Screening for Preeclampsia

Nan Okun

Fetal Medicine Update 2018

Adapted from Nicolaides et al

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Disclosures

- I have no conflicts of interest to declare

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Question

- How many in audience think there is enough evidence to introduce a first trimester, multiple marker, population based screen for preeclampsia in 2019?

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Objective

- To provide evidence to decide

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Characteristics of a Screening Test

Characteristics of a Screening Test	Preeclampsia screening
Condition should be important	✓
Should be a reliable test for the condition	✓
Facilities for diagnosis and treatment available	✓
Should be latent or asymptomatic phase	✓
Effective treatment	✓
Test should be acceptable to population	?
Natural history should be understood	✓
Should be agreement on who to treat	✓
Cost effective	?

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Condition should be Important

Down syndrome	Preeclampsia
1/800 (0.1%)	2-8% 14-20% maternal deaths, 40% of fetal mortality (WHO)

www.carahellps.com

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

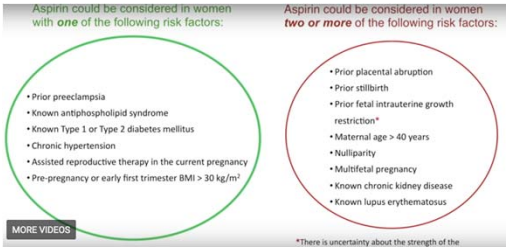
Reliable Test for Condition: Current Screening Guidelines

NICE (2010)[18]	WHO (2011)[20]	ACOG (2013)[14]
Previous hypertensive disease during a pregnancy*	Previous preeclampsia	Previous preeclampsia
Chronic kidney disease	Renal disease	Chronic renal disease
Autoimmune disease (including SLE/APS)	Autoimmune disease	SLE
Type 1 or type 2 diabetes	Preexisting diabetes mellitus	Preexisting diabetes mellitus
Chronic hypertension	Chronic hypertension	Chronic hypertension
Multiple pregnancy	Multiple pregnancy	Multiple pregnancy
Nulliparity		Primiparity
Age 40 years or older		Age 40 years or older
Pregnancy interval of more than 10 years		
Body mass index of ≥35 kg/m² at booking		Obesity
Family history of preeclampsia		Family history of preeclampsia

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Screening For Preeclampsia: Current Guidelines



MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — Bright Minds. Big Hearts. The Best Medicine.

BMJ 2016; 353:i1753

UNIVERSITY OF TORONTO

How well do current guidelines work?

Table. Rates of ASA prophylaxis for preeclampsia in the current and other published observational studies

First author[reference]	Setting, era	Study design	Participants assessed or surveyed	Number of participants included	Rate of ASA prophylaxis (%)
Wide-Swensson[7]	Sweden, 1992	Questionnaire	Obstetricians surveyed about ASA use in women with mild hypertension	79	8
			Obstetricians surveyed about ASA use in women with severe hypertension	79	20
Khedun[8]	South Africa, 1996–1997	Questionnaire	Obstetricians surveyed about ASA use in women with chronic hypertension	425	58
Heilmann[9]	717 childbirth clinics in Germany, era not reported	Questionnaire	Obstetricians surveyed about ASA use in women with moderate or severe hypertension	717	38.1
Chappell[10]	25 hospitals in the UK, 2003–2005	Analysis of a database from randomized clinical trial	Pregnant women at high risk for preeclampsia	2399	24
Current study	Single hospital, Toronto, 2012–2015	Retrospective cohort study	All consecutive pregnant women	8672	3.0
			Subset of pregnant women at high risk for preeclampsia	1727	7.6

ASA: aspirin.

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — Bright Minds. Big Hearts. The Best Medicine.

J Obstet Gynaecol Can 2017;39(9):722–723

UNIVERSITY OF TORONTO

How do NICE guidelines perform?

- Screening Program for Preeclampsia Study (SPREE)
- Comparison of screen by NICE guidelines to screen by "mini combined test" of FMF (maternal factors, MAP, PAPP-A) for any preeclampsia holding PR constant for both
- Women on ASA (4.5% of 16747) per NICE or other reasons accounted for in statistics

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — Bright Minds. Big Hearts. The Best Medicine.

Ultrasound Obstet Gynecol 2018; 51: 743–750.

UNIVERSITY OF TORONTO

How do NICE guidelines perform?

	NICE (%DR for 10% PR)	FMF Mini Test (maternal factors, MAP, PAPP-A) (%DR for 10% PR)
Any PE	30	42.5
Preterm PE	40.8	53.5

- Additional factors improved DR of FMF test
- Add PLGF and UtA-PI: DR 82.4%
- 23% NICE pos women took ASA

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — Bright Minds. Big Hearts. The Best Medicine.

Ultrasound Obstet Gynecol 2018; 51: 743–750.

