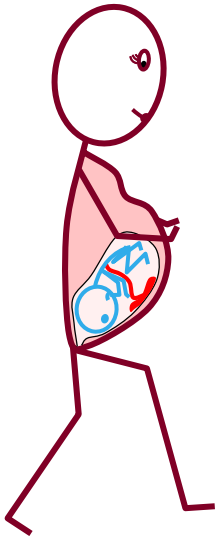
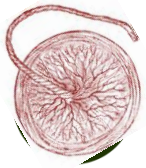
Current methods for assessing placental development and function, and their limitations



Yoel Sadovsky, MD
Magee-Womens Research Institute
Department of OBGYN and Reproductive Sciences, and Microbiology and Molecular Genetics
University of Pittsburgh School of Medicine



SI

Scores | MLS | England | Other | International

SOCCER

NFL | THE MMQB | NCAAF | MLB | NBA | NCAAB | GOLF | NHL | SOCCER | TENNIS | MORE | FANTASY | PHOTOS | VIDEO

Posted: Wed May 21, 2014 3:13PM; Updated: Wed May 21, 2014 3:13PM

Atletico Madrid turns to horse placenta for Diego Costa's treatment

Atletico Madrid star Diego Costa, center, is in a race against time to be fit for Saturday's Champions League final.

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Page last updated at 13:33 GMT, Tuesday, 17 November 2009

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The new miracle cure for injuries?

By Nick Triggle
BBC News health reporter

Arsenal striker Robin Van Persie has flown to Serbia for a novel form of treatment - placenta fluid is to be dripped on his injured ankle. Why is he doing this and will it work?

It is not unusual for sports starts to look for super cures for their injuries.

England footballer Wayne Rooney used an oxygen tent prior to the 2006 World Cup to help him recover from a broken foot and six years ago runner Paula Radcliffe rubbed oil from the belly of an emu to ease injuries sustained in a collision with a cyclist.

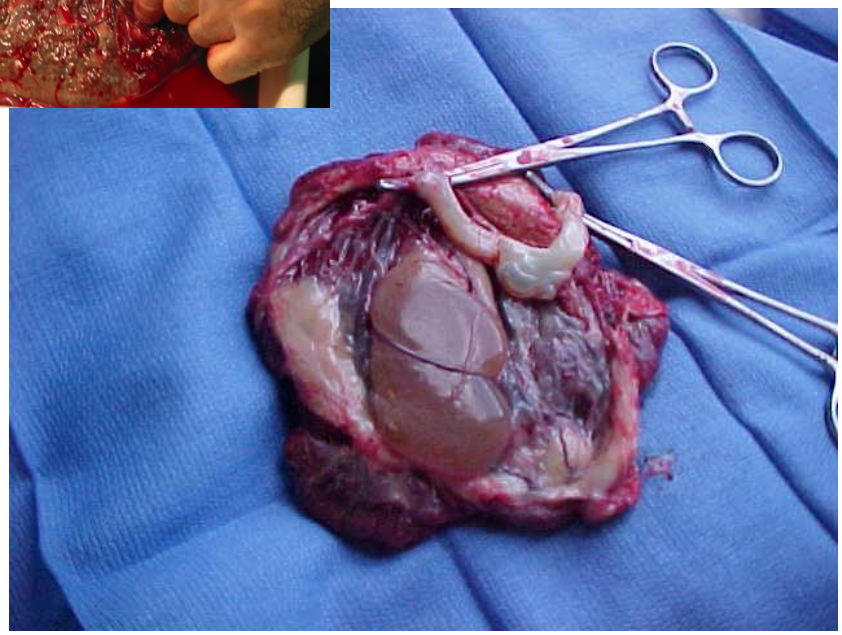
Van Persie has been a key player for Arsenal this season

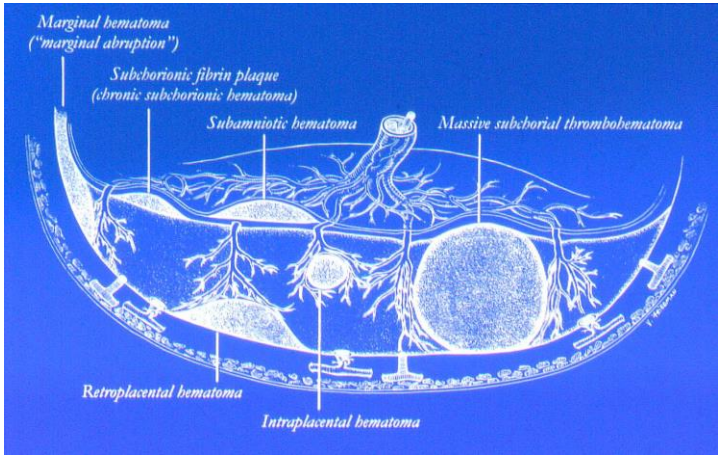
Disclaimers

- This is a general review, not a detailed analysis
- Minimal discussion of limitations or risk
- Common, but not all technologies are reviewed

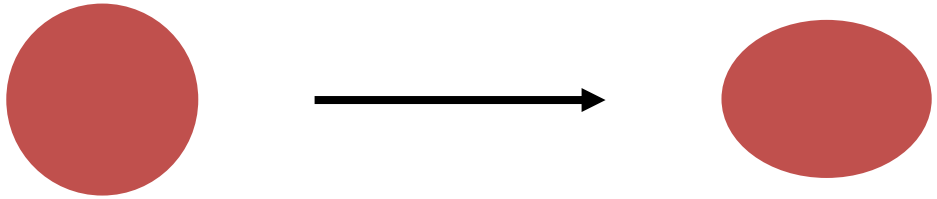
- No conflict of interest

Placental macroscopic analysis





Placental shape and disease



Reduced placenta width is associated with adult diseases

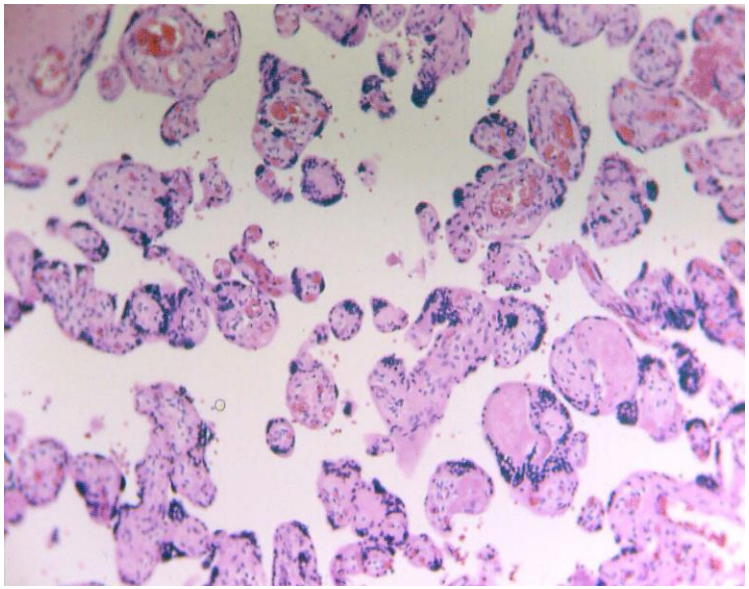
Placental width as a fetal nutrient sensor

Placental thinness associated with cardiac death

Higher cotyledon number and cardiac death

Barker & Thornburg, Placenta 2013

Placental histopathology



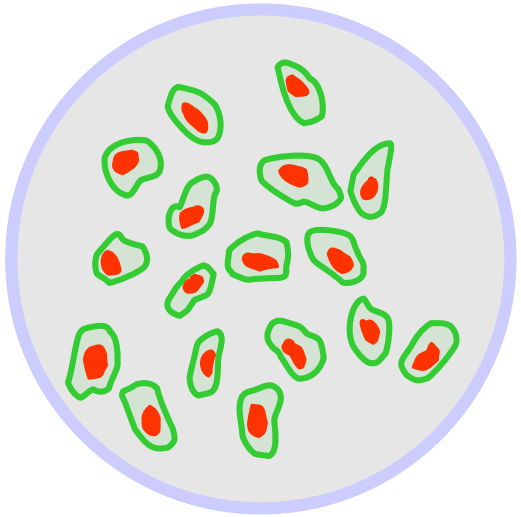
Not “real time”
Limited data

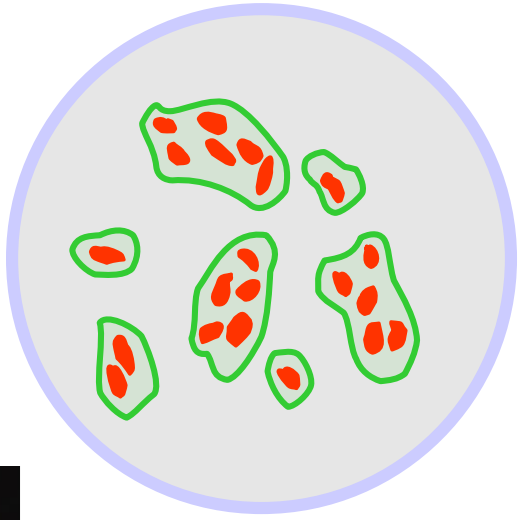
Benirschke, Pathology of Human Placenta 2000
Castellucci, Frontiers Gynecol Obstet Invest 1993

