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Uterine Artery Dysfunction in ACE2 Deficient Mice is Associated with Placental Hypoxia and Reduced Umbilical Flow

DISCLOSURE INFORMATION:
No relationships to disclose.
Uterine Artery Dysfunction in ACE2 Deficient Mice is Associated with Placental Hypoxia and Reduced Umbilical Flow

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Fetal Intrauterine Growth Restriction

- The failure of a fetus to reach his/her biological growth potential

- Leading cause of neonatal mortality

- IUGR is linked to a high risk for future perinatal morbidities and physical and/or mental abnormalities in later life including higher incidence of adult diseases (type 2 diabetes, hypertension and cardiovascular disease)
Uteroplacental Factors Leading to Intrauterine Fetal growth Restriction

Maternal portion of the placenta: uterine artery reactivity and hemodynamics

Fetomaternal interface: trophoblast invasion, placental vascular development and oxygenation

Fetal part: umbilical artery hemodynamics
Renin-Angiotensin System and Normal Pregnancy

Angiotensinogen

\[ \text{Renin} \rightarrow \text{ACE2} \]

\[ \text{Ang I} \rightarrow \text{Ang-(1-9)} \]

\[ \text{Ang II} \rightarrow \text{Ang-(1-7)} \]

\[ \text{AT}_1\text{R} \quad \text{AT}_2\text{R} \quad \text{Ang}_1\text{-7/MAS} \]

Vasoconstriction
Inflammation
Proliferation

Vasodilation
Anti-Inflammation
Anti-Proliferation
The Distribution of ACE2 in Placenta Suggests Its Paracrine Influence on Uteroplacental Physiology

G. Valdes et al., Placenta, 2006

syncytiotrophoblast (arrows), fetal endothelium (dashed arrows); normal term pregnancy

G. Valdes et al., Placenta, 2006
Pregnant ACE2 Knockout (ACE2 KO) Mouse – a Model of IUGR

- C57Bl/6 background (Gurley and Coffman, 2006)
- no cardiac abnormalities
- modest increase in blood pressure

**Late Pregnancy:**
- Reduced fetal growth and maternal weight gain
- Circulation: reduced Ang-(1-7)
- Placenta: increased Ang II

Bharadwaj MS et al., Hypertension, 2011
Hypothesis

ACE2 deficiency induces uteroplacental dysfunction as early as mid-gestation before the major growth of fetus occurs.
### Lower Maternal and Fetal Weights, Fetal-to-Placental Weight Ratio in ACE2 KO vs. C57Bl/6 Mice at Mid-Gestation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>C57Bl/6 (n=5)</th>
<th>ACE2 KO (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s BW(g)/tibia length (cm)</td>
<td>17.9±0.20</td>
<td>16.42±0.37*</td>
</tr>
<tr>
<td>(Mother’s BW – total pup BW), g/tibia length (cm)</td>
<td>16.63±0.30</td>
<td>15.30±0.38*</td>
</tr>
<tr>
<td>Pup BW (g)/tibia length (cm)</td>
<td>0.15±0.01</td>
<td>0.11±0.01*</td>
</tr>
<tr>
<td>Pup BW/placental weight ratio</td>
<td>3.15±0.28</td>
<td>2.44±0.11*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>85.1±1.90</td>
<td>102.3±5.10*</td>
</tr>
<tr>
<td>Proteinuria (mg of protein-to-g of mother’s BW)</td>
<td>1.02±0.09</td>
<td>1.03±0.42</td>
</tr>
<tr>
<td>Maternal serum creatinine (mg/dl)</td>
<td>0.29±0.02</td>
<td>0.34±0.03</td>
</tr>
</tbody>
</table>
No Differences in Vasodilatory Response to Acetylcholine and eNOS Immunostaining in the Uterine Arteries of ACE2 KO and C57Bl/6 Mice at Mid-Gestation
Higher Contraction to KCl and Phenylephrine in the Uterine Arteries of ACE2 KO vs. C57Bl/6 Mice at Mid-Gestation
Increased Sensitivity to Ang II in Uterine Arteries of ACE2 KO and C57Bl/6 Mice at Mid-Gestation

pD2:
ACE2 KO - 8.64±0.04
C57Bl/6 - 8.5±0.03
Differential Expression of AT_{1R} and AT_{2R} in the Uterine Arteries of ACE2 KO and C57Bl/6 Mice at Mid-Gestational
Uterine Artery Resistance is Similar in ACE2 KO and C57Bl/6 Mice

**Uterine Artery**

- **Peak Systolic Velocity**
  - C57Bl/6: [Graph]
  - ACE2 KO: [Graph]
- **Min Diastolic Velocity**
  - C57Bl/6: [Graph]
  - ACE2 KO: [Graph]
- **Resistance Index**
  - C57Bl/6: [Graph]
  - ACE2 KO: [Graph]
No Difference in Trophoblast Invasion in ACE2 KO and C57Bl/6 Mice at Mid-Gestation

C57Bl/6

ACE2 KO

L, labyrinth; JZ, junctional zone; D, decidua; M, mesometrium
Higher Expression of Hypoxia Markers in the Placenta of ACE2 KO vs. C57Bl/6 Mice
Lower Umbilical Artery Velocities and Resistance in ACE2 KO vs. C57Bl/6 Mice at Mid-Gestation

Umbilical Artery Velocities and Resistance in ACE2 KO vs. C57Bl/6 Mice at Mid-Gestation

**Peak Systolic Velocities**

- **C57Bl/6**
- **ACE2 KO**

**Min Diastolic Velocities**

- **C57Bl/6**
- **ACE2 KO**

**Resistance Index**

- **C57Bl/6**
- **ACE2 KO**
ACE2 Deficiency Induced Factors Leading to IUGR

**Maternal portion of the placenta:**
Higher uterine artery reactivity to vasoconstrictors (Phe, Ang II)

**Fetomaternal interface:**
Placental hypoxia

**Fetal part:**
Lower umbilical artery velocities
Conclusions

• Since placental hypoxia is associated with increased risk for fetal growth restriction, higher expression of hypoxia markers in ACE2 deficient mice suggests a protective role of ACE2 in the utero-placental unit.

• Increased contractility of uterine artery may not be related to hypoxia, but may represent an early event that later may translate into hemodynamic changes in the uterine artery.

• Placental hypoxia and uterine artery dysfunction develop before the major growth of fetus occurs and may exacerbate the IUGR phenotype.

• Reduced umbilical flow velocity, frequently associated with restricted fetal weight gain, may be a compensatory event in response to placental hypoxia.
Future Goals and Perspectives

Future studies will establish:

• molecular mechanisms of uteroplacental dysfunction in ACE2 deficiency-induced IUGR

• therapeutic effects of ACE2 replacement/supplementation on fetal growth in pathological pregnancies.
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