Am J Heart, 2008; Smith, Lancet, 2001

DIRECT RELATIONSHIP: FETAL CELLULAR MICROCHIMERISM AND CV DISEASE

- Danish cohort of women enrolled between ages 50-64 (secondary analysis, case cohort study of cancer)
- Male microchimerism studied at time of enrollment
- Subsequent development of disease considered

Male microchimerism negative (n = 82)	Male microchimerism positive (n = 190)	Crude OR (95% CI)
74 (32.2)	156 (67.8)	1 (ref.)
8 (19.1)	34 (81.0)	2.0 (0.9–4.6)

Kamper-Jorgensen, Chimerism, 2012

PREECLAMPSIA IS INVERSELY ASSOCIATED WITH BREAST CANCER RISK

- Linkage between Norwegian Medical Birth Registry and Cancer Registry

	Person-years	Cases of Breast cancer	RR (95% CI)
No PE	10,450,371	5,194	1.0
PE	663,311	280	0.81 (0.71-0.91)

- Unchanged by:
  - Length of gestation (term vs. preterm)
  - Offspring birthweight
  - Woman's age

Vatten, Brit J Cancer, 2002

DIRECT RELATIONSHIP: MICROCHIMERISM AND BREAST CANCER PROTECTION

Cases	Blood - Stage 0-IV[1]	Blood - Stage I-III	Cancer-free breast
Controls	Blood – healthy women	Blood – matched women	Mammoplasty reduction
Prevalence Case:Control	14% : 43%	26% : 56%	26% : 63%
OR (95%-CI)	0.23 (0.06-0.75)	0.29 (0.11–0.83)	0.17 (0.04–0.76)
p-value	0.006	0.02	0.02
Comments	• Unselected breast cancer patients • Some with Chemo	Pre-menopausal (age 21-45)	

Gadi V. Cancer Res. 2007; 67:9035-8
Gadi V. PLoS One. 2008; 3:e1706
Gadi V. Breast Cancer Res Treat. 2010; 121:241-4

