New Insights for an Old Disease: Preeclampsia

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University of Iowa Center of Immunology
Obesity Research & Education Initiative
3. Find $x$. Here it is.

SIMPLICITY
The simplest solutions are often the cleverest.
They are also usually wrong.
Headache
Blurry Vision
Hypertension
Shock
Kidney Failure
Liver Failure
Pancreatic Failure
Removal of Bowel
Lots of Rehab
87 days in the hospital

September 2012
Overview

- Clinical Overview of Preeclampsia
- The Etiologic Challenge of Preeclampsia
- Brief Stats Review
- Novel Biomarkers of Preeclampsia
- The Vasopressin Story
What is Preeclampsia?
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure.</td>
</tr>
<tr>
<td></td>
<td>Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy.</td>
</tr>
<tr>
<td>and</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection).</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>Protein/creatinine ratio greater than or equal to 0.3*</td>
</tr>
<tr>
<td></td>
<td>Dipstick reading of 1+ (used only if other quantitative methods not available).</td>
</tr>
<tr>
<td>Or in the absence of proteinuria</td>
<td>New-onset hypertension with the new onset of any of the following:</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count less than 100,000/microliter</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease.</td>
</tr>
<tr>
<td>Impaired liver function</td>
<td>Elevated blood concentrations of liver transaminases to twice normal concentration.</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td></td>
</tr>
<tr>
<td>Cerebral or visual symptoms</td>
<td></td>
</tr>
</tbody>
</table>
**BOX E-1. Severe Features of Preeclampsia (Any of these findings)**

- Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100,000/microliter)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- Progressive renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset cerebral or visual disturbances
Preeclampsia

- 5-10% of all pregnancies (500,000/year)
- 15% of perinatal morbidity/mortality (76,000 maternal deaths/year)
- **Short term:** Maternal headache, blurry vision, seizure, multiorgan failure, fetal growth restriction, maternal-fetal death
- **Long term:** Increased maternal CV events, future adult stroke, metabolic disease, and epilepsy for the children

26 wks
8.6 ounces
Delivered due to Severe Preeclampsia
## Long Term Manifestations: Maternal

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>Risks</th>
</tr>
</thead>
</table>
| Jonsdottir et al 1995| 1. Eclampsia  
2. Preeclampsia | 1. MI Death RR 2.61  
2. MI Death RR 1.90 |
| Hannaford et al 1997 | Preeclampsia                              | 1. HTN: RR 2.35  
2. Heart Attack: RR 2.24  
3. Clot in Leg or Lung: RR 1.62 |
| Irgens et al 2001    | Preeclampsia                              | 1. CV Death Term PreE: HR 1.65  
2. CV Death Preterm PreE: RR 8.12 |
| Wilson et al 2003    | Preeclampsia and Eclampsia                | 1. HTN: OR 3.98  
2. Fatal Stroke: RR 3.59 |
| Arnadottir et al 2005| Eclampsia, Preeclampsia and Gest. HTN    | 1. MI Death: RR 1.66  
2. Stroke Death: RR 1.46 |
### Long Term Manifestations: Fetal

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kajantie et al 2009</td>
<td>Stroke</td>
<td>RR 1.9</td>
</tr>
<tr>
<td>Wu et al 2009</td>
<td>Epilepsy</td>
<td>RR 1.2</td>
</tr>
<tr>
<td>Wu et al 2009</td>
<td>Nutritional / Metabolic Dz</td>
<td>RR 1.6</td>
</tr>
<tr>
<td>Wu et al 2009</td>
<td>Blood Diseases</td>
<td>RR 1.5</td>
</tr>
<tr>
<td>Swamy et al 2008</td>
<td>Fertility in Preterm Born</td>
<td>RR 0.24</td>
</tr>
</tbody>
</table>
Who gets preeclampsia?

Worldwide:
• Affects 10% of all pregnancies
• Kills 76,000 mothers / year
• Kills 500,000 infants / year

>500,000 / year in the United States

4,000 /year pregnancies are affected by preeclampsia in Iowa.
Who gets Preeclampsia?