UNIVERSITY OF TORONTO

Screening for Down Syndrome: Bayes Theorem

Posterior ∝ Prior x Likelihood

Reverend Thomas Bayes: 1702 - 1761

Maternal history: *a priori risk*

+

Biophysical markers

+

Biochemical markers

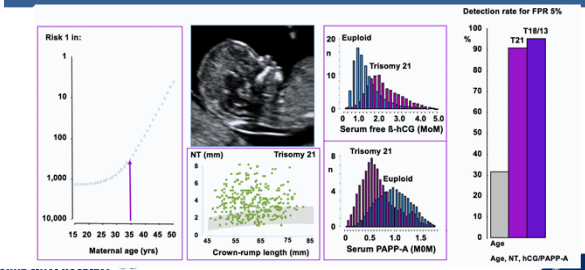
Adjusted risk

Nicolaides et al

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

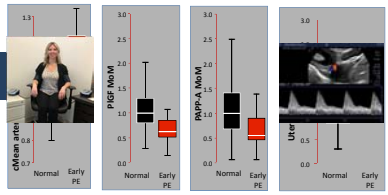
Screening for aneuploidies: The first trimester combined test (FTS)



MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — UNIVERSITY OF TORONTO

T1 Combined Marker Screen for Preeclampsia

- Mat Demographic Factors
- History



MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — Poon *et al.* 2009 — UNIVERSITY OF TORONTO

How well does T1 screen for PE work?

AJOG: The training data set used for model fitting n = 35,948

SQS: The ASPRE screening quality study data n = 8,775

SPREE: NIHR validation study n = 16,451

Combined **n = 61,174**

SQS and SPREE are independent validation data using the pre-specified risk algorithm with pre-determined parameters

Risks produced blinded to pregnancy outcomes

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — With permission from Dave Wright — UNIVERSITY OF TORONTO

Performance of screening: DR for a 10% screen positive rate

Outcome	Data	Cases	Positive	DR
PE < 34w	SPREE	60	54	90%
	SQS	27	25	93%
	AJOG	128	112	88%
	Combined	215	190	88%
PE < 37 w	SPREE	142	116	82%
	SQS	59	44	75%
	AJOG	292	217	74%
	Combined	493	371	75%
Any PE	SPREE	473	255	54%
	SQS	239	116	49%
	AJOG	1058	550	52%
	Combined	1770	899	51%

Maternal factors+: UtA-PI, PAPP-A, PlGF

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — *Ultrasound Obstet Gynecol* 2018; 52: 186–195 — With permission from Dave Wright — UNIVERSITY OF TORONTO

The PREDICTION Study

First-trimester prediction of preeclampsia and other placenta-mediated pregnancy complications

***Bujold E**, Audibert F, Johnson J, Okun N, Forest JC, Chaillet N, Giguere Y, Masse B*

Primary Objective:
To validate the 11-13 week FMF*screening test for preterm preeclampsia

* Fetal Medicine Foundation UK

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — UNIVERSITY OF TORONTO

The PREDICTION Study

Secondary Objectives:

1) To evaluate performance of FMF screen for:
   - All cases of PE
   - Composite outcome of placenta-mediated complications of pregnancy
2) To compare performance with/without UtA Doppler.
3) To assess alternative models if FMF not validated
4) To evaluate association/predictive values of specific markers for early PE
   - PlGF, PAPP-A, sFlt-1, fBhCG, AFP*
   - Placental and subplacental volume; placental vascularization

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex — UNIVERSITY OF TORONTO

The PREDICTION Study

Methods

- Multicenter prospective observational study (Laval, MTL, Toronto, Calgary)
- **Nulliparous women** between 11 0/7 – 13 6/7 weeks gestation
- Eligible women invited to undergo a PE risk evaluation
- Participants/providers blinded to the results/analyses.

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

The PREDICTION Study

Preliminary results
7549 nulliparous women
Follow up: 99%
Preeclampsia: 3.3% (preterm 0.8%)

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Characteristics of a Screening Test

Characteristics of a Screening Test	Preeclampsia screening
Condition should be important	✓
Should be a reliable test for the condition	✓
Facilities for diagnosis and treatment available	✓
Should be latent or asymptomatic phase	✓
Effective treatment	✓
Test should be acceptable to population	?
Natural history should be understood	✓
Should be agreement on who to treat	✓
Cost effective	?