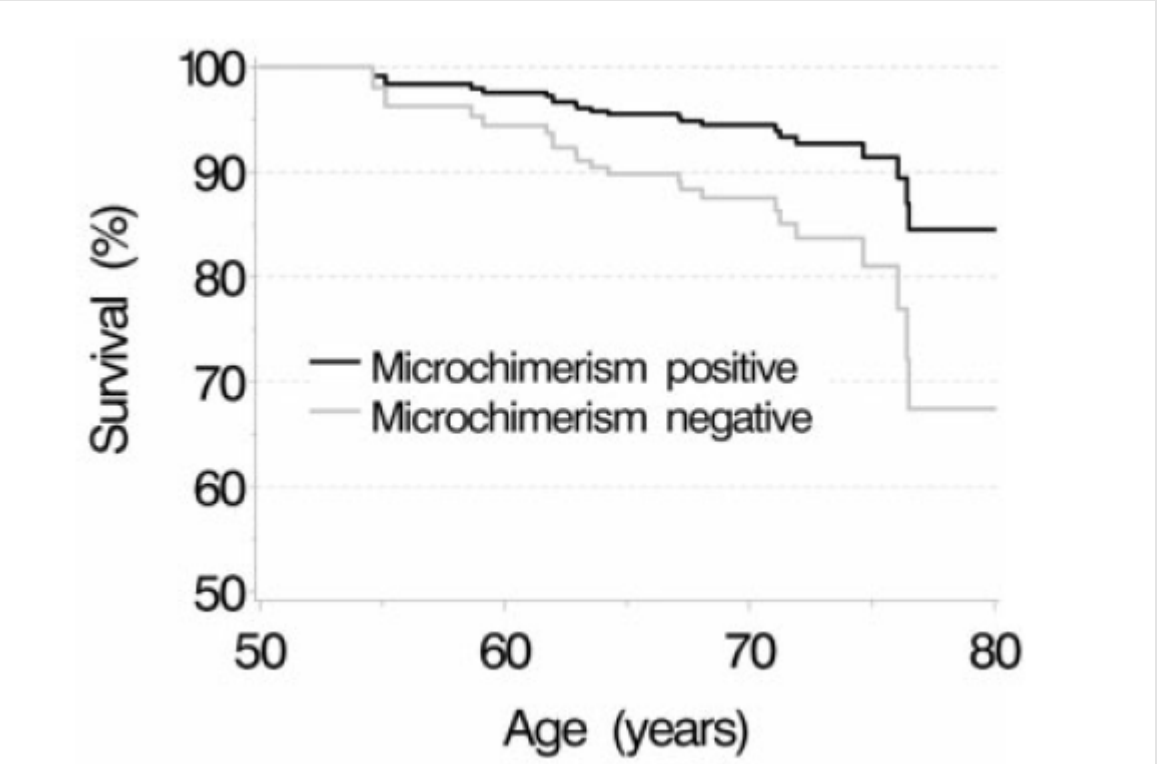
FETAL CELLULAR MICROCHIMERISM AND PROTECTION FROM BREAST CANCER

- Danish Diet, Cancer, and Health Cohort
  - Microchimerism **preceding** disease onset

	Breast cancer ($n = 89$)	Cancer-free ($n = 272$)
Detection of microchimerism (n, column %)		
No	53 (59.6)	82 (30.1)
Yes	36 (40.4)	190 (69.9)
Odds ratio (95% confidence interval (CI))		
Adjusted	0.30 (0.17–0.52)	1 (Ref.)

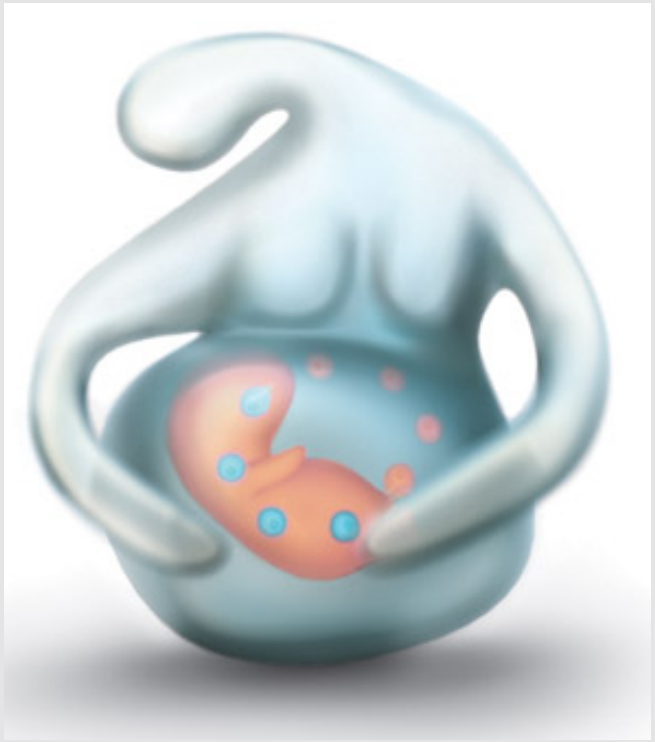
Kamper-Jorgensen, Eur J Cancer, 2012

OVERALL SURVIVAL: BOTH RISK AND PROTECTION



Status	All-cause mortality	Cancer mortality	Cardiovascular mortality
Microchimerism positive	0.42 (0.17–1.03)	0.24 (0.08–0.79)	1.66 (0.18–15.48)
Microchimerism negative	1 (ref.)	1 (ref.)	1 (ref.)

Kamper-Jorgensen, International Journal of Epidemiology, 2014



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COLLABORATIVE STUDIES: FETAL/ PLACENTAL GENETICS

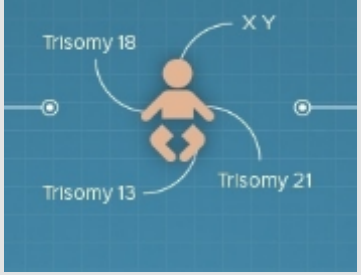
- Rapid evolution of the field of noninvasive prenatal testing (NIPT)