- 1st Pregnancy
- New Partner
- Previous preeclampsia esp. if in 3\textsuperscript{rd} trimester
- CHTN – Renal Disease
- Diabetes
- Thrombophilia
- Family Hx of PreE
- High BMI
- Multiple Gestation
- Extremes of reproductive age > 40 y/o < 18 y/o
Preeclampsia: By the Numbers

- 4,000 cases/year in Iowa
- 500,000 cases/year in U.S.A.
- 100,000 maternal deaths/year
- 500,000 fetal & newborn deaths/year
- 8x higher incidence than heart attack
- 25x higher incidence than prostate cancer
- 50x higher incidence than colon cancer

Still today:
- No Diagnostic Test
- No Animal Models
- No Treatments

Originally described by Hippocrates... 2,400 years ago
The Challenge of Preeclampsia

• Difficult to predict:
  • Who will get it preeclampsia?
  • Who will get severe preeclampsia?

• No preventative measures
• No treatment options using standard antihypertensives
• Only true “cure” is delivery, which is often preterm

A greater understanding of the physiological initiators of preeclampsia is desperately needed to develop novel predictive and therapeutic tools.
The Disease of Theories

- Poor Placentation
  - Placental Dysfunction
    - Vascular Dysfunction
      - RAS Changes
      - Increased Oxidative Stress
      - Calcium deficiency
      - Endothelial Dysfunction
      - Renal Changes
  - Anti-angiogenesis
  - Hyper-inflammation
  - Altered Immunology

PREECLAMPSIA
# Biomarkers: Preeclampsia Forecasting

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variable</th>
<th>ROC AUC</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>Preeclampsia symptoms</td>
<td>0.58-0.74</td>
<td>Thangatatham et al Acta Obs Gynecol Scand 2011 (TIPPS)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Preeclampsia history, labs, and symptoms</td>
<td>0.88</td>
<td>Von Daedelzen et al Lancet 2011</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Maternal risk factors</td>
<td>0.72-0.79</td>
<td>Poon et al J Hum Hypertension 2010</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>UAD PI + Mat. Factors</td>
<td>0.88-0.91</td>
<td>Poon et al Ultrasound Obstet Gynecol 2009</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>UAD PI + Mat.Factors + Biochem.</td>
<td>0.91-0.96</td>
<td>Poon et al Ultrasound Obstet Gynecol 2010</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>sFLT-1:PlGF</td>
<td>0.74</td>
<td>Odibo et al. J Perinat. 2013</td>
</tr>
</tbody>
</table>
Temporal relationships

Conception

First Trimester

13 wk

Second Trimester

26 wk

Third Trimester

Birth

Boundary of widely-accepted mechanisms

SFLT1 viral model (tissue initiation)

RUPP model (vascular initiation)

Clinical Symptoms of PreE

Vascular Dysfunction

Immune Dysfunction

Renal Dysfunction

Angiogenic Dysfunction

UAD dysfunction evident

Angiogenic markers appear

Clinical Symptoms

UAD dysfunction evident

Angiogenic markers appear

Clinical Symptoms of PreE
Vasopressin (AVP)
- 9 amino acids
- 10 minute half-life in blood (very short!)
- Acts via 4 receptors to increase blood volume and pressure

Copeptin
- Released in 1:1 ratio to vasopressin
- No known biological function
- Very useful as a biomarker for vasopressin
Vasopressin in Controls and Preeclampsia

Low-Renin Hypertension and Vasopressin (AVP)

Circulating RAS Activity in Essential Hypertensives

- **Low** (27%)
- **High** (16%)
- **Normal** (57%)

**African Americans**
- Elderly
- Renal Failure
- Heart Failure

Same subset of patients that can benefit from AVP blockade

Relative to normal pregnancy, Preeclampsia = Low-Renin Hypertension


**General Hypothesis:** Early-pregnancy increases in maternal vasopressin secretion may predict (and cause?) preeclampsia
Copeptin in Preeclampsia

Copeptin is elevated when preeclampsia symptoms are already present...
What about before symptoms show up?

Zulfikaroglu (2011): Copeptin ↑ in PreE (third trimester)
Foda (2012): Copeptin ↑ in PreE (at delivery)
Maternal plasma [Copeptin] is elevated in women who develop preeclampsia.