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Prevention of Preeclampsia: Role of ASA

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

PREVENTION OF PRE-ECLAMPSIA BY EARLY ANTIPLATELET THERAPY

M. BEAUFILS
R. DONSIMONI

S. UZAN
J. C. COLAU

THE LANCET, APRIL 13, 1985

RCT 102 patient at high risk for PE randomized to Group A (300 mg dipyridamol1/150 mg ASA) or group B (no treatment

TABLE II—OUTCOME OF PREGNANCY

	Group A (n = 48)	Group B (n = 45)	p
Normal pregnancy	29	12	<0·005
Hypertension (isolated)	19	22	NS
Pre-eclampsia	0	6	<0·01
Fetal and neonatal loss	0	5	<0·02
Severe IUGR (live births)	0	4	<0·05

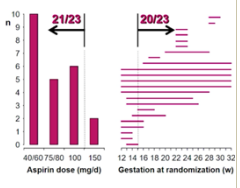
MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data Lancet 2007

32,217 women in 31 RCT's (ASA 23)
- RR for PE: 0.90 (95% CI 0.84-0.97)
- RR < 34 w: 0.90 (95% CI 0.83-0.98)

Interpretation
Antiplatelet agents during pregnancy are associated with moderate but consistent reductions in the RR of PE, PTB <34 w and serious adverse outcome

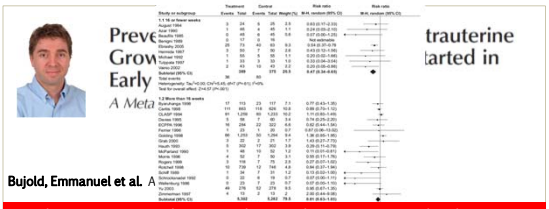


14 different definitions of PE

MOUNT SINAI HOSPITAL Joseph and Wolf Lebovic Health Complex Bright Minds. Big Hearts. The Best Medicine.

Lisa M Askie, Lelia Duley, David J Henderson-Smart, Lesley A Stewart, on behalf of the PARIS Collaborative Group*

Prevention of preeclampsia



Bujold, Emmanuel et al. A

Low-dose aspirin started at 16 weeks or earlier was associated with a significant reduction in preeclampsia (relative risk [RR] 0.47, 95% CI 0.34–0.65

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Prevention of PE: aspirin

ASPRE project

Screening at 11-13w
N = 26,941

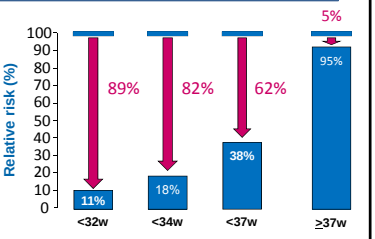
High-risk group agreeing to RCT

Assigned to aspirin
N = 798

Assigned to placebo
N = 822

150 mg/day
12 to 36 w

Placebo



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2017;377:613-22.

With permission from Dave Wright

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Conclusions

In high risk pregnancies

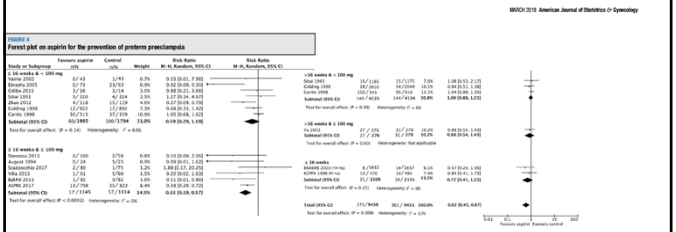
- Aspirin (150 mg/d) reduces the incidence of PE <32 w by about 90% and the incidence of PE <37 w by about 75%
- Aspirin has little effect on the incidence of PE ≥ 37w

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis

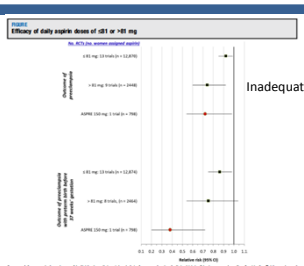
Stephanie Roberge, PhD; Emmanuel Bujold, MD, MSc; Kypros H. Nicolaides, MD



MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Optimal aspirin dosing for preeclampsia prevention



Inadequate certainty to conclude effective dose

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

Associations between the timing and dosing os aspirin prophylaxis and term and preterm pre-eclampsia

- Bujold review is insufficient evidence to restrict ASA to <16 weeks, or to increase dosage to >100 mg.
- ASPRE trial "welcome addition" but only compared one dose and one start time
- RCT's directly comparing timing and dosing are needed

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

10.1136/bmjebm-2018-110931

UNIVERSITY OF TORONTO

What is next best step?

- Standardized T1 screening seems to be validated and better than clinically based screening for detection of preeclampsia
- ASA decreased preeclampsia, especially preterm preeclampsia
- ASA seems to be optimal <16 weeks and >100 mg
- TIME TO IMPLEMENT (and evaluate)

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO

How to implement

- Small, controlled settings across Canada
- Standardized, quality assured processes for screening
- Evaluate metrics such as acceptability, extra time taken, logistics and cost to system
- Rigorous data collection to combine cohort of 7000 to compare screening and prevention to screening alone on rates of preeclampsia
- Scale up to provincial systems

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

UNIVERSITY OF TORONTO