Ariosa DIAGNOSTICS Harmony™ PRENATAL TEST

natera™ panorama™ prenatal screen

MaterniT21™ PLUS

sequenom. Laboratories



verifi® prenatal test illumina®

COLLABORATIVE STUDIES: FETAL/ PLACENTAL GENETICS

- Breadth

RESEARCH ARTICLE

GENOMICS

Noninvasive Whole-Genome Sequencing of a Human Fetus

Jacob O. Kitzman,[1]* Matthew W. Snyder,[1] Mario Ventura,[1,2] Alexandra P. Lewis,[1] Ruolan Qiu,[1] LaVone E. Simmons,[3] Hilary S. Gammill,[3,4] Craig E. Rubens,[5,6] Donna A. Santillan,[7] Jeffrey C. Murray,[8] Holly K. Tabor,[5,9] Michael J. Bamshad,[1,5] Evan E. Eichler,[1,10] Jay Shendure[1]*

www.ScienceTranslationalMedicine.org 6 June 2012 Vol 4 Issue 137 137ra76

- Refinement

BRIEF REPORT

Copy-Number Variation and False Positive Prenatal Aneuploidy Screening Results

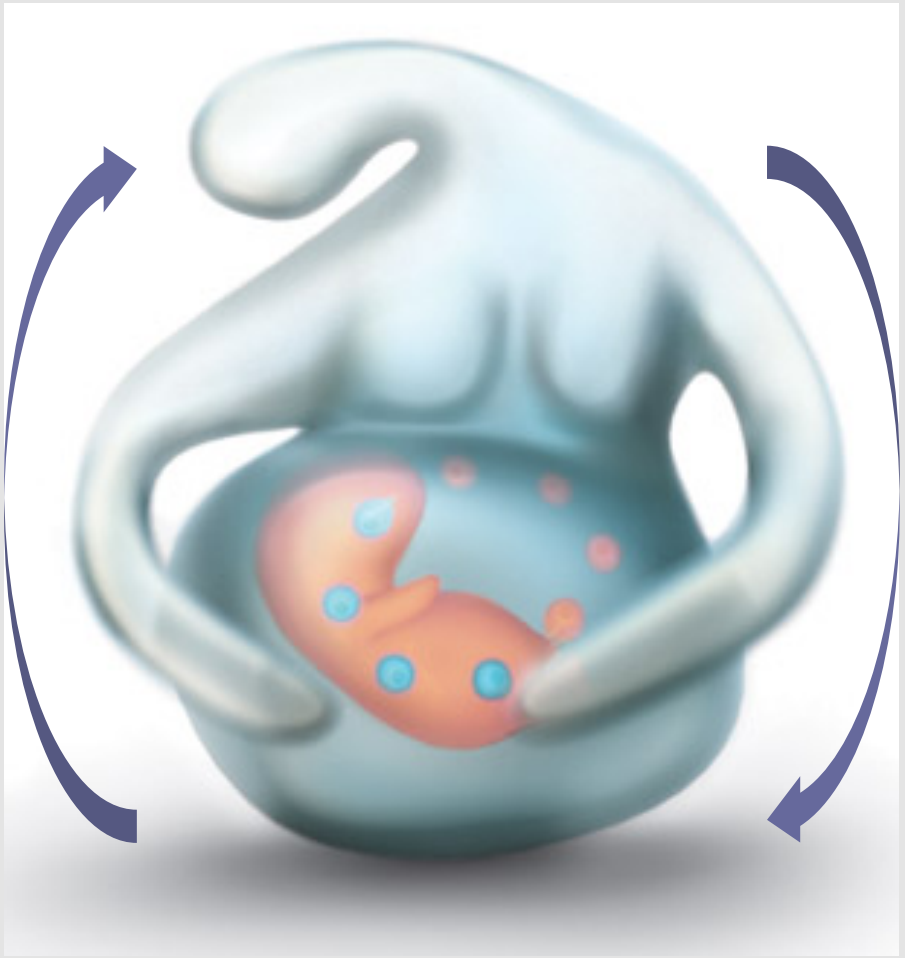
Matthew W. Snyder, M.S., LaVone E. Simmons, M.D., Jacob O. Kitzman, Ph.D., Bradley P. Coe, Ph.D., Jessica M. Henson, B.S., Riza M. Daza, B.S., Evan E. Eichler, Ph.D., Jay Shendure, M.D., Ph.D., and Hilary S. Gammill, M.D.