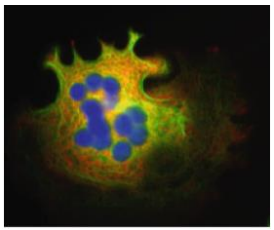
Culture of primary human trophoblasts

cytotrophoblast

syncytiotrophoblast







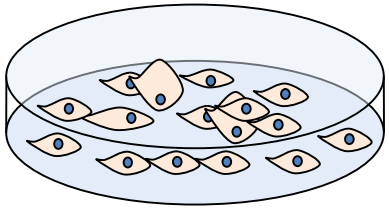
LOW

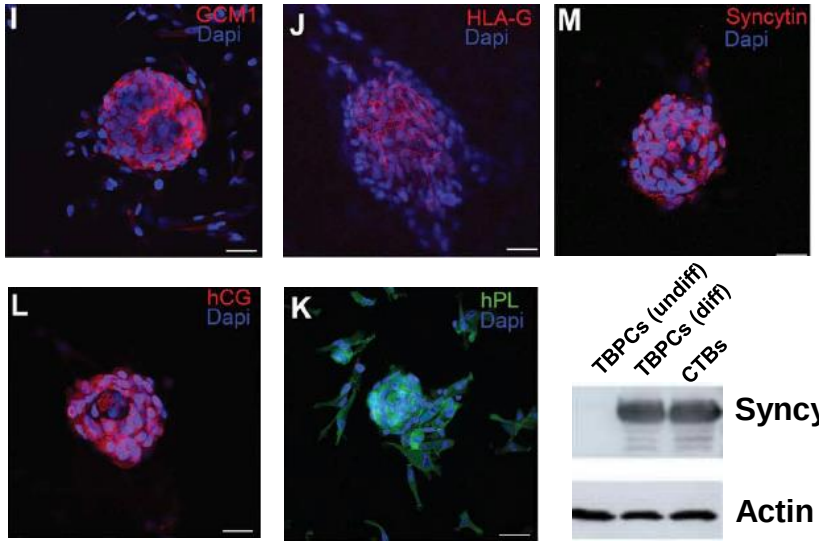
hCG HIGH

Human trophoblast cell lines and progenitor cells: Model for normal or diseased trophoblasts

Cell lines:

- **BeWo**
- **JEG3**
- **JAR**
- **HTR-8/SvNeo**





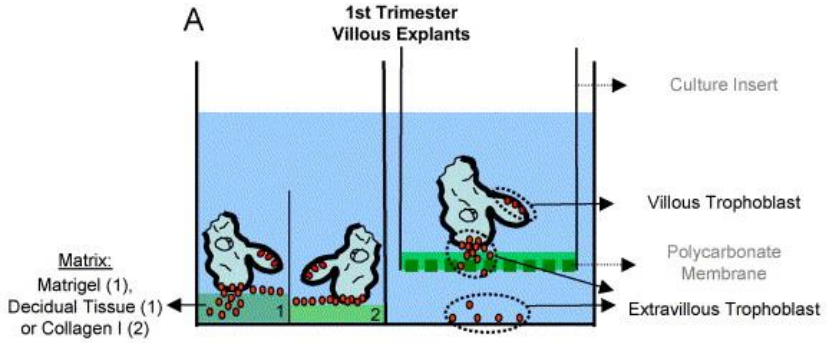
Limitations

Not “real time”
Tissue context

Genbachev, Stem Cells 2011

Placental explants

1st trimester explants on plate, matrix

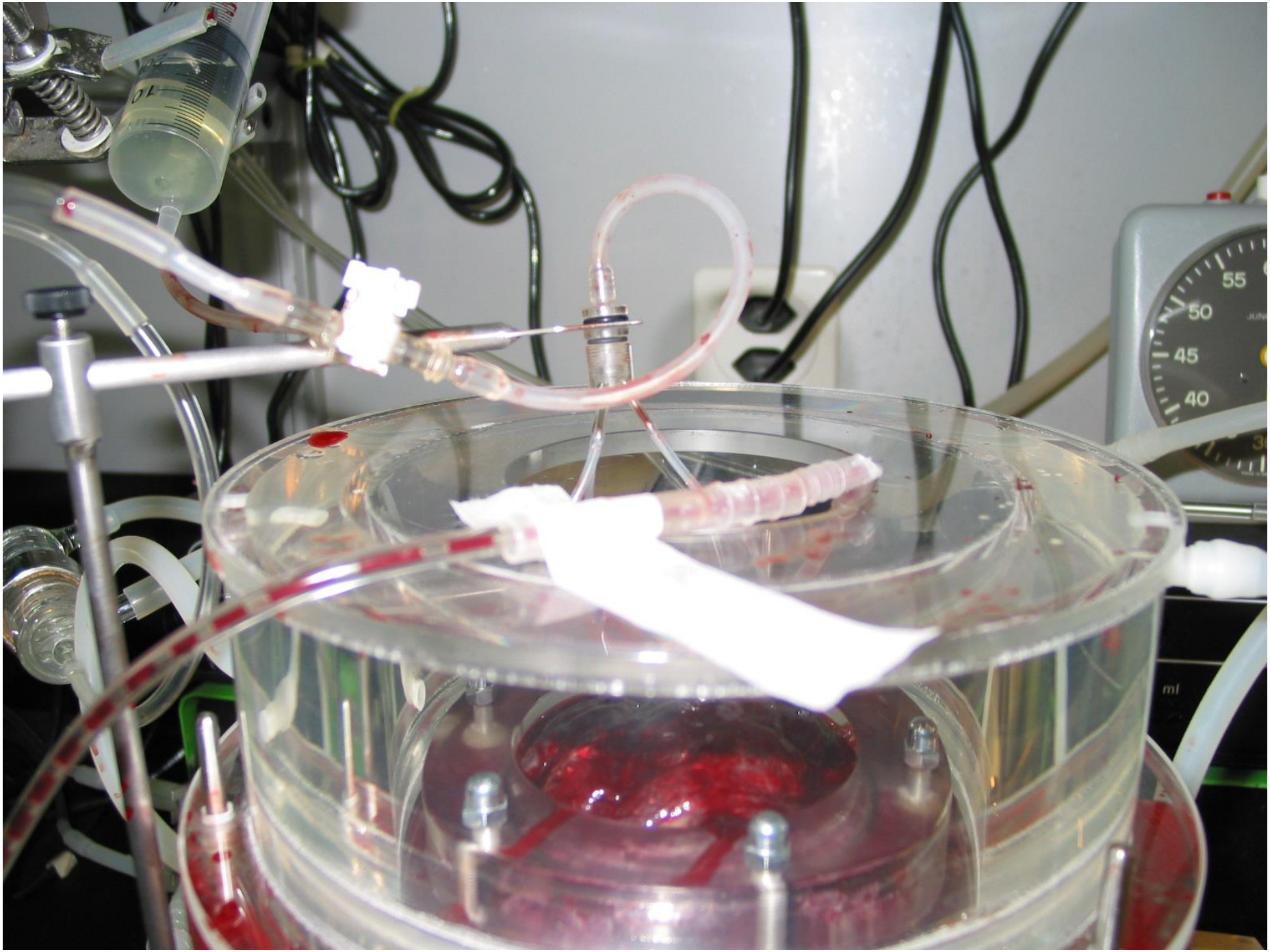


3rd trimester explants on mesh, plate

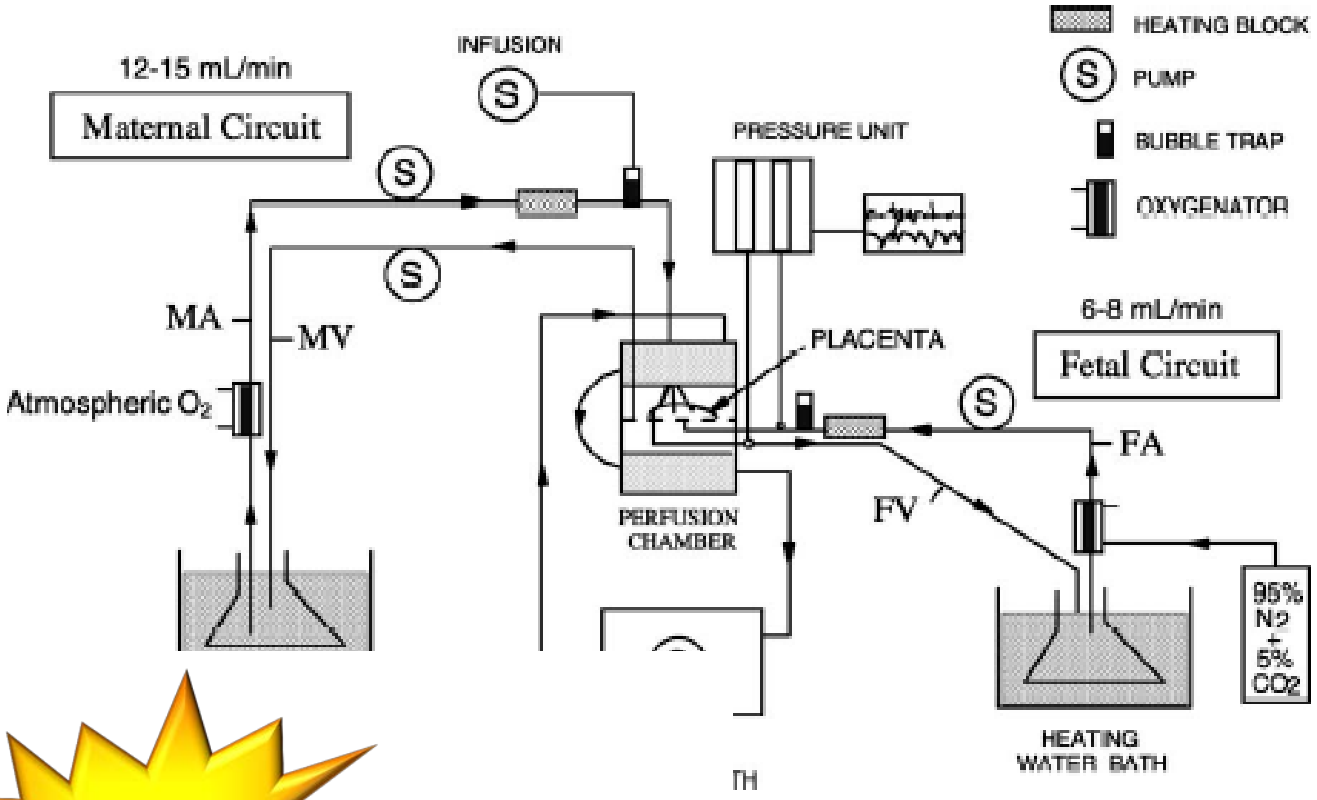
Limitations

Not "real time"
Explant architecture

Miller RK, Placenta 2005


55
50
45
40
ml

Schematic diagram of the human placenta perfusion system



Limitations

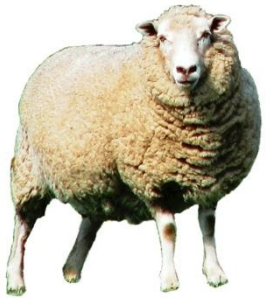
Not “real time”
Complexity

FA: fetal artery; FV: fetal vein; MA: maternal artery; MV: maternal vein

Schneider H, In vitro Perfusion of Human Placental Tissue, 1984

Animal models for research

Sheep



Mice

Rats

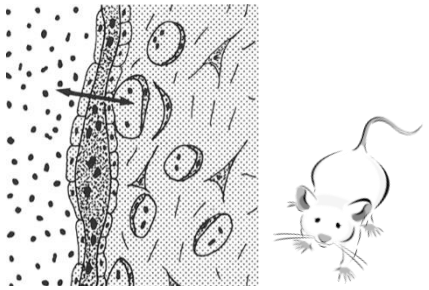
Guinea pigs

Limitations

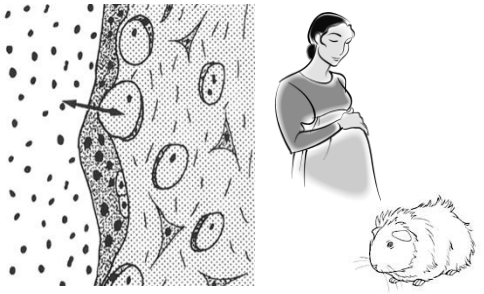
Not human
Not “real time”

The human (villous) and mouse labyrinthine placenta

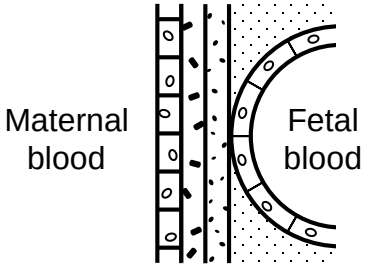
Placenta discoidalis:
rodents, humans



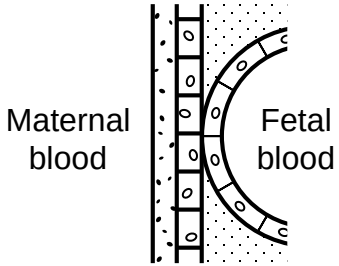
Hemo-tricorial:
Mice



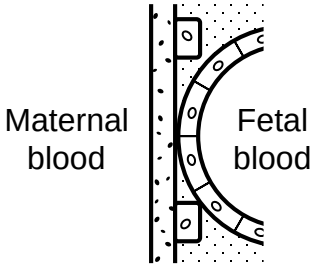
Hemo-monochorial:
Guinea pigs 3rd Δ



Hemo-trichorial



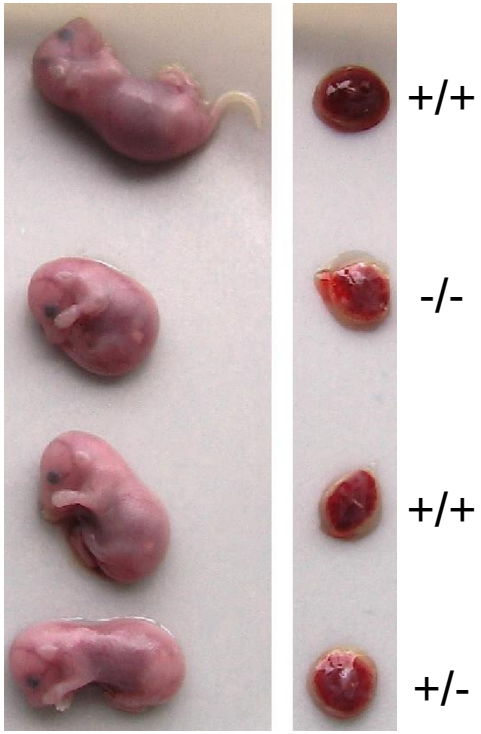
Hemo-dichorial

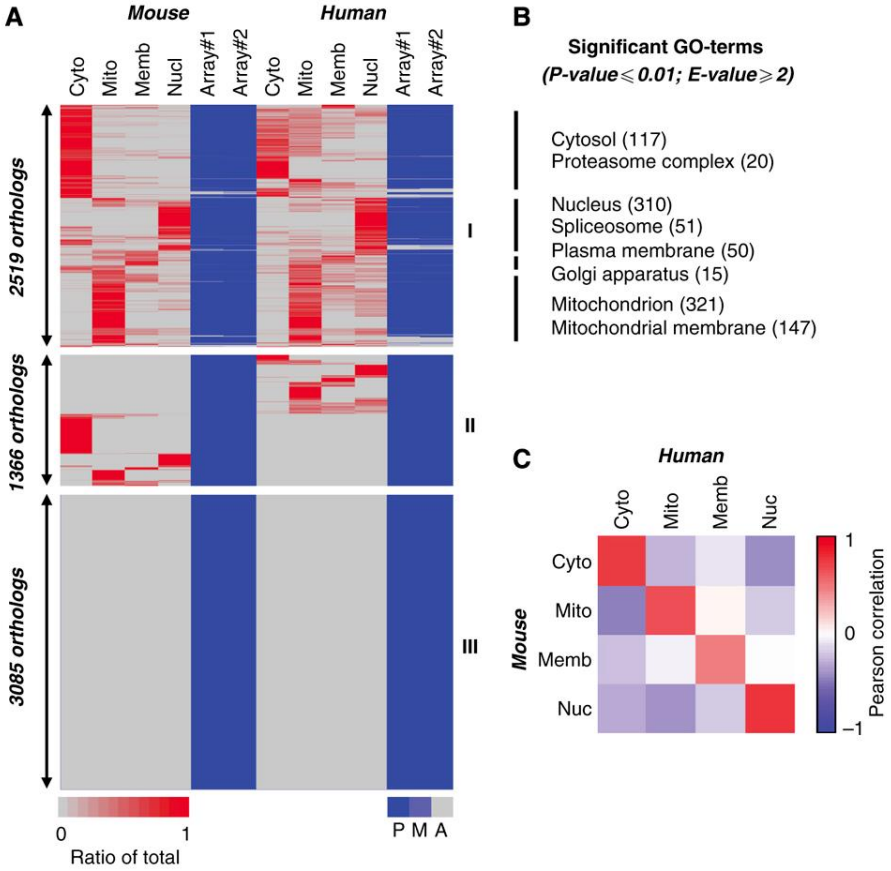


Hemo-monochorial

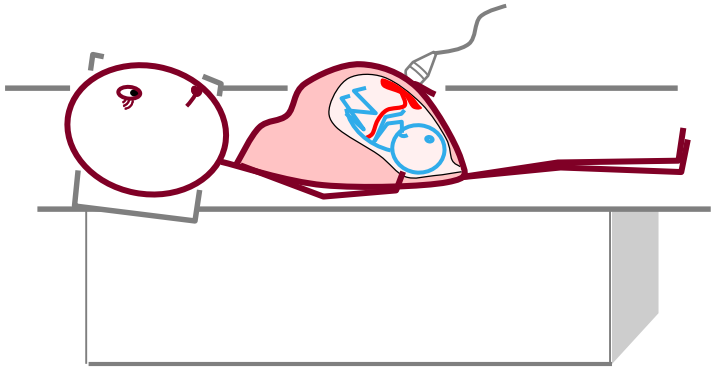
Modified from Benirschke & Kaufmann, Pathology of the Human Placenta