3rd Trimester data similar to Zulfikaroglu et al 2011

Santillan MK, et al Hypertension 2014
Maternal plasma [Copeptin] is elevated throughout pregnancy in women who develop preeclampsia.

Control
Preeclampsia

3rd Trimester data similar to Zulfikaroglu et al 2011

Santillan MK, et al Hypertension 2014
Maternal plasma [Copeptin] is not affected by renal function and vasopressin degradation.

Maternal plasma [Copeptin] is predictive of the development of preeclampsia.

Maternal plasma [Copeptin] is predictive of the development of preeclampsia

<table>
<thead>
<tr>
<th>Incidence of Preeclampsia</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>34%</td>
<td>98%</td>
</tr>
<tr>
<td>20%</td>
<td>54%</td>
<td>96%</td>
</tr>
<tr>
<td>30%</td>
<td>67%</td>
<td>94%</td>
</tr>
<tr>
<td>40%</td>
<td>76%</td>
<td>91%</td>
</tr>
<tr>
<td>50%</td>
<td>82%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Santillan MK, et al *Hypertension* 2014
[Copeptin] still associated after controlling for covariates

<table>
<thead>
<tr>
<th>First Trimester Model [Copeptin] Cutoff = 811 pg/mL</th>
<th>β [Copeptin]</th>
<th>Adjusted Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Trimester [Copeptin]</td>
<td>3.5</td>
<td>33.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1st Trimester [Copeptin] + Maternal Age</td>
<td>3.8</td>
<td>44.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1st Trimester [Copeptin] + Body Mass Index</td>
<td>3.5</td>
<td>33.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1st Trimester [Copeptin] + Diabetes</td>
<td>3.8</td>
<td>44.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1st Trimester [Copeptin] + Chronic Essential Hypertension</td>
<td>3.7</td>
<td>40.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1st Trimester [Copeptin] + History of Preeclampsia</td>
<td>4.5</td>
<td>90.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1st Trimester [Copeptin] + Twin Gestation</td>
<td>3.4</td>
<td>30.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1st Trimester [Copeptin] + All Clinical Covariates</td>
<td>6.1</td>
<td>446.0</td>
<td>= 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second Trimester Model [Copeptin] Cutoff = 866 pg/mL</th>
<th>β [Copeptin]</th>
<th>Adjusted Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Trimester [Copeptin]</td>
<td>3.1</td>
<td>22.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd Trimester [Copeptin] + Maternal Age</td>
<td>3.4</td>
<td>30.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd Trimester [Copeptin] + Body Mass Index</td>
<td>3.2</td>
<td>24.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd Trimester [Copeptin] + Diabetes</td>
<td>3.1</td>
<td>22.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd Trimester [Copeptin] + Chronic Essential Hypertension</td>
<td>3.8</td>
<td>44.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd Trimester [Copeptin] + History of Preeclampsia</td>
<td>3.8</td>
<td>44.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd Trimester [Copeptin] + Twin Gestation</td>
<td>3.4</td>
<td>30.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd Trimester [Copeptin] + All Clinical Covariates</td>
<td>7.1</td>
<td>1212.0</td>
<td>= 0.015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Third Trimester Model [Copeptin] Cutoff = 758 pg/mL</th>
<th>β [Copeptin]</th>
<th>Adjusted Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd Trimester [Copeptin]</td>
<td>2.1</td>
<td>8.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3rd Trimester [Copeptin] + Maternal Age</td>
<td>2.2</td>
<td>9.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3rd Trimester [Copeptin] + Body Mass Index</td>
<td>2.1</td>
<td>8.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3rd Trimester [Copeptin] + Diabetes</td>
<td>2.5</td>
<td>12.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3rd Trimester [Copeptin] + Chronic Essential Hypertension</td>
<td>2.3</td>
<td>10.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3rd Trimester [Copeptin] + History of Preeclampsia</td>
<td>2.3</td>
<td>10.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3rd Trimester [Copeptin] + Twin Gestation</td>
<td>2.5</td>
<td>12.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3rd Trimester [Copeptin] + All Clinical Covariates</td>
<td>2.9</td>
<td>18.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Clinical Symptoms of PreE:

- Zulfikaroğlu (2011): Copeptin ↑ in PreE (third trimester)
- Foda (2012): Copeptin ↑ in PreE (at delivery)
- Yeung (Dec 2014): Copeptin ↑ in PreE (16th week through birth)

Subset of Calcium for Preeclampsia Prevention trial: N=136 control, 169 PreE 53% & 70% non-white

N=54 control, 50 PreE 10% non-white
First Trimester Preliminary Urine Data

Urine [Copeptin] (pg/mL)

Control

Preeclampsia

0
20
40
60
80
100
120
140

Urine [Copeptin] (pg/mL)
Early Warning System Still Needed!