N ENGL J MED 372;17 NEJM.ORG APRIL 23, 2015

FUTURE COLLABORATIVE STUDIES

- Several UW departments
- Human Placenta Project proposal, aiming to:
  - Isolate and evaluate placental-derived cells, subcellular particles, and cell-free nucleic acids to assess placental function
    - Normal pregnancy
    - Preeclampsia

PLACENTA AS EMISSARY



Nelson, Scientific American, 2008

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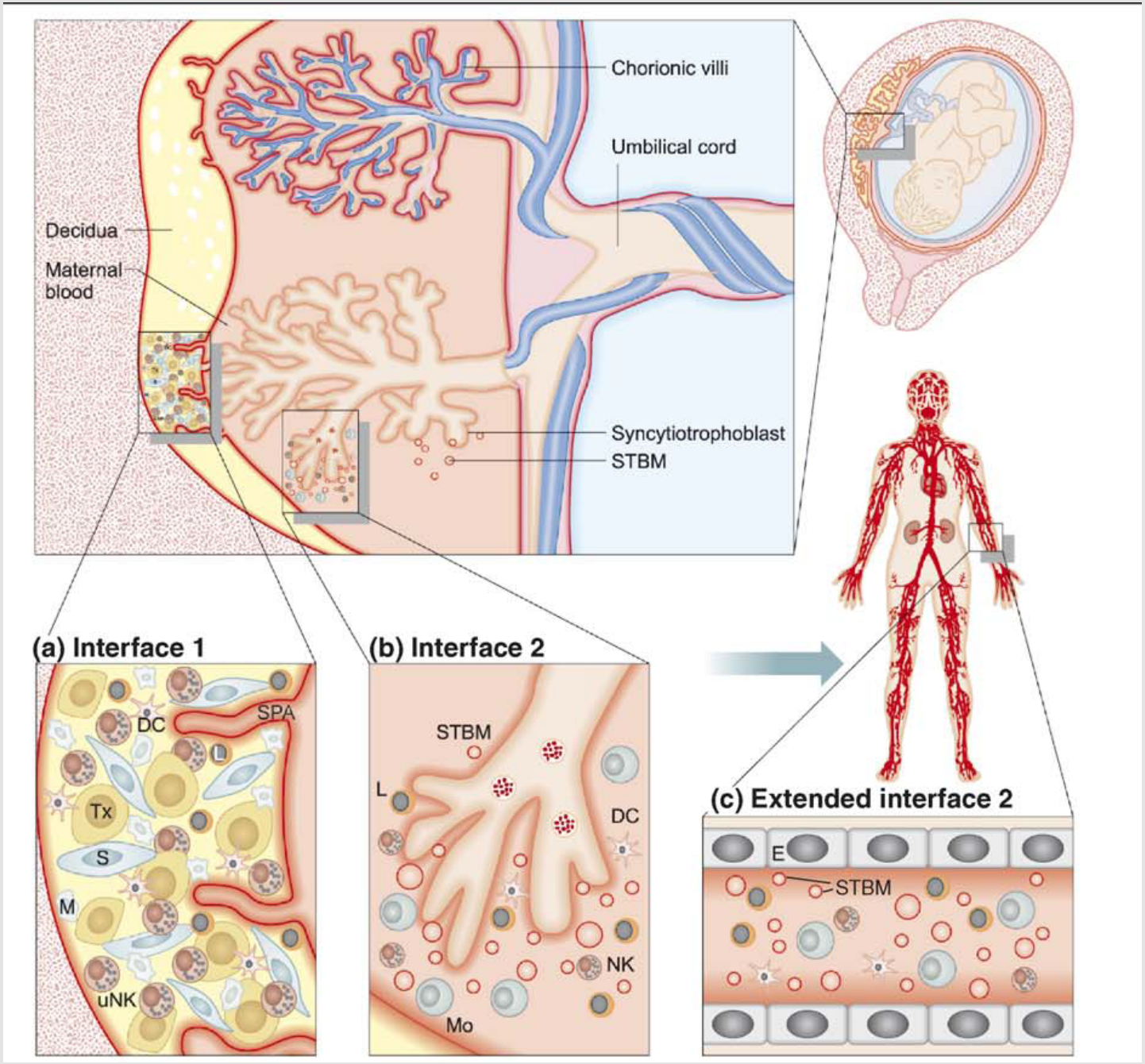


