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
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.

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 stars 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

Limitations
- 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
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

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
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)
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
Limitations

Real time assessment

Safety
Placental needle biopsy

- Histopathology
- Genome
- Epigenome
- Transcriptome
- Proteome
- Metabolome
- Lipidome
- Microbiome
- Single cells analysis?

Placental communication: shedding molecules and nucleic acids

Limitations

Selection of fetal markers
Predictive values
Microvesicle Apoptotic bodies cell fragments

Maternal blood

Trophoblast

Basement membrane

Multivesicular body

Fetal capillary

Fibroblast

Ouyang et al, Placenta 2014
Blood protein markers of placental function

- MSAFP
- hCG
- Estriol E₃
  (urinary estriol and pregnanediol)
- Activin-A and inhibin-A
- hPL
- sFlt/PIGF 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)
- GCM1 (Pree)
- PLAC1 (Pree)
- hPL (Pree, FGR)
- PAPP-(Pree, FGR)
- VEGF (Pree)
- Inhibin A (Pree, FGR)
- KiSS-1 (Pree, FGR)
- P-selectin (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