Similarity between protein and mRNA ortholog expression in human and mouse



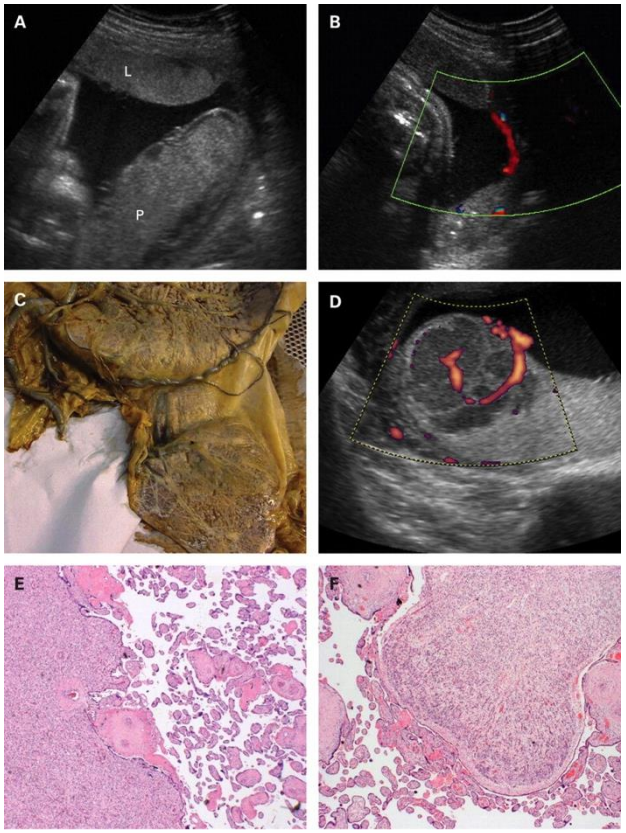


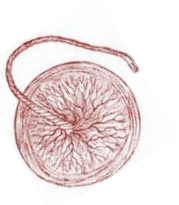
Cox B, Mol Syst Biol 2009



US is the mainstay in placenta imaging

Sonographic appearance of a placenta with a succenturiate lobe

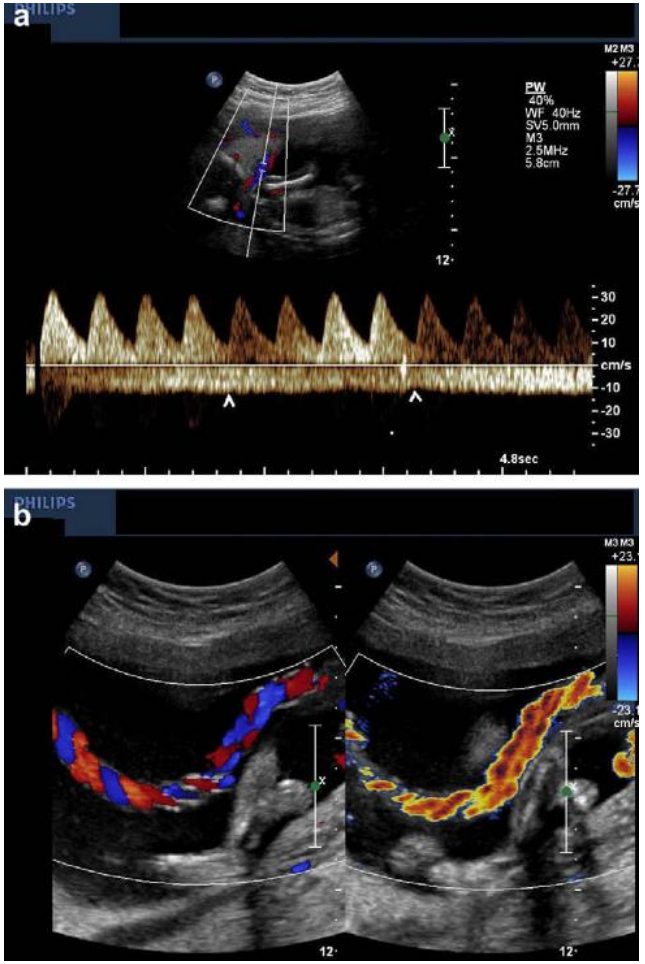




Sebire, J Clin Pathol 2008

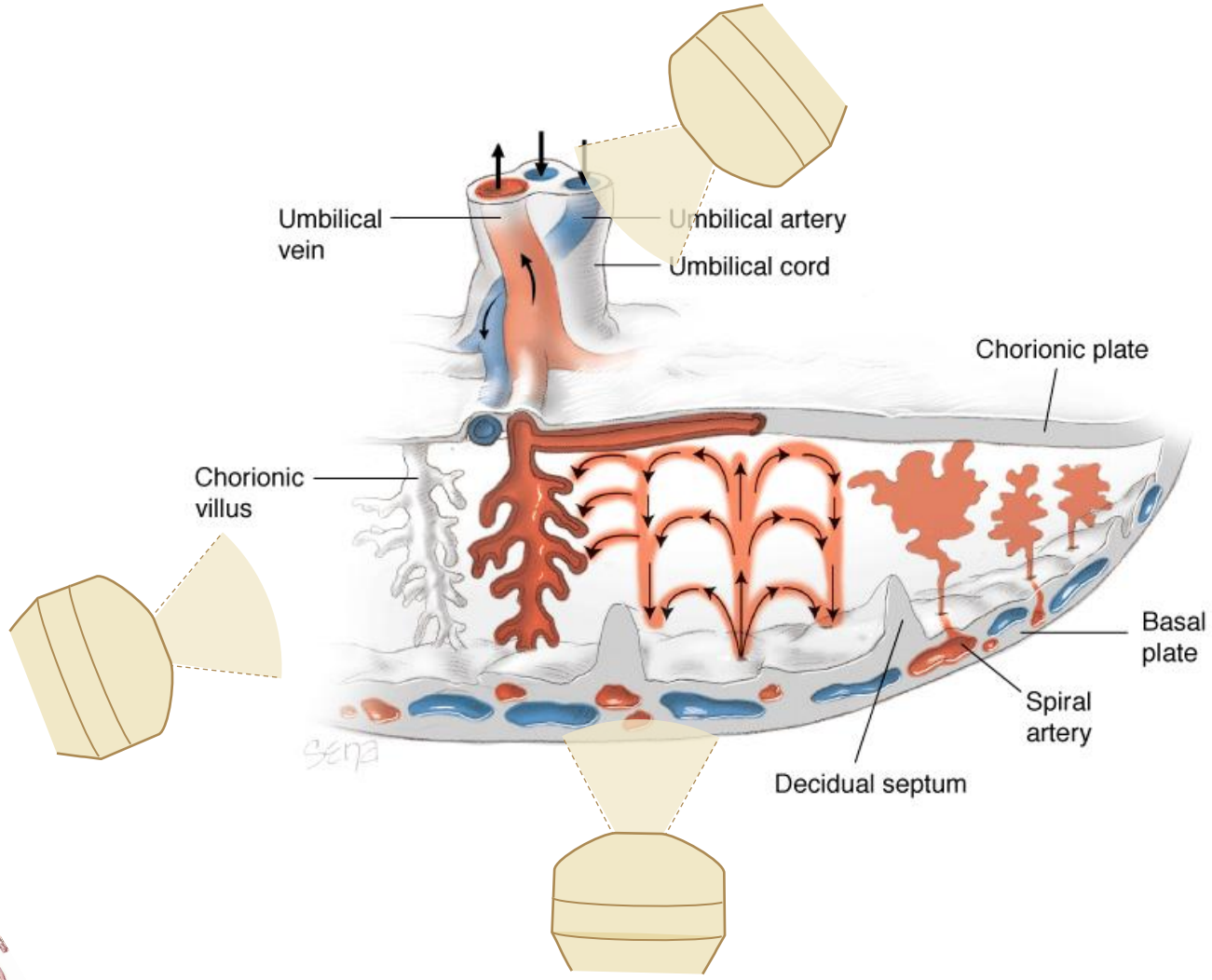
Placental perfusion

- 25% of the maternal cardiac output is directed to the placenta
- 30% of the fetal cardiac output is directed to the placenta
- Blood flow analysis:
  - Uterine artery
  - Umbilical artery
  - Umbilical vein
  - Intervillous space