92%

Where are the OB/Gyns?
**Temporal relationships**

**First Trimester**
- 13 wk
- Elevated AVP secretion
- Poor placentation
- Elevated AVP action
- Copeptin elevated

**Second Trimester**
- 26 wk
- Angiogenic markers appear
- Immune dysfunction
- Renal dysfunction
- Angiogenic dysfunction
- Vascular dysfunction

**Boundary of widely-accepted mechanisms**

**SFLT1 viral model (tissue initiation)**

**RUPP model (vascular initiation)**

**Clinical Symptoms of PreE**

**OVERALL HYPOTHESIS**
Novel Therapeutics?

Vasopressin secretion & receptors as the first rational, specific, preventative / curative therapeutic for preeclampsia
Vasopressin secretion precedes & correlates with vascular dysfunction

2nd Trimester

Endothelial function

Aortic stiffness

Blood pressure
Does vasopressin actually cause preeclampsia?

Correlation ≠ causation!
Chronic AVP Infusion in Mice Phenocopies Human Preeclampsia: Blood Pressure

Santillan MK, et al Hypertension 2014
Chronic AVP Infusion in Mice Phenocopies Human Preeclampsia: Renal Findings


**B**

<table>
<thead>
<tr>
<th>Serum Protein (mg/d)</th>
<th>Saline</th>
<th>AVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>GD17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* indicates statistical significance.

Saline | AVP

Santillan MK, et al *Hypertension* 2014
Chronic AVP Infusion in Mice Phenocopies Human Preeclampsia: IUGR and Fetal Loss

Santillan MK, et al Hypertension 2014
Excess Maternal AVP Induces Cardiovascular and Metabolic Dysfunction in Offspring

AVP infusion only during gestation

Mother was infused with:  
- Untreated
- AVP (24 ng/hr, sc, GD -3 to 18)

Offspring (9 weeks old)

Blood pressure, renal function, and intake behavior tests

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Renal Dysfunction</th>
<th>Metabolic Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>K+ (mM)</td>
<td>Body (g)</td>
</tr>
<tr>
<td>95</td>
<td>115</td>
<td>22</td>
</tr>
<tr>
<td>*</td>
<td>*</td>
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<td>480</td>
<td>80</td>
<td>3.4</td>
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<td>*</td>
<td>400</td>
<td>3.8</td>
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<td>400</td>
<td>0</td>
<td>2.4</td>
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<tr>
<td></td>
<td>0</td>
<td>3.0</td>
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</table>
# The CIV Model Summary

<table>
<thead>
<tr>
<th>Characteristic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pregnancy-Specific</em> Hypertension</td>
<td>✓</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>✓</td>
</tr>
<tr>
<td>Pathognomonic Glomerular Endotheliosis</td>
<td>✓</td>
</tr>
<tr>
<td>Fetal Growth Restriction</td>
<td>✓</td>
</tr>
<tr>
<td>Increased Fetal Loss</td>
<td>✓</td>
</tr>
<tr>
<td>Maternal: Th1 &gt; Th2</td>
<td>✓</td>
</tr>
<tr>
<td>Maternal: ↑ IL-17 → ↑ Th17</td>
<td>✓</td>
</tr>
<tr>
<td>Maternal AVP ↑ → ↑ IL12-p40 = ↑</td>
<td>✓</td>
</tr>
<tr>
<td>Stimulatory DC Activity</td>
<td>✓</td>
</tr>
<tr>
<td>Fetal Renal: Th1 &gt; Th2, ↑ Th17</td>
<td>✓</td>
</tr>
<tr>
<td>Placenta: Th1 &gt; Th2</td>
<td>✓</td>
</tr>
<tr>
<td>Offspring Metabolic and Cardiovascular Phenotypes</td>
<td>✓</td>
</tr>
</tbody>
</table>
Block vasopressin to treat preeclampsia?