Sargent 2006

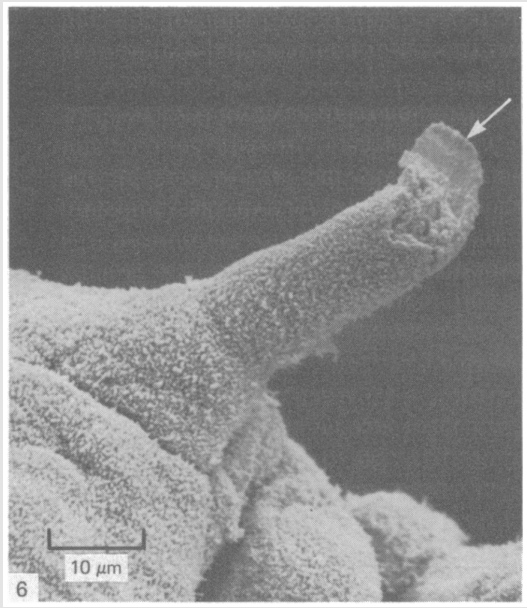
SYNCYTIAL TRANSFER

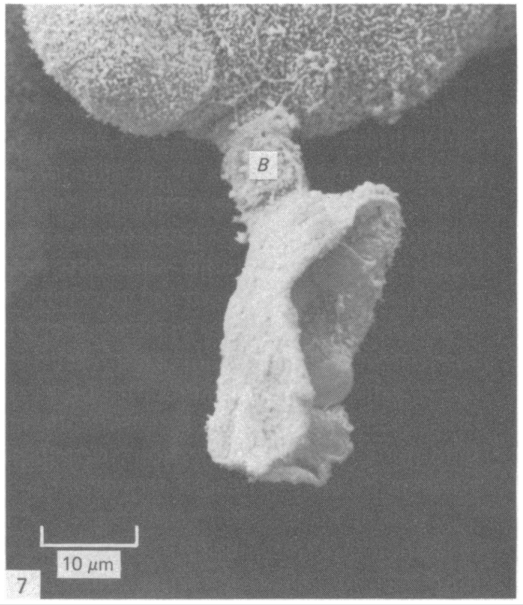
J. Anat. (1986), **147**, pp. 245–254
With 11 *figures*
Printed in Great Britain

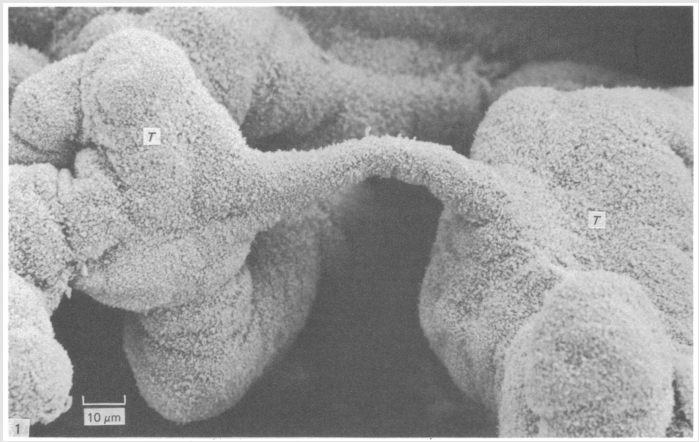
Scanning electron microscopy of intervillous connections in the mature human placenta

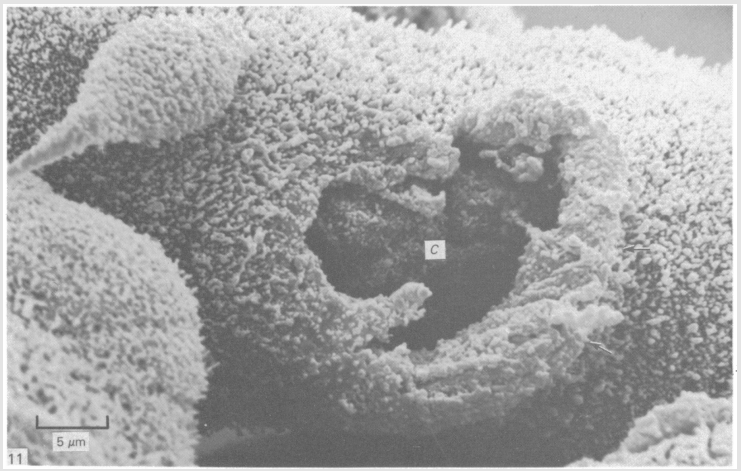
G. J. BURTON

Department of Anatomy, University of Cambridge, Downing Street, Cambridge CB2 3DY









