

Prenatal Screening Part II

Hot off the Press for Pre-Eclampsia

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› FIGO (Poon, Internal Journal of Gynecology and Obstetrics)

› Released May 22, 2019

› Guidelines for the Universal first trimester screening of pre-eclampsia

› *“FIGO is pleased to launch our first evidence-based guidelines to support first trimester screening and prevention of pre-eclampsia. Health is a human right, and every woman, wherever she lives, deserves the highest standards of health and wellbeing. These guidelines provide another essential tool to health professionals, health policy makers and FIGO’s 132 member societies in addressing the NCD (non-communicable disease) epidemic long-term, and accelerating progress in reducing maternal mortality.” Carlos Fuchtnner, President, FIGO*

› *This is the first guideline of its kind, and has the potential to make a massive impact on maternal and child health*

> Pre-eclampsia (PE)

- > Multisystem prenatal disorder defined by the onset of hypertension accompanied by significant proteinuria after 20w
- > Affects 2-5% of women (**1:20 versus T21 aneuploidy at 1:700**)
- > One of the leading causes of maternal and perinatal morbidity and mortality, especially the early subtype of PE
- > Annual attributable global mortality:
 - > **76,000 women**
 - > **500,000 babies**
- > Early PE (prior to 34w) is associated with substantial risks of short and long term maternal and perinatal morbidity

> Pre-eclampsia (PE) Etiology – TWO stages

1. Shallow invasion of trophoblast giving poor remodeling of spiral arteries in placenta
2. Maternal response to endothelial dysfunction and imbalance between angiogenic and antiangiogenic factors
3. The hypertension is a late finding due to increased fetoplacental demands on a system which can't supply the demand

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Factor	Risk of PE
Age over 35	gives 1.2-3X increase in risk
Nulliparity	increases risk by OR of 2.71
Parous women without prior PE	Decreased risk
Prior history of PE	15% recurrence risk, 32% if PE occurred twice before
Pregnancy Interval	Short (<12m) and long (>72m) are bad
ART	1.3-1.8 increased risk, increase in donor egg also
Family history of PE	increased
Obesity	increased
Other medical disease (DM, SLE, APAS)	Increased
Race/ethnicity	Higher in some

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> PE Maternal Morbidity

- > Most common death secondary to intracranial bleeding
- > HELLP syndrome, pulmonary edema, RDS, acute renal failure
- > Women with PE have a RR of 3.13 to develop chronic HTN, and 1.8X OR of developing a cardiovascular accident

> PE Perinatal morbidity

Short Term	Long Term
Fetal growth restriction	Cerebral palsy
Oligohydramnios	Low IQ
IUFD	Hearing loss
Preterm birth	Visual impairment
Low APGARS	Insulin resistance
Nonassuring FHR during labor	DM
Need for NICU	Coronary artery disease and HTN

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- PE is clearly terrible for both mother and baby
- So is there a way to screen and prevent?

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PE Screening – there are only three options:

Maternal Characteristics and
Medical History

Biomarkers

Combination

PE Screening – there are only three options:

Maternal Characteristics and Medical History

- Poor detection rates (39% for early PE with 10% false positive rate)

Biomarkers

- Mean Arterial pressure
- Uterine artery pulsatility index (UTPI)
- PAPP-A
- Placental Growth Factor (PLGF)

Combined Assessment

Maternal Characteristics and Medical History

- Data is based on regression algorithm from a study of screening 120,492 patients at 11-13 weeks
- Includes
 - age, height, weight,
 - ethnicity, past history
 - Inter-pregnancy interval
 - Family history
 - Gestational age at last delivery
 - Method of conception
 - Smoking
 - History of HTN
 - History of DM
 - History of SLE or APAA

Measuring Blood pressure

- Recommended using a semi-automated device
- Sitting position with arms supported at level of heart
- Appropriately sized cuffs depending on mid-arm circumference
- Rest for 5 minutes
- BP measured in **both arms simultaneously** x 2 at 1 minute intervals (giving 4 sBP and 4 dBP)
- Studies: MAP in combination with history gives a 63% DR for PE with 10% false positive

Placental Growth Factor (PLGF)

- Is secreted by trophoblast and part of angiogenic vascular endothelial growth factor family (VEGF) – has antiangiogenic functions
- Women who develop PE will have low PLGF in the first trimester
 - Using PLGF alone at 11-14w for early PE screening has:
 - 56% detection rate
 - 9% false positive rate

Pregnancy-associated Plasma protein A (PAPP-A)

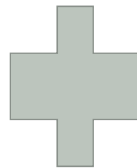
- Also has a role in placental growth and development and is low in women who go on to develop early PE
- Alone has poor detection rates, but with maternal history has higher detection rates for PE

Uterine Artery Pulsatility index (UTPI)

- Done using ultrasound at 11-14w during the First Trimester screen
- Using UTPI alone at 11-14w for early PE screening has:
 - 48% detection rate
 - 8% false positive rate