- **V₁₅A** receptor
  - Gαq/11
  - PLC-PIP₂-DAG-IP₃-PKC
  - Vascular contraction
  - Neuronal function
  - Relcovaptan
  - Conivaptan

- **V₂** receptor
  - Gαs
  - AC-cAMP-PKA
  - Water retention
  - Tolvaptan

- **V₁₅B** receptor
  - Gαq/11
  - PLC-PIP₂-DAG-IP₃-PKC
  - ACTH release
  - Nelivaptan

**Cullin-5**

- SOCS/BC-box/eloBC/cul5/RING-E3 ligase complex
Preliminary findings: $V_{1A} / V_2$ appear involved in maternal hypertension.
Preliminary findings – \( V_{1A} / V_2 \) involvement

- Blocking \( V_{1A} + V_2 \) receptors appears to reverse maternal & fetal consequences of elevated vasopressin during gestation
- Future studies will dissect role of \( V_{1A} \) versus \( V_2 \)
Gestational Age Timing of AVP Exposure

- Saline through gestation
- AVP for all 18 days
- AVP for first 10 days
- AVP for first 3 days

Δ SBP (mmHg)

Baseline  GD3  GD7-11  GD14-15

- Saline (n=23)
- AVP to GD18 (n=13)
- AVP to GD10 (n=7)
- AVP to GD3 (n=8)

Saline to GD 18  to GD 10  to GD 3
AVP (24 ng/hr)
Conclusions, working model, and ongoing questions

V_{1A}/V_2 mediated

Critical period of AVP action

First Trimester

Second / Third Trimester

What stimulates AVP release? Relative role of V_{1A} vs V_2? Second-messengers?

Is AVP brain-derived? Target tissue(s)? Can AVP interference protect clinically?

Maternal vs fetal symptoms? AVP-based fetal programming?

Sandgren, ... & Grobe. AJP:Regulatory. [in press], 2015.
# American Heart Association Strategically Focused Research Network

## Institution

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Director</th>
<th>Basic Study</th>
<th>Clinical Study</th>
<th>Population Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cincinnati Children’s Hospital</td>
<td>Elaine Urbina, MD, FAHA</td>
<td>Richard Becker, MD, FAHA Influence of Regulatory Genome on Target Organ Damage in Youth with Primary Hypertension</td>
<td>Joseph Flynn, MD, MS Hemodynamic and Metabolic Predictors of Target Organ Damage in Youth with Primary Hypertension</td>
<td>Elaine Urbina, MD, FAHA Threshold for Development of Blood Pressure-Related Target Organ Damage in Youth</td>
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<tr>
<td>Medical College of Wisconsin</td>
<td>Mingyu Liang, MB, PhD,</td>
<td>David L. Mattson, PhD, FAHA Epigenetic Modification of Immune Mechanisms in Salt-Sensitive Hypertension and Renal Damage</td>
<td>Srividya Kidambi, MD Epigenomics of Hypertension in Monozygotic Twins and Effect of Salt Intake</td>
<td>Theodore A. Kotchen, MD, FAHA Epigenomic Modifications in Hypertension and Hypertension-Related Cardiovascular Diseases</td>
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<td>University of Alabama, Birmingham</td>
<td>Paul Muntner, PhD,</td>
<td>Jennifer Polluck, PhD, FAHA Novel Mechanisms of Salt-sensitivity and Diurnal Blood Pressure Rhythm</td>
<td>David Calhoun, MD Mechanisms of Nocturnal Hypertension and Non-dipping Blood Pressure</td>
<td>Paul Muntner, PhD, MHSce Racial Differences and US population estimates of Nocturnal Hypertension and Non-dipping</td>
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<td>University of Iowa</td>
<td>Curt Sigmund, PhD, FAHA</td>
<td>Justin Grobe, PhD, FAHA Molecular Mechanisms of Vasopressin-Induced Preeclampsia</td>
<td>Gary Pierce, PhD, MS Early Vascular Dysfunction and Elevated Copeptin in Human Preeclampsia</td>
<td>Mark Santillan, MD Predicting Preeclampsia via Copeptin: Underrepresented Minorities &amp; Synergy with Other Biomarkers</td>
</tr>
</tbody>
</table>
American Heart Association
Iowa Population Study Overview

