Vitamin D And Preeclampsia: Maternal Adverse Outcomes

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Objectives of Presentation

- Overview of preeclampsia & placentation
- Critical assessment of evidence linking vitamin D and preeclampsia
- Role of vitamin D in placenta
  - immunomodulation at maternal-fetal interface
  - regulation of placental hormonal function
- Knowledge gaps & research needs
Functions of Vitamin D

Sun-UVB → Skin

Vitamin D

Intestine → Diet

25OHD

25OHDase

1αOHas

1,25(OH)₂D

VDR

Gene expression

Ca-P homeostasis
Target cells

e.g.
Bone
Intestine
Kidney
Parathyroids

D = D₂+D₃

Other functions
Target cells

e.g.
Placenta
Uterus/decidua
Ovary, testes
Immune system
Cardiovascular system
Muscle
Cartilage
Adipose tissue
Liver
Pancreas
Brain
Lung
Skin
Breast

Endocrine functions

Intra/Para/autocrine functions

1αOHase

1,25(OH)₂D

VDR

Gene expression
Preeclampsia (PE)

- Major cause maternal mortality & maternal/fetal morbidity
  - 50,000 maternal deaths/yr worldwide
- Characterized > 20 weeks by
  - Pregnancy induced hypertension
    - >140 mmHg systolic or >90 mmHg diastolic
  - Proteinuria
    - >300 mg 24 hr urine or >1+ dipstick
    - >0.3 protein to creatinine ratio
- Prevalence similar US & India
  - 5-8% US and 4-10% India
  - > in nulliparous or multiparous with new partner
  - > prior PE or family history of PE
Impaired Placentation in Preeclampsia

Incomplete trophoblast (Tb) invasion

Multifactorial Model of Preeclampsia

Inadequate Tb differentiation

Incomplete Tb invasion

Abnormal placentation

Oxidative stress

Disrupt angiogenesis ($\uparrow$ sFlt-1)

Endothelial dysfunction

Vasospasm  Coagulopathy  $\Delta$ capillary permeability

Immune maladaptation

Genetic influences

Environmental factors

??Vitamin D??

Multifactorial Model of Preeclampsia

??Vitamin D??

Intrinsic Placental Factors
- Increased Placental Mass/Surface:
  - Diabetes
  - Multiple Pregnancies
  - Hypoxia (Anemia, High Altitude)

Extrinsic Factors
- Inadequate Maternal Response or Removal

Maternal Factors
- Overload of Apoptotic Removal
- Secondary Necrosis of Apoptotic Particles
- Preeclampsia

Villous Cytotrophoblast
- Differentiation adequate
- Inadequate

Villous Syncytiotrophoblast
- Differentiation adequate
- Inadequate

Apoptosis
- increased

Syncytial Knots

Aponecrosis/Necrosis
- STMB, Non-Apoptotic Trophoblast Fragments
- Systemic Effects of Necrotic Material

Engulfment of Apoptotic Particles in the Lungs

Normal Pregnancy

Preeclampsia

Huppertz, B. Hypertension 2008;51:970-975
<table>
<thead>
<tr>
<th>Study</th>
<th>PE n</th>
<th>C n</th>
<th>21 wk</th>
<th>28 wk</th>
<th>36 wk</th>
<th>Terminally</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halhali 2004 (MX)</td>
<td>10</td>
<td>40(160)</td>
<td>77.5</td>
<td>107.5</td>
<td>137.5</td>
<td>77.5</td>
</tr>
<tr>
<td>Bodner 2007 (US; NP)</td>
<td>49(59)</td>
<td>216(220) &lt;22 wk</td>
<td>45.4*</td>
<td>53.1</td>
<td></td>
<td>54.7*</td>
</tr>
<tr>
<td>Halhali 1995 (MX)</td>
<td>26</td>
<td>26</td>
<td>106.5*</td>
<td>130.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halhali 2000 (MX; Term)</td>
<td>24</td>
<td>24</td>
<td>117.5*</td>
<td>157.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halhali 2007 (MX; 3rd)</td>
<td>26</td>
<td>26</td>
<td>107.5*</td>
<td>125</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** * indicates a significant difference between groups.
Dose-Response Association Early Maternal 25OHD and Risk of PE

### Clinical Trials on Vitamin D and PE or PIH

#### Randomized Clinical Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marya et al. 1987</td>
<td>+Ca/vit D 200</td>
<td>NS</td>
</tr>
<tr>
<td>Rohtak, India</td>
<td>+ 375 mg Ca</td>
<td></td>
</tr>
<tr>
<td>Dietary Ca 500mg;</td>
<td>1200 IU D</td>
<td></td>
</tr>
<tr>
<td>vit D 40 IU</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PE</strong> 12</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td><strong>Blood Pressure (32 wk)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>109.6*</td>
<td>117.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70*</td>
<td>66</td>
</tr>
</tbody>
</table>