Combined Risk assessment

Maternal
Characteristics and
Medical History



Biomarkers
MAP
UTPI
PAPP-A
PLGF

Combined Risk assessment

- Current best practice recommendation is to develop a personalized risk assessment at 11-14w based upon:
 - A. Maternal Characteristics and History
 - B. MAP
 - C. PLGF
 - D. UTPI
 - E. With or without PAPP-A
- The biomarkers are placed into Multiples of medians (MoMs) and into risk screening software
- **High risk** is when higher than 1:100
- Can also be used with twin pregnancies
- *Where resources are limited, contingency based screening (second tier being PLGF and UTPI)*

Example of risk screening engine

Fetalmedicine.org

Combined Risk assessment

- So now what? – you've used combined assessment and you have a patient with a risk higher than 1:100
- *What do you do?*

Prevention/treatment of the at-risk woman using ASA

- Aspirin is thought to reduce PE by inhibiting the biosynthesis of placental thromboxane A2
- This alters the prostacyclin/thromboxane A2 ratio
- May prevent or delay on the onset of PE
- Studies;
 - 1979 – first study demonstrating the benefit of ASA on PE
 - Landmark meta-analysis (31 trials) showed 10% reduction in PE (2007)
 - Bujold – first study to analyze the use prior to 16w (2016)
- Meta-analyses since showed that administration prior to 16w gives:
 - *RR reduction of 0.22 for PE*
 - *50% reduction in risk of FGR*
 - *60% reduction in fetal death*

Prevention/treatment of the at-risk woman using ASA

- First large prospective trial (**ASPREE**)
- Showed that ASA started at 11-14w gives:
 - 62% reduction in the rate of preterm delivery due to PE
 - Significantly lower NICU stay in the ASA group versus placebo (by 68%)
 - 150mg nightly from 11-14w until 36w
 - No difference in adverse events versus placebo
 - But does not affect term PE risk
 - Spotting should not stop the ASA
 - Abruptio and PPH risk did not increase in the ASA group

Prevention/treatment of the at-risk woman using Calcium

- In women with low Calcium intake, replacement or supplementation (1.5-2g daily) may reduce the burden of early and late PE

Cost Effectiveness

- Canadian trial (Ortved, Johnson, 2019) suggested that the introduction of First trimester screening with PE screening would reduce health care consumption by \$220M nationally
 - (based on both aneuploidy detection and NICU stay for PE)
- No current analytics take into account the long term effects of PE on the newborn and its future cardiovascular health
 - the upstream savings on child and adult health are immeasurable

Current FIGO Guidelines and Recommendations

- **Public Health Focus**
 - Draw greater attention to the scope and issue
- **Universal Screening**
 - All pregnant women should be screening for preterm PE during early pregnancy with the first-trimester combined test with maternal risk factors and biomarkers
 - All countries should adopt and promote this
 - Algorithm is high risk over 1:100
- **Contingent Screening**
 - Where resources are limited, routine screening done by Maternal factors and MAP followed by PLGF and UTPI for the positive subgroup
- **Prophylaxis**
 - Women at high risk should receive Aspirin prophylaxis at 11-14w at a dose of 150mg nightly until 36w
 - Calcium supplementation or replacement if indicated

Current First Trimester Screening at PCRM

- We currently use a risk assessment based on history and PAPP-A
- *Summer – Fall 2019 – introduction of PLGF, MAP and UTPI to the markers*

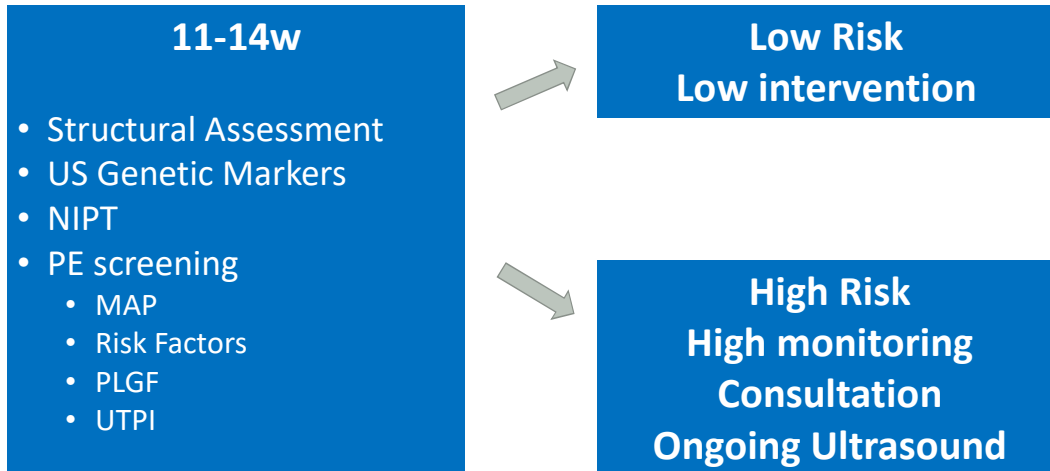
Current First Trimester Screening in Canada

- Both Ontario and Alberta are planning on adding PE screening into their First Trimester Screening programs in late 2019-2020

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Putting it all together....First trimester care in the next 10 years will be pivotal to prenatal risk management



Pearls

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> If you get lost and don't know what to do?

- > Genetics@pacificfertility.ca – you or your patient can email our counselors, or call us to assist
- > My talk – at pacificfertility.ca >top of the page – physician resources