Abramowicz, Placenta 2008

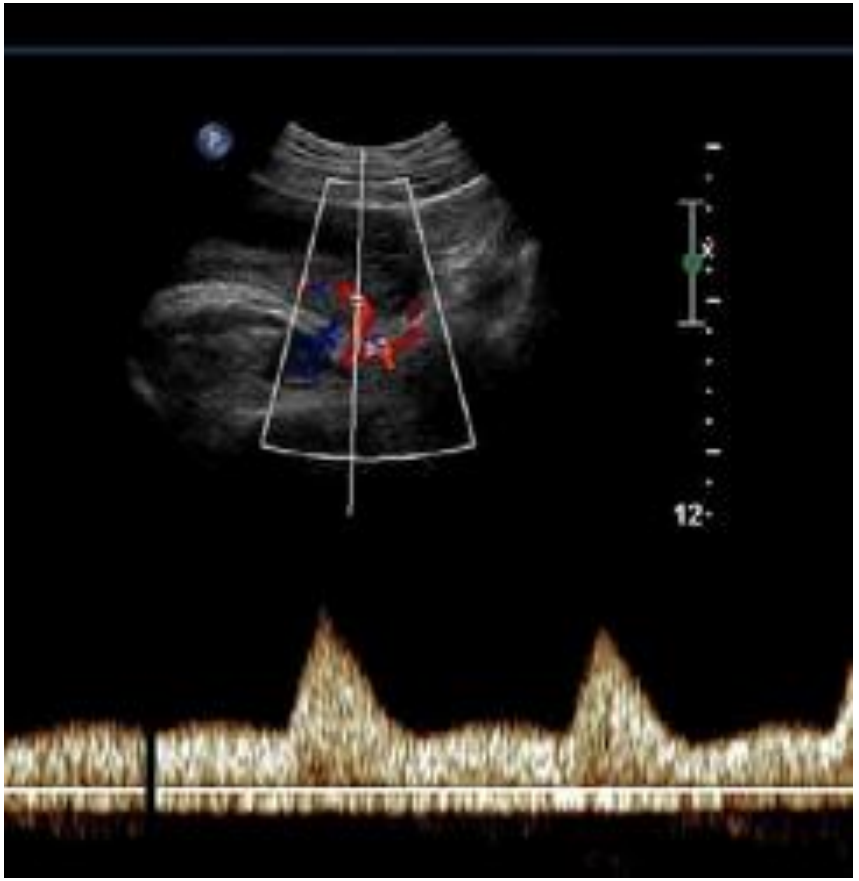
Human placental blood flow



Williams, Obstetrics, 23rd Ed

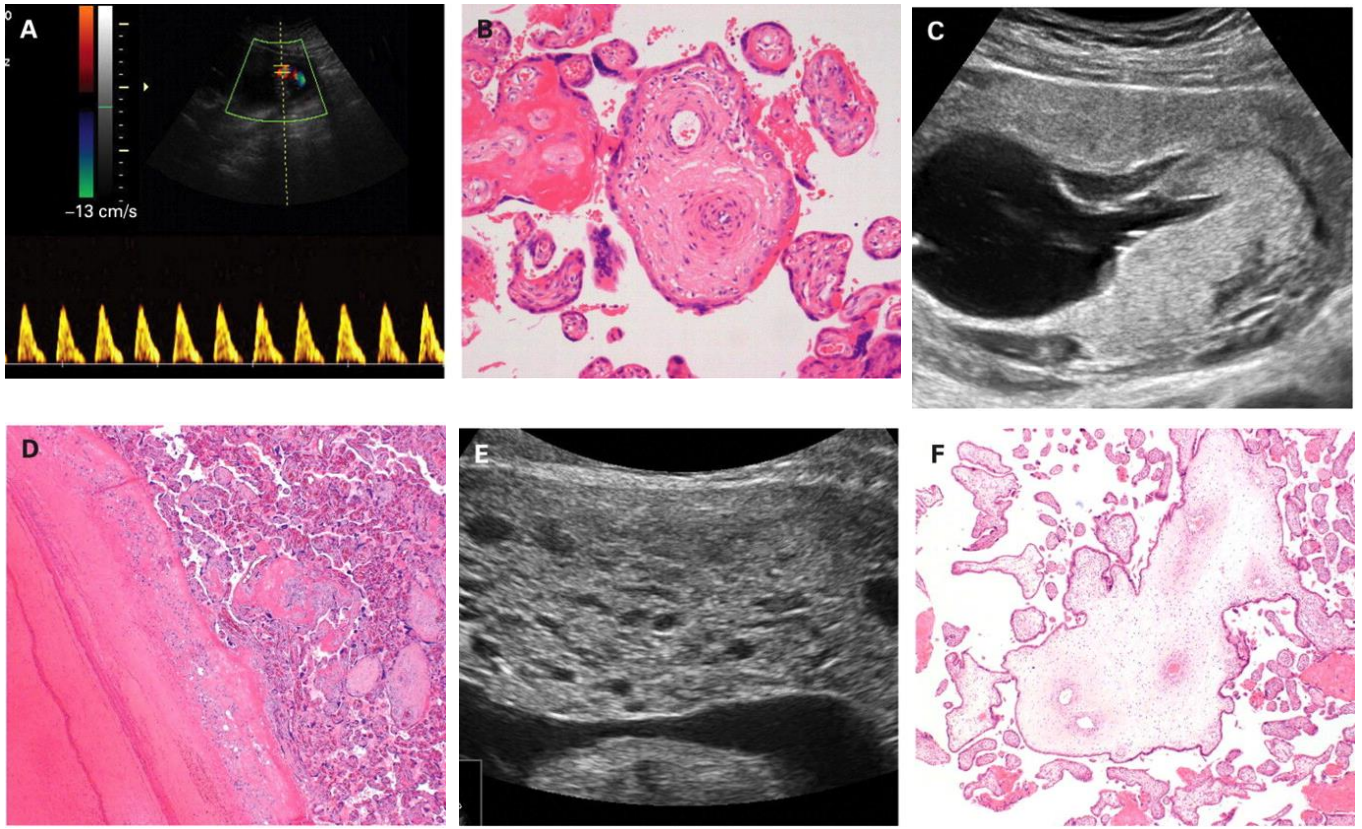
Uterine artery flow

- Reflects invasion of uterine arteries and their conversion to dilated vessels
- Notch representing impedance to flow



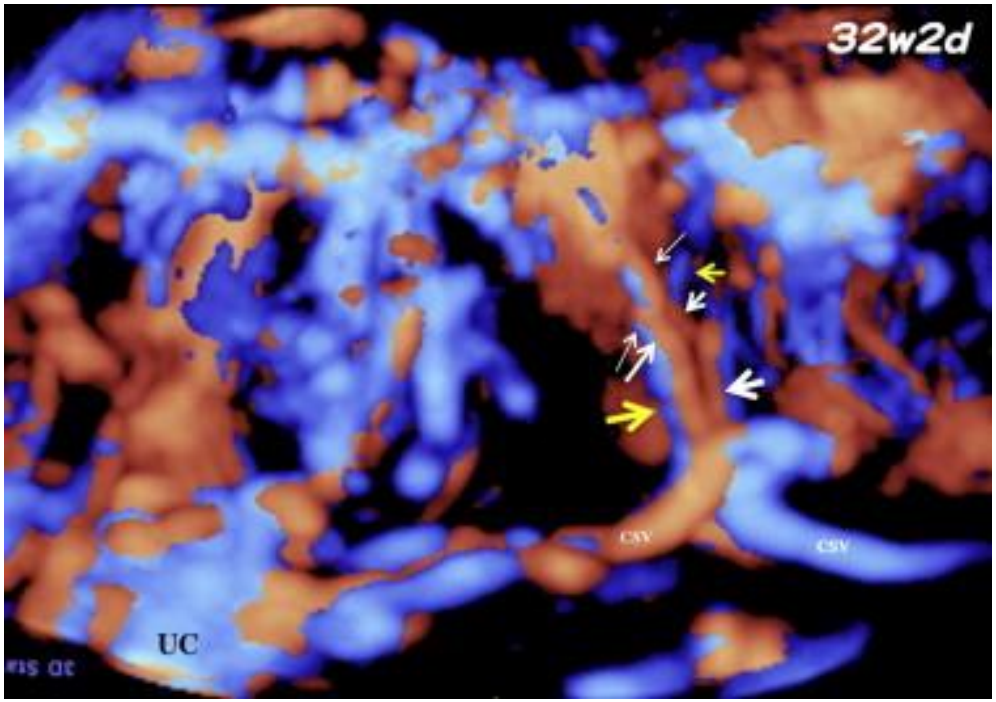
Abramowicz, Placenta 2008

Abnormal umbilical artery Doppler flow velocity waveforms with an absent end-diastolic component, associated with growth restriction and fetal hypoxia



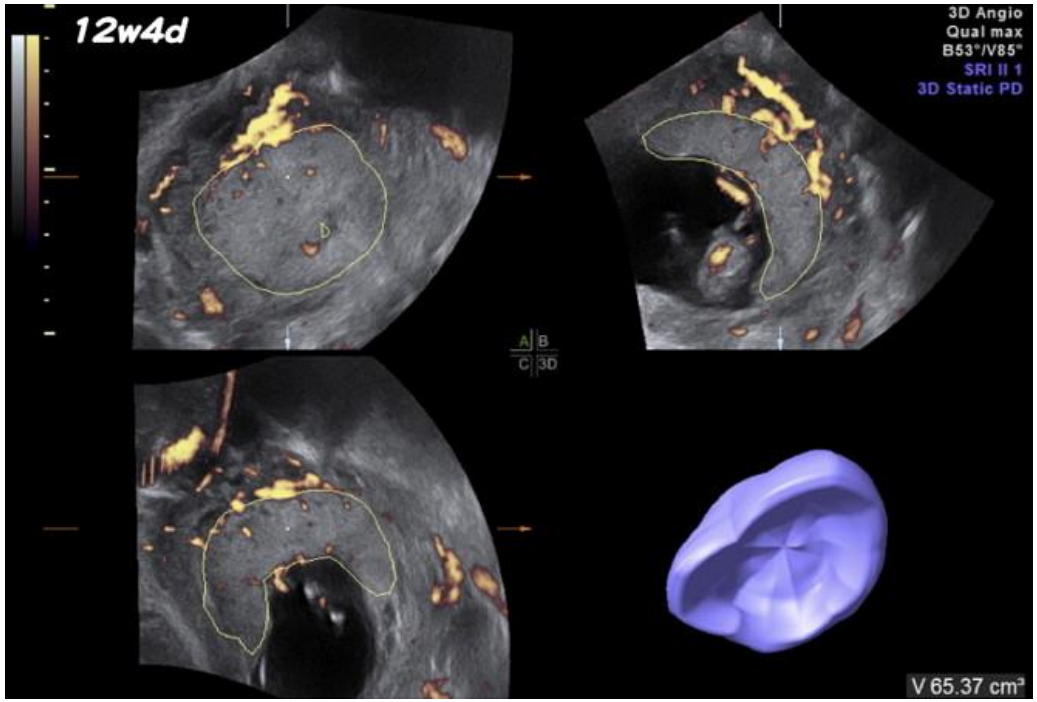
Sebire, J Clin Pathol 2008

Placental intervillous space: 3D high definition US (32 weeks)



Hata, Placenta 2011

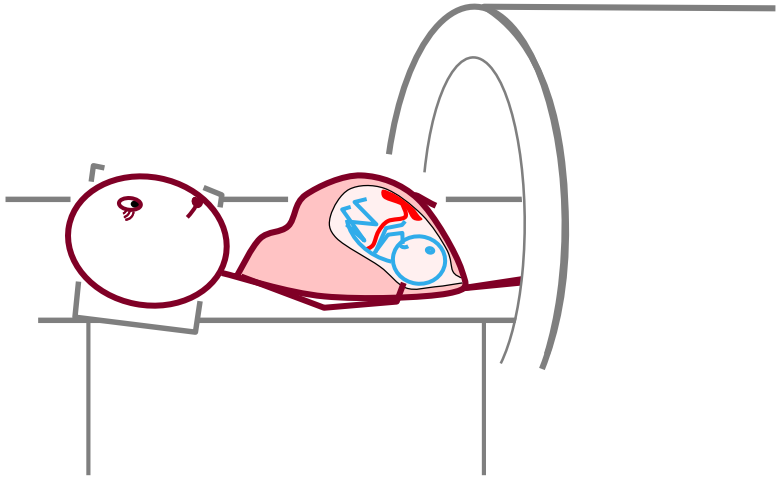
Placental volume: Virtual organ computer-aided analysis (VOCAL), 12.5 wks



Limitations

Resolution
Placental function

Hata, Placenta 2011

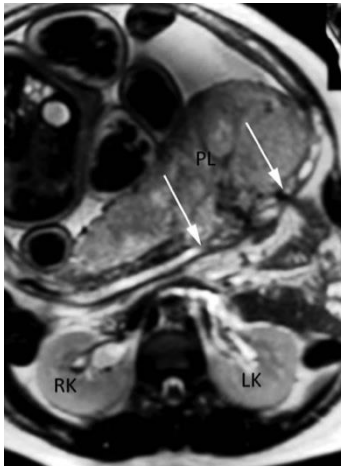


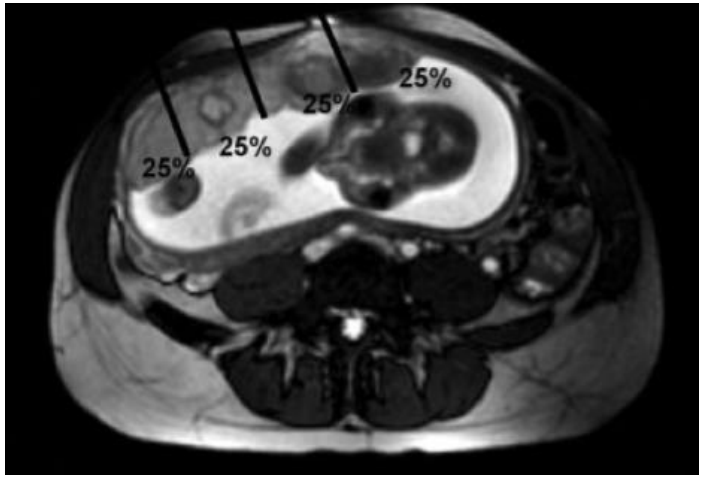
Limitations

Cost
Accessibility
Placental function
Safety

Placental MRI: Main indications

- Placental location (e.g., placental previa)
- Depth of invasion (e.g., placenta accreta)
- Placental volume (and fetal growth)
- Placental morphology in obese patients