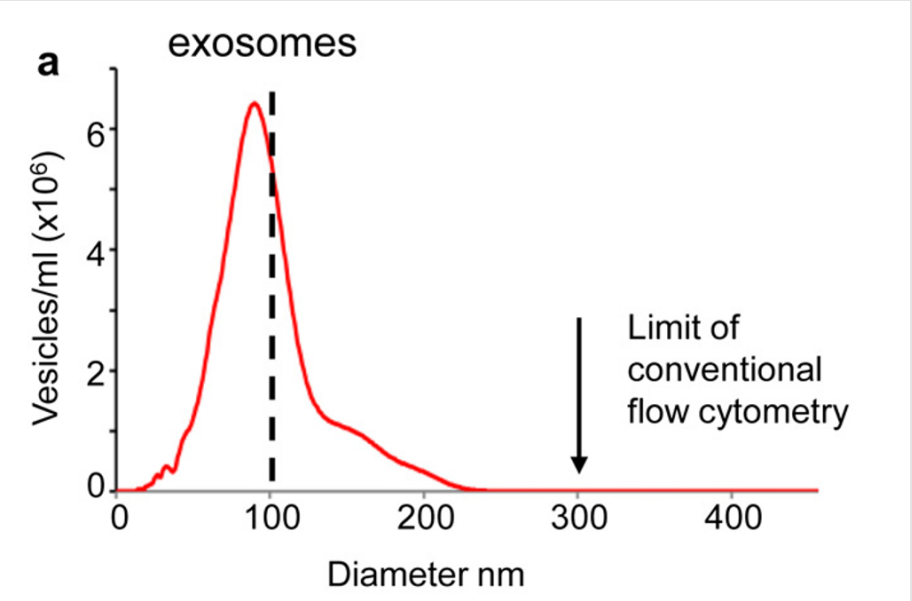
SYNCYTIAL "SECRETION"

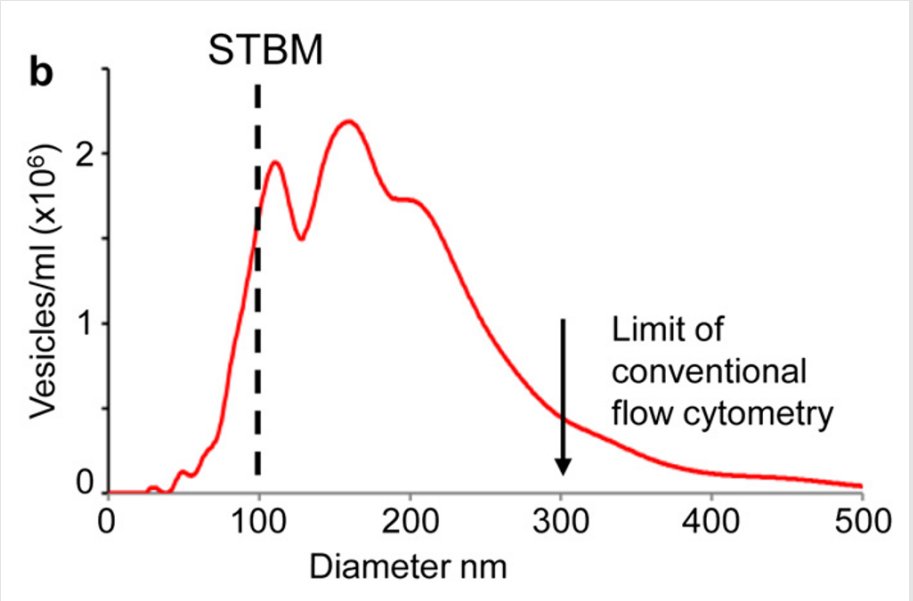
Review: Does size matter? Placental debris and the pathophysiology of pre-eclampsia

