Does Sexual Dimorphism in Placental Function Relate to Adverse Outcomes in Females versus Males?

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Sexual Dimorphism in Fetal Outcomes

- Male fetuses are larger but have more adverse outcomes:
  - preterm birth, PPROM, placenta previa, preeclampsia, lagging lung development, macrosomia, late stillbirths.

- “Boys live dangerously in the womb” *(Eriksson et al 2010)*

- Differences in fetal programming of metabolic syndrome based on sex of fetus.

Q.’s What are the mechanisms? Are boys more reckless or have girls evolved a protective mechanism?
The Placenta is the Center of the Perinatal Universe
How does the placenta contribute to alterations in fetal development?

- **Passive:**
  - Exposure to altered levels of nutrients, EDC’s and transfer

- **Physical:**
  - Altered vascular resistance (heart)

- **Functional:**
  - Effect of adverse intrauterine environment e.g. oxidative stress, nitrative stress, altered expression of nutrient transporters, receptors, synthesis of steroids and peptides regulating maternal metabolism and fetal growth and development eg hPL, serotonin

- **Role of genetic/epigenetics:**
  - Imprinted genes, environmental influences on placental (and fetal) gene expression and function
Evidence for Sexual Dimorphism in Placental Function

- Differences in placental gene expression:
  - immune genes expressed at higher level in female placenta (JAK1, IL2RB, Clusterin, LTBP, CXCL1, IL1RL1, TNFR)
- Response to maternal inflammatory status
- Response to maternal adiposity
- microRNA expression different in males vs females in normal pregnancy
- Differences in:
  - aromatase expression with preeclampsia
  - expression of antioxidant enzymes
  - lipid uptake and metabolism
Maternal Obesity

Adverse Intrauterine Environment

- Oxidative/Nitrative Stress
- Inflammation
- Dyslipidemia
- Epigenetic Changes

Sexual Dimorphism

- Altered Placental Function

- Adverse pregnancy outcome
- Fetal programming
Sexual Dimorphism in the Effect of Adiposity on Placental Antioxidant Enzyme Activity

A. SOD activity (U/mg protein)
   - Lean: 0.6
   - Obese: 0.4

B. CAT activity (nmol FC/10 min/mg protein)
   - Lean: 0.5
   - Obese: 0.4

C. TAC (μmol Trolox/mg protein)
   - Lean: 40
   - Obese: 30

A. GPx activity (nmol/min/mg protein)
   - Lean: 800
   - Obese: 600

B. TrxR activity (nmol NTB/min/mg protein)
   - Lean: 6
   - Obese: 4
Conclusions

- In the lean woman the placenta of a male fetus has the highest antioxidant enzyme activity.
- Maternal obesity is associated with decreased placental antioxidant enzyme activity.
- In the obese woman the placenta of a male has the highest oxidative and nitrative stress.
- Selenoprotein antioxidant enzymes may increase as a compensatory response to oxidative stress.
- Obesity causes placental oxidative stress in a sexually dimorphic manner to increase adverse outcomes for the male fetus.
Expression of Inflammatory and Apoptotic Markers in Male and Female Placentae with PE

Data expressed are mean ± SD; n=4; ANOVA followed by Tukey’s post hoc test p< 0.05

Sexual dimorphism in Placental miR-210 Expression
Effect of TNFα on miR-210 Expression in Male and Female Trophoblasts
Inhibition of NFkB1 prevents a TNFa-induced decrease in mitochondrial respiration in trophoblasts of females but not males.
Conclusion

• There is a sexual dimorphism in placental miR-210 expression with increasing maternal adiposity.

• miR-210 expression can be regulated by TNFα via the NFκB pathway.

• The increase in miR-210 expression could represent an integral part of the adaptation to an adverse in utero environment in placentas from the female fetus.

• This could underlie previously shown reduced susceptibility of female fetuses to perinatal complications when compared to a male fetus.
Fatty Acid Uptake and Metabolism in Placenta

Maternal circulation

SLC27A4
CD36/FAT
LPL

SLC27A4
CD36/FAT

FABP1
HADHA
HADHII

Placental cell

Fatty Acid B-oxidation

3-ketoacyl CoA
acyl-CoA
2,3-enoyl-CoA
3-hydroxyacyl-CoA

Fetal circulation

SLC27A4
CD36/FAT
LPL

SLC27A4
CD36/FAT

* = Affected by BMI
+ = Affected by gender
Effect of Maternal Adiposity on Expression of Fatty Acid Oxidation Enzymes

G

H

I

J
Sexual Dimorphism
Conclusions

• Abundant and increasing evidence for sexual dimorphism in placental function
• Linked to different outcomes male vs female
• Underlying mechanism not known – endocrine milieu, X-linked genes
• Is the male reckless or the female smart?
Minimum Requirements for Placental Studies

• Stratify by fetal sex
• Control for gestational age
• Random sampling protocol across placental surface for placental tissue
• C section, no labor to avoid oxidative stress
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