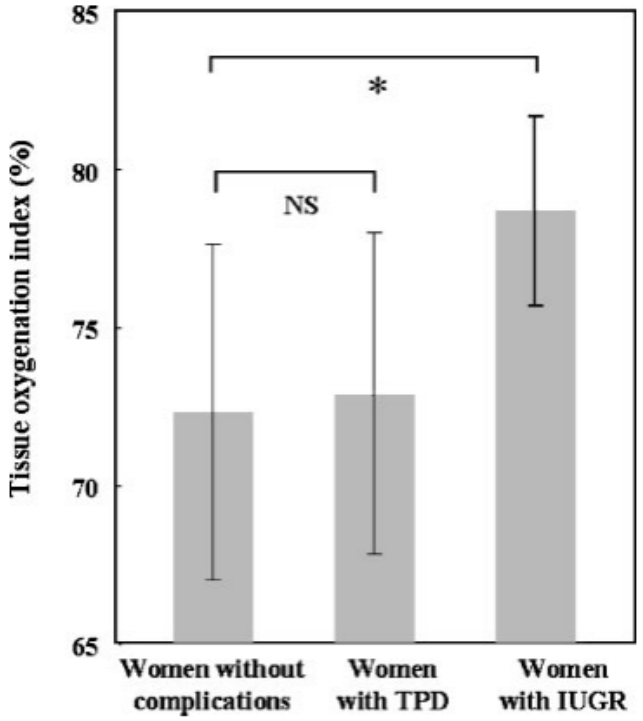


Palacios-Jaraquemada, Acta OBGYN 2013
Messerschmidt, Ultrasound Obstet gynecol 2011

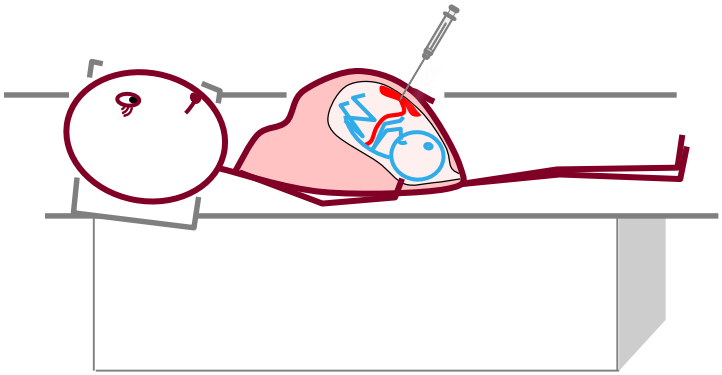
Placental MRI: Functional perfusion analysis

- Arterial Spin Labeling (flow-sensitive alternating inversion recovery (FAIR)
  - Non invasive arterial blood labeling
- Intravoxel incoherent motion (IVIM)
  - A pulse field gradient- diffusion independent contrast
- Fast:
  - Echo planar imaging
  - Single shot fast spin echo imaging
- Blood oxygen level-dependent (BOLD) MRI:
  - Signals depend on hemoglobin-deoxyhemoglobin

Near Infrared Spectroscopy



Kakogawa, Am J Perinatol 2010

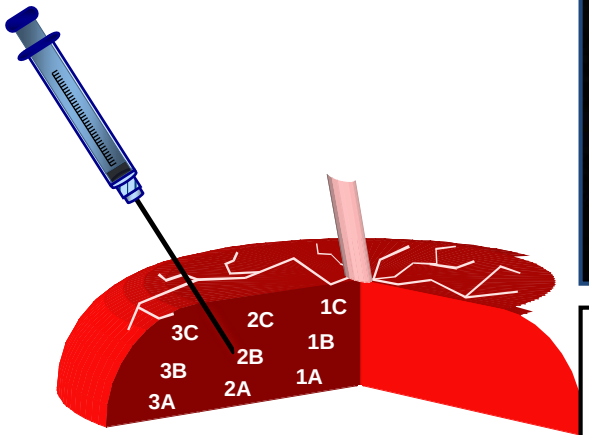


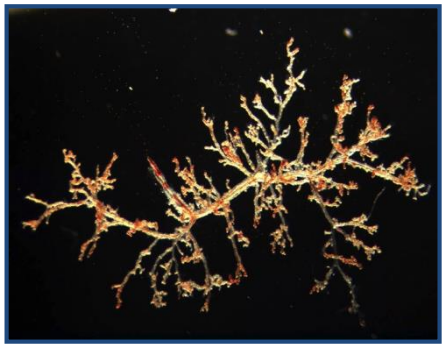
Safety
Real time assessment

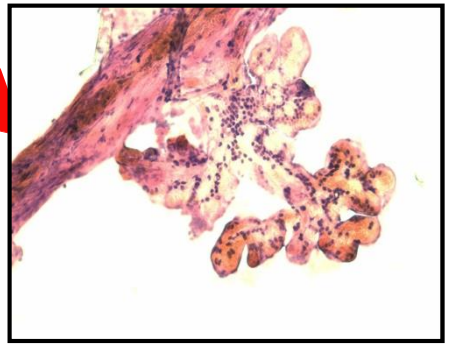
Placental needle biopsy

- Histopathology
- Genome
- Epigenome
- Transcriptome
- Proteome
- Metabolome
- Lipidome
- Microbiome

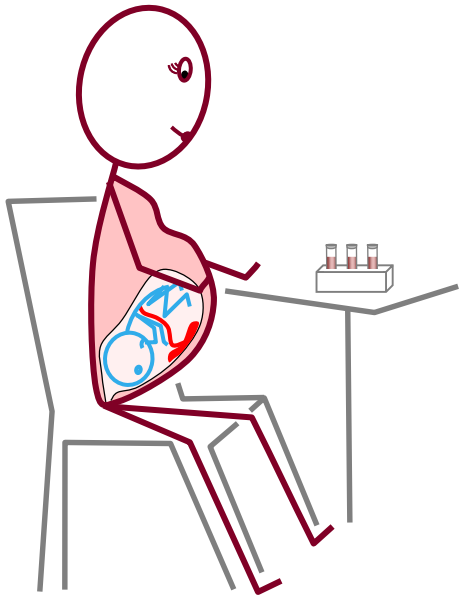
- Single cells analysis?



