Can We Decipher Different Phenotypes of Preeclampsia?

Leslie Myatt PhD FRCOG
Dept of Obstetrics and Gynecology
Oregon Health & Science University
The Problem

• Despite an ever increasing literature describing studies on preeclampsia, currently we still do not understand the proximate pathophysiology, and cannot predict or prevent preeclampsia, a common condition of pregnancy that generates a high level of perinatal morbidity and mortality.
Contrasts Between Developed and Underdeveloped Countries

• Differences in access to healthcare

• Rates of eclampsia 1/2000 vs 1/100- 1/1700

• Underdeveloped countries – leading cause of maternal mortality (75,000 per annum)

• Developed countries – limited morbidity and mortality, iatrogenic delivery of preterm neonates, 5x Increased fetal and neonatal morbidity and mortality
Long Term Implications of Preeclampsia

**Maternal:** Increased risk of
- Hypertension
- Coronary artery disease
- Stroke
- Type 2 diabetes mellitus
  - ? *Pregnancy as a stress test*
  - ? *Does preeclampsia damage vascular system*
  - ? *Implications for pathophysiology*
  - ? *Common biomarkers (? Genetic)*

**Fetal:** Subsequent development of
- Cardiovascular disease
- Metabolic syndrome
The Dogma

Inadequate Trophoblast Invasion

Relative Hypoxia/Ischemia

Placental Signal (Toxin, Angiogenic factors)

Development of Preeclampsia

Maternal Susceptibility/Predisposition

Placenta

Maternal
Multi-Organ System Involvement in Preeclampsia
Biomarker Selection

- Trophoblast Invasion
- Placental function
- Angiogenic/Antiangiogenic markers
- Vascular Function
- Hematopoietic System
- Inflammation
- Renal Function
- Metabolism
Final Model - Combination of Clinical Factors and First Trimester Biomarkers for Prediction of Preeclampsia

AUC = 0.73 (95%CI 0.69-0.77)

Clinical and biochemical factors individually identified as significant predictors of preeclampsia (African American race, systolic blood pressure and BMI at enrollment, education level, ADAM-12 MoM, PAPP-A MoM and PlGF MoM) were included in the final multivariable predictive model.

Why can we not predict preeclampsia in the first trimester?

- Biomarkers are not specific for preeclampsia but are markers of placental health
- Heterogeneity of subjects. Not all show the same pathophysiologic changes i.e. there are different pathways to get to the final syndrome
Heatmap of Analyte Measurements Within 2 Weeks of Delivery
What are the Preeclampsia Phenotypes?

• Early vs late onset
• Recurrent vs non-recurrent
• PE with different types of high risk pregnancy or maternal predisposition
• Mild vs severe + IUGR
• Primary organ involvement hepatic, renal, cardiovascular or placental
• Do these define different molecular phenotypes that require different strategies?
The Approach

• Big Science
• Standardized study design (patient selection, data collection, definition of outcome)
• This allows comparable studies and trials to be performed, comparison of datasets and integration for meta-analyses
• Unambiguous and unbiased definitions
• Collect clinical and laboratory information to make diagnosis that is then examined retrospectively in a blinded manner by impartial observers rather than point of care diagnosis.

Myatt et al. Hypertension 2014
COLLECT
The Global CoLaboratory Database

What it Offers:
Web-based database

Minimal or Optimal datasets: agreed and defined

Standardized data fields: Collected in same format – Facilitates study merging

Choice of entry: real time online via PC, laptop or handheld device; delayed online access or paper version

Avoids point of care diagnosis: Enough primary clinical / laboratory data collected to enable retrospective diagnosis by impartial investigators.

Enables Variable Definitions by Subtyping Preeclampsia: Dataset allows retrospective specification of definitions for PE.

Optional data items: Are available for specific investigators and for local site or study specific requirements.
Reverse Phenotyping

• Unsupervised or semi-supervised analysis of molecular data to enable enrichment for cohorts with a common etiology for subsequent multi-omic data generation and characterization

• e.g. clustering of samples based on gene expression profiles may identify phenotypically homogeneous subgroups to be sequenced and analyzed for shared genomic variants underpinning the pathophysiological phenotype.
Clustering of Placental Gene Expression from Placentas of Preeclamptic Pregnancies

Proposed model of observed placental outcomes and preeclamptic etiologies

Conclusions

• Still no closer to defining, predicting or preventing PE
• PE may be different in under-developed vs developed countries
• Future studies need better clinical phenotyping with standardization and harmonization of study design and data
• Use of big data, omics and bioinformatics is needed to solve the issue
Over-represented GO ontologies in clusters 2 to 5 compared with the healthy cluster 1 by gene-set enrichment analysis (GSEA)

Sexual Dimorphism and Preeclampsia

- Toivanen and Hirvonen 1970
  - Pregnancies with PE the ratio of male/female fetuses is 1.24
  - Ratio increases with severity of disease:
    - 1.71 where urinary protein is >3g/24hr
    - 1.42 with DBP≥110mmHg

- Lopez-Llera 1990
  - Antepartum eclampsia ratio is 1.23, postpartum eclampsia 1.07

- Hsu and Witter 1994
  - Predominantly female fetuses in preterm vs term PE (Ratio 0.85).
  - No difference in mild or severe PE with male or female fetus

- Makhseed et al 1998
  - No difference in fetal sex ratio with PE,
  - Greater incidence of PE in primips vs multips (both M and F)
Overall ratio 1.05 (95%CI 1.03 -1.07), n=44,440, 1967-1998

Vatten & Skjaerven 2004
Sex-ratio of perinatal mortality in preeclamptic pregnancies by length of gestation.

N=1,325

Vatten & Skjaerven 2004