C.W.G. Redman, D.S. Tannetta, R.A. Dragovic, C. Gardiner, J.H. Southcombe, G.P. Collett, I.L. Sargent*

Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

Placenta 33, Supplement A, Trophoblast Research, Vol. 26 (2012) S48–S54





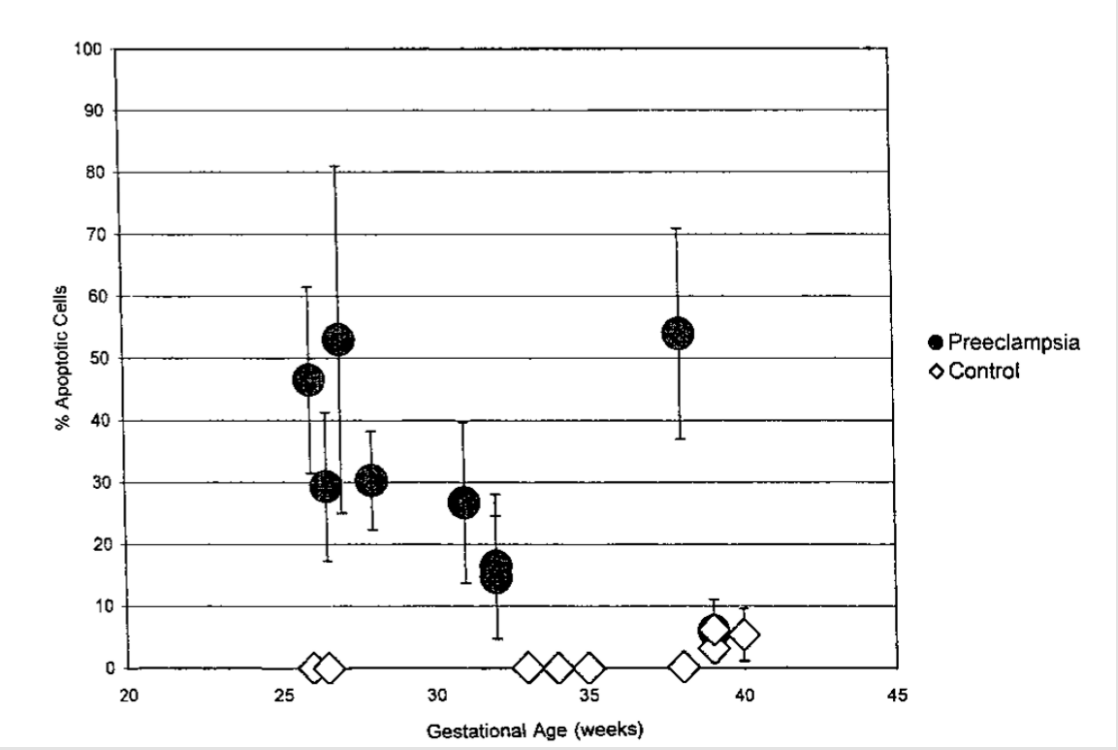
EXTRAVILLOUS CYTOTROPHOBLAST INVASION

Preeclampsia Is Associated with Widespread Apoptosis of Placental Cytotrophoblasts within the Uterine Wall

Elaine DiFederico,* Olga Genbacev,† and Susan J. Fisher*†‡§

From the Departments of Obstetrics, Gynecology, and Reproductive Sciences, Stomatology,† Pharmaceutical Chemistry,‡ and Anatomy,§ University of California San Francisco, San Francisco, California*

American Journal of Pathology, Vol. 155, No. 1, July 1999



CONCLUSIONS

- Maternal-fetal transplacental exchange includes cells, subcellular fragments, and cell-free nucleic acids
- Long-term persistence of exchanged cells may influence post-reproductive health
- Placental-derived material may provide a window into pregnancy status
- Many questions remain regarding the mechanism and nature of transplacental exchange

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Jay A. Shendure, MD, PhD
Matthew W. Snyder, PhD

NICHD WRHR HD01264
NICHD K08HD067221
Preeclampsia Foundation

QUESTIONS?