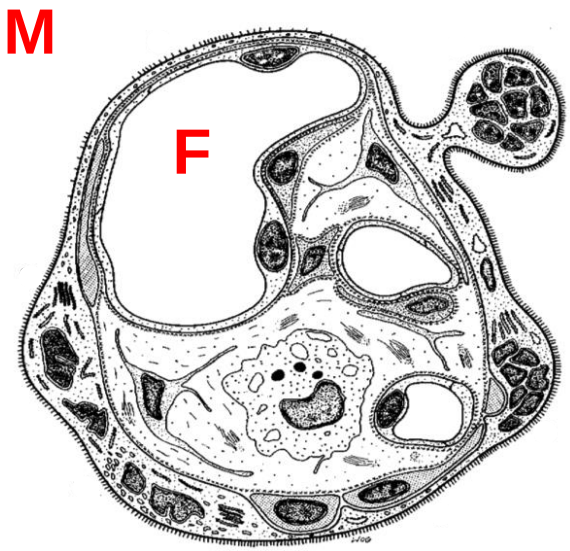


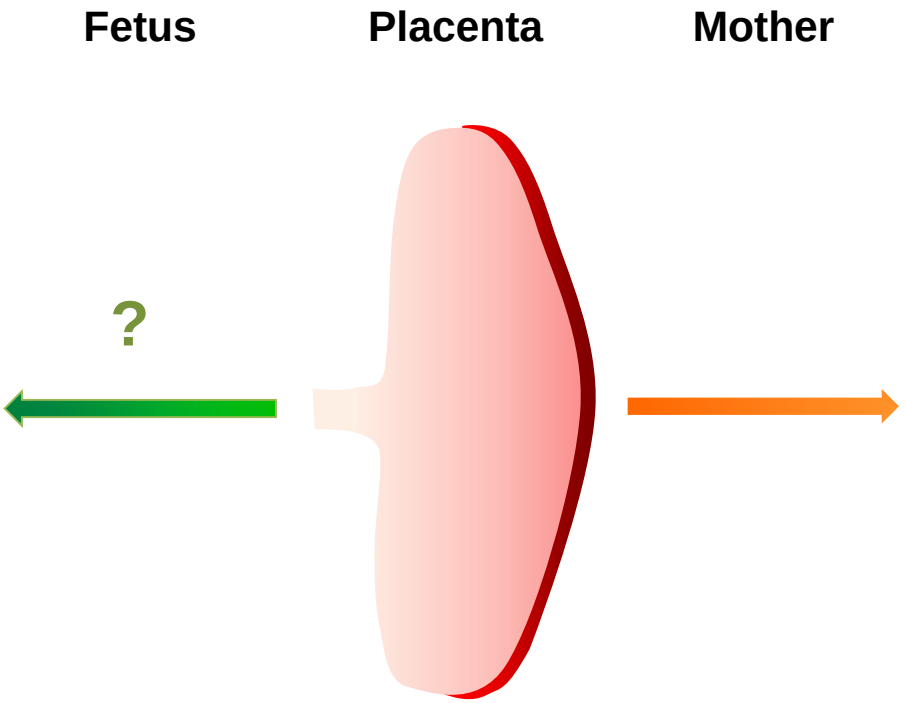


Sadovsky…Nelson, Am J Obstet Gynecol 2006



Placental communication: shedding molecules and nucleic acids





Selection of fetal markers
Predictive values

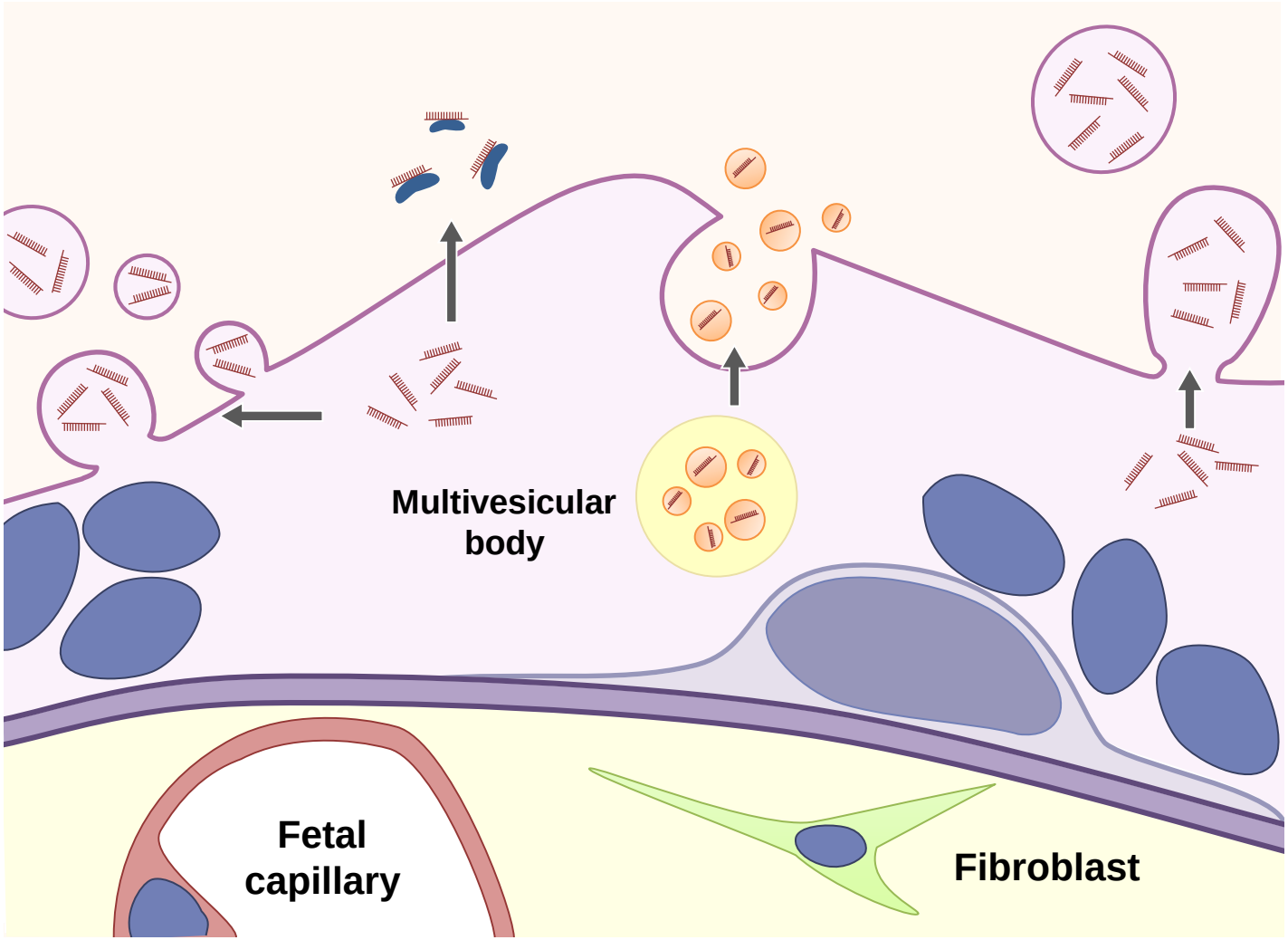
Microvesicle

Proteins

Exosome

Apoptotic bodies
cell fragments

Maternal
blood



Trophoblast

Basement
membrane

Ouyang et al, Placenta 2014

Blood protein markers of placental function

- MSAFP
- hCG
- Estriol E_3
  (urinary estriol and pregnanediol)
- Activin-A and inhibin-A
- hPL
- sFlt/PlGF ratio
- sEndoglin
- PLF
- PTX3
- P-selectin
- PAPP-A
- PP13

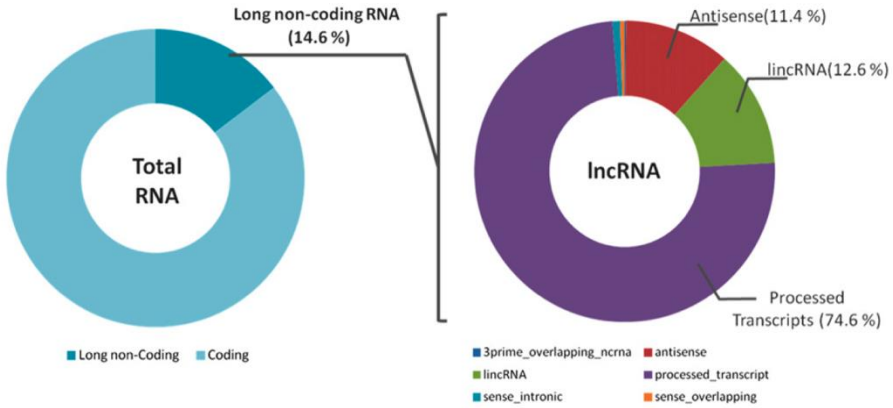
Blood biomarkers - fetal DNA

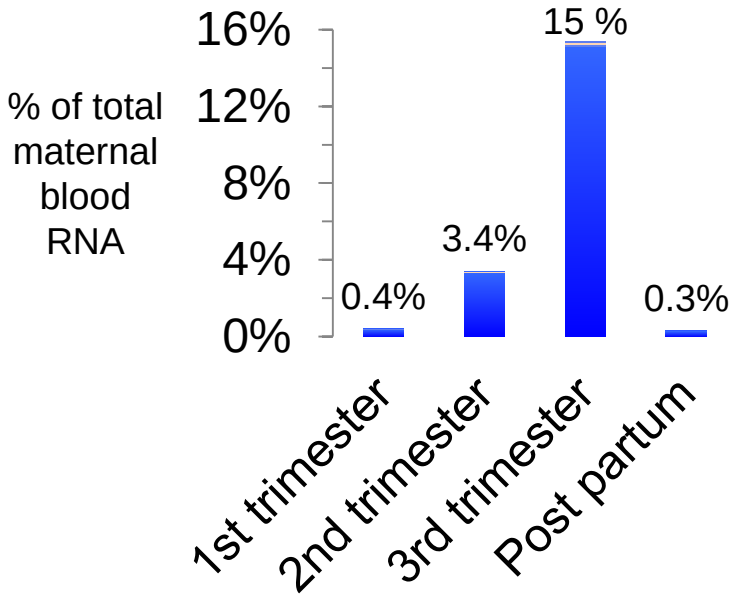
Free feto-placental nucleic acids (Quantity? Type?)

- SRY gene (pree, FGR)
- DYS-14 sequence (on Y-chromosome, Pree, FGR)
- DYS-1 sequence (Pree, FGR)
- Hypermethylated RASSF1A (Pree, FGR)
- Total extracellular DNA
  - Ubiquitous beta-globin (GLO gene, Pree, FGR)
  - GAPDH gene (Pree)

Hromadinkova, DNA Cell Biol 2014

Cell free fetal RNA in maternal circulation



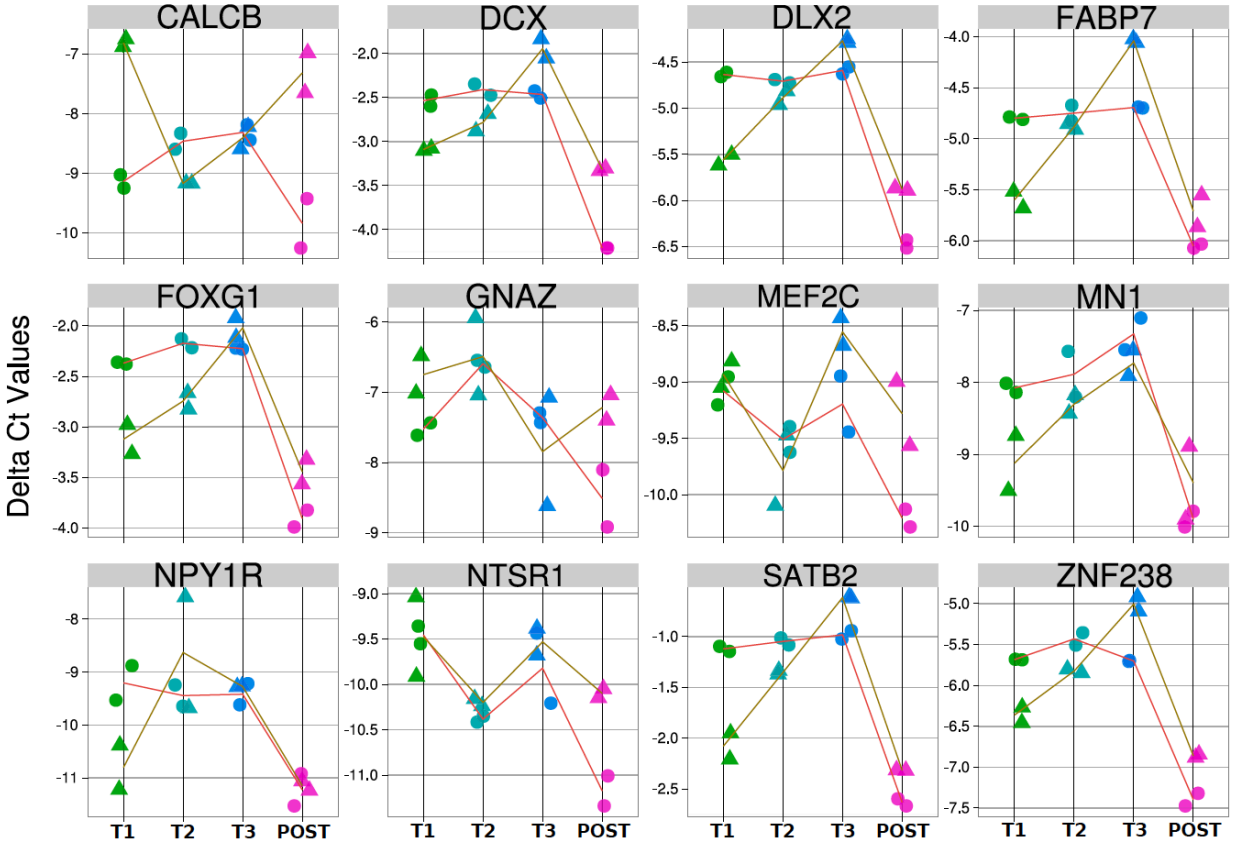


Different expression in different trimesters

CRH (pree, FGR)	VEGF (Pree)
GCM1 (Pree)	Inhibin A (Pree, FGR)
PLAC1 (Pree)	KiSS-1 (Pree, FGR)
hPL (Pree, FGR)	P-selectin (Pree, FGR)
PAPP-(Pree, FGR)	
	miRNAs