#### Non-randomized Clinical Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ito et al. 1994</td>
<td>High Risk</td>
<td>PE</td>
</tr>
<tr>
<td>Kuramoto, Japan</td>
<td>+ 312 mg Ca/d</td>
<td>2/10</td>
</tr>
<tr>
<td></td>
<td>+ 312 mg Ca/d + 20 IU vit D/3 days</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Assessed risk based on Angiotensin Sensitivity Test BUT differed between the 2 groups
Observational and Trial Evidence for Vitamin D and PE

- No double-blind placebo controlled RCT on vitamin D and incidence of PE

- 1 RCT (no placebo) found no effect on PE but a small ↓ in systolic and diastolic BP with Ca/vitamin D supplements

- Inconsistent association of $1,25(OH)_2D$ and PE
  - 29% lower $1,25(OH)_2D$ in PE in cross-sectional case studies
  - No association in prospective nested case control study

- Inconsistent association of $25(OH)D$ and PE
  - No association in 2 cross-sectional case studies
  - 15% lower in PE in prospective nested case control study
Vitamin D Metabolism in Placenta

- Placental trophoblasts and decidua express 1α OHase

Vitamin D Metabolism in Placenta

- Placental trophoblasts and decidua express 1α OHase
- Placental specific methylation of 24OHase promoter may ↓ capacity of 1,25(OH)_2 D to induce 24OH-lase

% Methylation

<table>
<thead>
<tr>
<th>24 OHase</th>
<th></th>
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<tbody>
<tr>
<td>Placenta</td>
<td>57</td>
</tr>
<tr>
<td>Placental Fb</td>
<td>3</td>
</tr>
<tr>
<td>Decidual cells</td>
<td>2</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1αOHase</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta</td>
<td>5</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VDR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>87</td>
</tr>
</tbody>
</table>

Vitamin D Metabolism in PE Placenta

- Conflicting reports on 1αOHase in PE placenta at term
  - Fischer and co-workers report ↑
  - Diaz and co-workers report ↓ in cultured syncytiotrophoblasts

- Fischer and co-workers also report ↓ 24OHase

Diaz, L. et al. J Clin Endocrinol Metab 2002;87:3876-3882

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Vitamin D Function in Placenta & Decidua In Vitro

- Immunomodulatory regulation of cytokines and cathelicidin (CAMP)
  - ↓ TNFα induction of placental IFNγ, IL6, TNFα
  - ↓ decidual NK cell IL1, IL6, TNF & CSF2
  - ↑ placental & decidual CAMP

Vitamin D Function in Placenta & Decidua In Vitro

- **Immunomodulatory regulation of cytokines and cathelicidin antimicrobial peptide (CAMP)**
  - ↓ TNFα induction of placental IFNγ, IL6, TNFα
  - ↓ decidual NK cell IL1, IL6, TNF & CSF2
  - ↑ placental & decidual CAMP

- **Regulation of placental hormonal function**
  - ↑ hPL mRNA & secretion (10-100 0nmol/L)
  - ↑ hCG mRNA & secretion (0.1-10 nmol/L)
  - ↑ E & P secretion 0.1-100 nmol/L)
Functions of Vitamin D: Placenta

Sun-UVB → Skin
Vitamin D
Intestine → Diet
Vitamin D

Ca-P homeostasis
Target cells
e.g.
Bone
Intestine
Kidney
Parathyroids

D = D2+D3

VDR
Gene expression
Endocrine functions

1αOHase
1,25(OH)₂D

Intestine

25OHD
25OHDase

PL Tb

24OHase
24,25(OH)₂D

1αOHase
1,25(OH)₂D

25OHD → 1αOHase → 1,25(OH)₂D → Gene expression → VDR

Para/autocrine functions

Decidua

25OHD
1αOHase
1,25(OH)₂D

Gene expression

VDR

↑ CAMP
↓ IL 1 & 6, TNF, CSF2

↓ TNFa induction
IL 5, IFNγ, TFNα

↓ hCG, E, P
Vitamin D and PE
Gaps in Our Knowledge and Research Needs

- Understand the regulation by vitamin D of normal placentation and abnormal placentation in PE
  - immunomodulatory role
    - Placenta
    - Decidua
  - regulation of placental hormonal function

- Need a double-blind placebo RCT on vitamin D and incidence of PE
Acknowledgements

- Jane Caty
- Sara Jones