Aim 1
Retrospective:
CoLab
Worldwide
Repository

Aim 2 Prospective:
Iowa Collaborative

First Trimester
Maternal Urine

First Trimester
Maternal Plasma

First Trimester
Highest and
Lowest Quartile
Maternal Plasma
Copeptin

First Trimester Urine and
Plasma Prediction
Characteristics

Aim 3:
Comparison with
sFLT1, PIGF, and Endoglin

Subject
Recruitment for
Project 2:
Clinical Study

Maternal Fetal
Tissue Bank

Mercy Medical Center
Des Moines

Mercy
Cedar Rapids

University of Iowa Hospitals & Clinics

Iowa Women’s Health
University of Iowa Health Care
Iowans working together

The University of Iowa Healthcare Alliance

1. Mercy Medical Center, Sioux City
2. Oakland (NE) Mercy Hospital
3. Baum-Harmon Mercy Hospital, Primghar
4. Mercy West Lakes, West Des Moines
5. Mercy Medical Center, Des Moines
6. Mercy Medical Center, North Iowa
7. Mercy Medical Center, Centerville
8. Mercy Medical Center, New Hampton
9. Mercy Medical Center, Dyersville
10. Mercy Medical Center, Dubuque
11. Mercy Medical Center, Clinton
12. Genesis Medical Center, DeWitt
13. Genesis Medical Center, Silvis
14. Genesis Medical Center, Aledo
15. Genesis Medical Center, Davenport
16. University of Iowa Hospital
17. Mercy, Cedar Rapids
18. Covenant Medical Center, Waterloo
19. Sartori Memorial Hospital, Cedar Falls
20. Mercy Hospital, Oelwein
American Heart Association
Iowa Population Study: Workflow

Contact Person
Local Consenter(s)

Women in 1st trimester (< 13 weeks) in clinic who is getting blood drawn and leaving urine sample.

Collect Urine in Clinic or Lab (?)

Draw 1 Extra ACD-A Tube in Clinic or Lab (?)

Initial Data Collection

Keep Samples Refrigerated for no longer than 3 days

Ship samples to UIHC within 3 days of collection

Pregnancy Outcome Data Collection
Preeclampsia and VNTR

My First Instrument

You may view an existing record/response by selecting it from one of the drop-down lists below. The records are separated into each drop-down list according to their status for this particular data collection instrument. To create a new record/response, type a new value in the text box below and hit Tab or Enter. To quickly find a record without using the drop-downs, the text box will auto-populate with existing record names as you begin to type in it, allowing you to select it.

<table>
<thead>
<tr>
<th>Total records: 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete Records (4)</td>
</tr>
<tr>
<td>Complete Records (0)</td>
</tr>
<tr>
<td>Enter a new or existing Record ID</td>
</tr>
</tbody>
</table>

Download PDF of instrument(s)

VIDEO: Basic data entry

Show Unverified Records above
Clinics will be remunerated on a per participant basis
Our multidisciplinary SFRN: Hypertension team at the University of Iowa

**Director**
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- Mark K. Santillan, MD
- Gary L. Pierce, PhD
- Justin L. Grobe, PhD
- Kimberly K. Leslie, MD
- Donna A. Santillan, PhD
- Katherine N. Gibson-Corley, DVM, PhD
- Gideon K.D. Zamba, PhD

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- Allyn L. Mark, MD
- Frank M. Faraci, PhD

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- James Y. Min
- Anand R. Nair, PhD **(SFRN Fellow)**
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- Katherine J. Perschbacher
- Jeremy A. Sandgren
- Sabrina M. Scroggins, PhD
- Jessica Steidele
- Amy M.K. Young, RN, MSN

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- Justin L. Grobe, PhD
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- Katherine N. Gibson-Corley, DVM, PhD
- Gideon K.D. Zamba, PhD
Join the Iowa/AHA Preeclampsia Team!

QUESTIONS?

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- University of Iowa Medical Student Research Program
Questions?