Koh, Proc Natl Acad Sci USA 2014

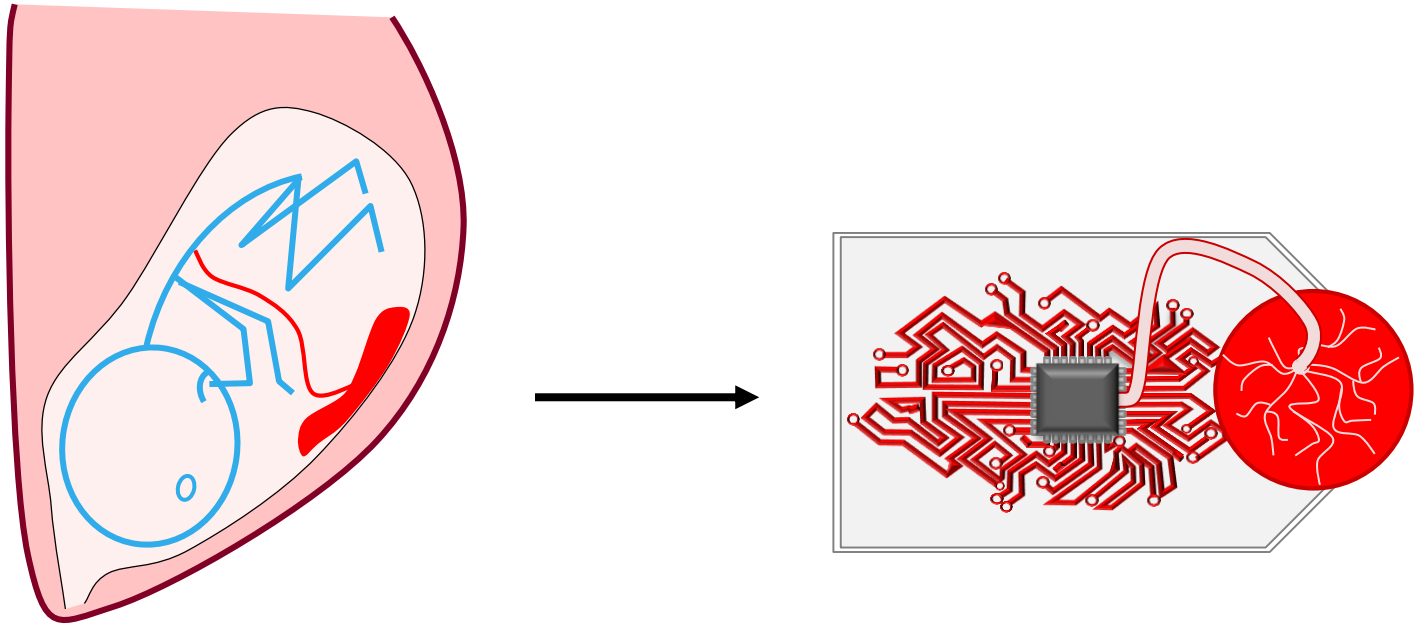
Cell free fetal brain-specific genes in the maternal circulation



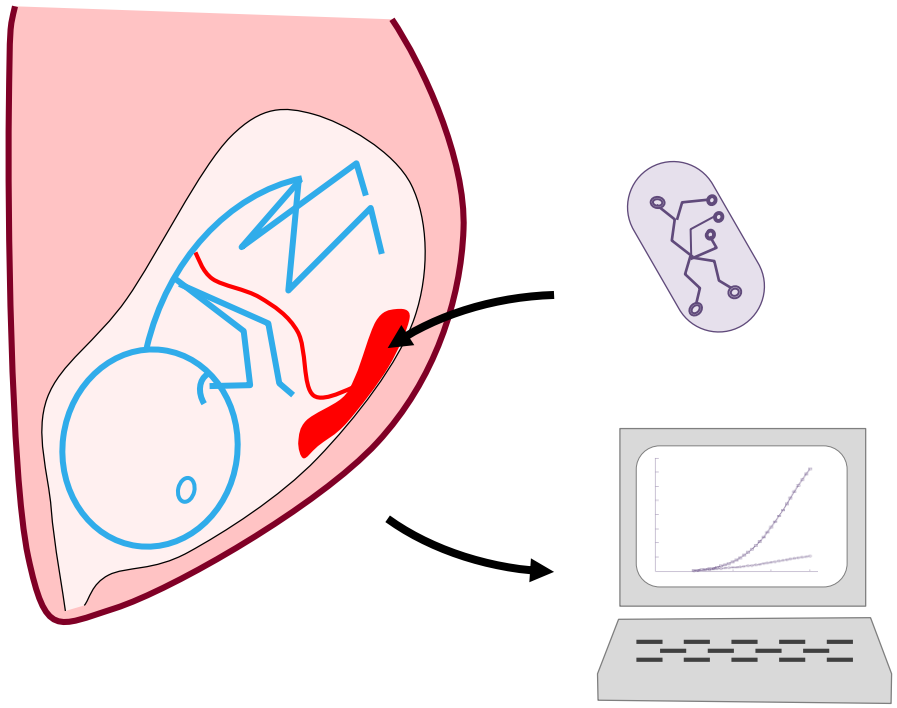
Koh, Proc Natl Acad Sci USA 2014

It is tough to make predictions, especially about the future—Yogi Berra

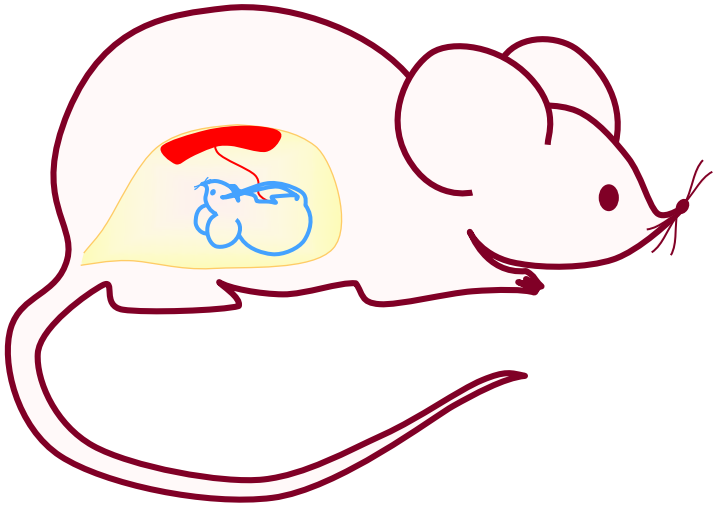
Future technologies: Placenta on a chip

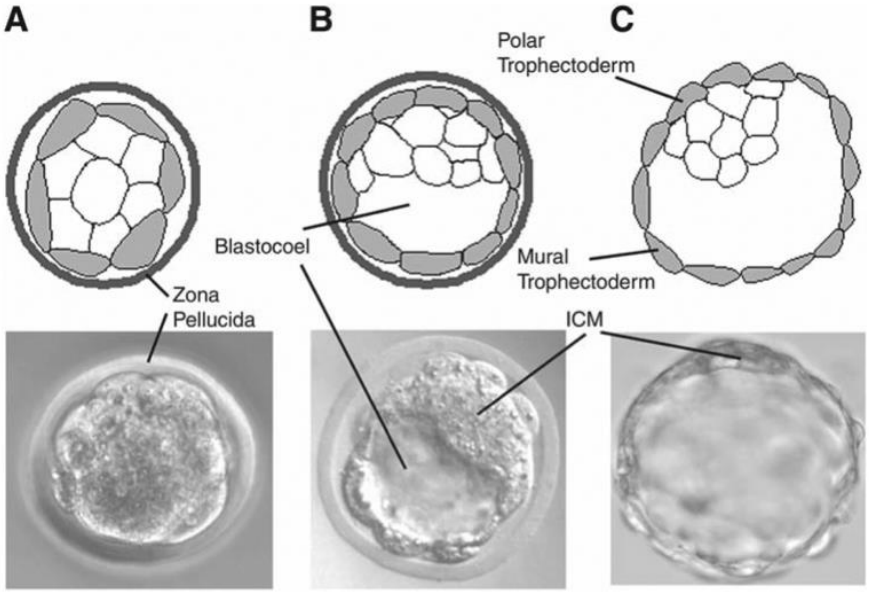


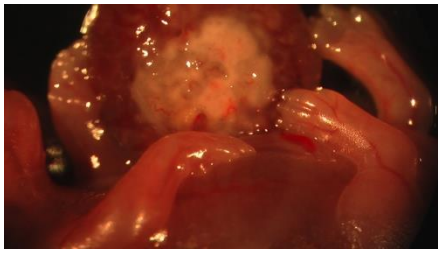
Future technologies: Nano-plac

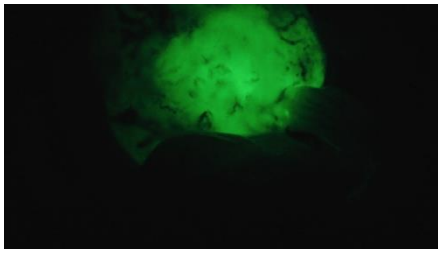


Lentivirus-mediated placental transduction









Mishima and Sadovsky, in preparation

Future technologies: Gestometer