Biomarkers of Exposure and Risk: The Quest for Early Diagnosis and Intervention

Maternal Circulating MicroRNAs Control The Placental Response To PAE*

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Conflict of Interest Statement:
I do not have an affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.
miRNAs are small non-coding RNAs that act as translational repressors.
Predicting birth outcomes with secreted miRNAs
Predicting birth outcomes

Plasma miRNA Profiles in Pregnant Women Predict Infant Outcomes following Prenatal Alcohol Exposure

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<table>
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<th>ID</th>
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<th>Late Pregnancy</th>
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Exiqon qRT-PCR miRNA arrays (752 miRNAs)
HEa-predictive miRNAs

ANOVA Model: HEa > (HEua ≈ UE) = HEa-miRNAs
miRNAs Are Predicted to inhibit Epithelial Mesenchymal Transition (EMT) which is critical for Early Development

Epithelium
Lamina Propria

SNAIL
TWIST
Vimentin
E-Cadherin

Cytotrophoblasts & Syncytiotrophoblasts
Endometrium

SNAIL
TWIST
Vimentin
E-Cadherin

Extra-villous trophoblasts

Source: wikipedia
miRNAs are:

Placentally Abundant

Dysregulated in Birth Pathologies due to Placental Dysfunction

- Preterm Birth
- Fetal Growth Restriction
- Spontaneous Abortion
- Preeclampsia
miRNAs are likely to be

- Secreted by placenta
- Into maternal circulation
- As a response to placental stress
- To coordinate (we hypothesize) the placental response to stress
- Do miRNAs explain the effects of prenatal alcohol exposure on placental EMT?
  - Rodent and Primate PAE models
Alcohol Exposure Disrupts Placental EMT In A Mouse Model of PAE
Alcohol Exposure Affects Placental EMT In A Primate Model of PAE

P=0.034 Main Effect of Ethanol Exposure

P=0.425
Alcohol exposure significantly inhibits EMT transcripts in rodent and primate.

Do HÉa miRNAs control EMT?
Summary of effects of HEa miRNAs

- HEa miRNAs collectively (but not individually) inhibit placental growth and result in aberrant endocrine maturation
- Do they therefore inhibit fetal growth?

<table>
<thead>
<tr>
<th>HEa miRNA Over Expression</th>
<th>Cytotrophoblast</th>
<th>Syncytiotrophoblast</th>
<th>Extravillous Trophoblast</th>
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Maternal miRNAs, elevated in the HEa group result in decreased placental and fetal growth, and blood flow.
HC (Head Circumference)

Weigh

Height

Preterm Birth

Fetal Growth Restriction

Spontaneous Abortion

Preeclampsia

Gestational Pathologies

hsa-miR-222-5p

hsa-miR-519a-3p

Preeclampsia/Fetal Growth Restriction

hsa-miR-885-3p

hsa-miR-518f-3p

hsa-miR-204-5p

• HC (Head Circumference)

• Weigh

• Height
miRNAs which predict PAE effect on infant growth outcomes

• Are elevated in the plasma of pregnant women at mid-pregnancy
• Moderate effects of PAE on placental EMT in rodent and primate
• Inhibit placental trophoblast EMT and invasion and reduce placental size
• Result in fetal growth restriction

Manipulating maternal miRNAs may be a means to ameliorate effects of PAE
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