Preterm Birth Prevention:
A role for Aspirin?

- No conflicts to declare
- Aspirin use in pregnancy is off-label

Kent Heyborne
Chief of Obstetrics
Associate Director of OB/GYN
Denver Health Hospital
Associate Professor of OB/GYN
University of Colorado

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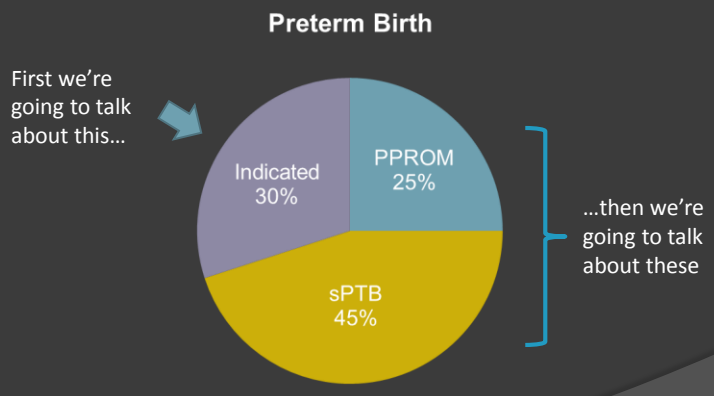
Preterm Birth: Epidemiology



Goldenberg 2008

Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality From Preeclampsia: U.S. Preventive Services Task Force Recommendation Statement

Michael L. LeFevre, MD, MSPH, on behalf of the U.S. Preventive Services Task Force*

Recommendation: The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia. (B recommendation)

Level of Risk	Risk Factors
High risk† *Single risk factors consistently associated with the greatest risk of preeclampsia*	Prior preeclampsia Multiple gestation pregnancy Chronic hypertension Type 1 or 2I diabetes Renal disease Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)
Moderate risk‡ *The presence of multiple moderate risk factors may be used by clinicians to identify women at high risk of preeclampsia*	Never having borne children Obesity (i.e., BMI >30 kg/m^2) Family history of preeclampsia (i.e., mother, sister) Sociodemographic characteristics (i.e., black race, low socioeconomic status) Age ≥35 years Personal history factors (e.g., born low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)
Low risk	Prior uncomplicated term delivery

The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

LeFevre 2014

Practice Advisory on Low-Dose Aspirin and Prevention of Preeclampsia: Updated Recommendations

- ACOG supports the recommendation to consider the use of low-dose aspirin (81 mg/day), initiated between 12 and 28 weeks of gestation, for the prevention of preeclampsia, and recommends using the high-risk factors as recommended by the USPSTF.
  - July 11, 2016

USPSTF/ACOG Guidelines

- How did we get here?
- What is the impact of ASA on preE, and how does that translate to PTB prevention?
- Is this all about iPTB prevention?
- Can aspirin prevent PTB in women not at risk for preE?

A quick review – Aspirin for preeclampsia prevention

- One of the complications of preeclampsia is indicated preterm birth
- Preventing preeclampsia will translate to (at least some) PTB prevention
- So, let's review the aspirin story
  - Does abnormal prostaglandin metabolism cause preeclampsia?
  - Can aspirin fix it?

A tale of two prostaglandins…

- PGI_2 (prostacyclin) is a potent vasodilator and potent inhibitor of platelet aggregation (favors normal pregnancy)
- TXA (thromboxane) is a potent vasoconstrictor and potent promoter of platelet aggregation (favors preeclampsia)
- An imbalance between these two is a plausible cause of preeclampsia
- LDA reduces TXA without affecting PGI_2
- Extensive research to test whether LDA can prevent preE

PGI2/TXA imbalance, LDA and preeclampsia: Summary

- YES! Does abnormal PG metabolism have a plausible biologic role in mediating preeclampsia?
- YES! Is preeclampsia associated with an altered TXA:PGI_2 ratio?
- YES! Does LDA impact the TXA:PGI_2 ratio?
- YES! Does correction of the abnormal ratio correlate with the prevention of preeclampsia?

Lots of trials ensued…

- Low-risk nulliparous patients
- Nulliparous women with positive screening tests (Doppler, etc.)
- Pregnant women with medical problems
- Twins
- Poor OB history
- Many positive studies and much enthusiasm!

LOW-DOSE ASPIRIN TO PREVENT PREECLAMPSIA IN WOMEN AT HIGH RISK

- 2539 women at high risk of preeclampsia (471 IDDM, 774 chronic hypertension, 688 multi-fetal gestation, 606 previous preeclampsia)
- Randomized to 60 mg LDA 13-26 weeks
- No effect on incidence of preeclampsia or any other perinatal outcome
- Caused a major loss of enthusiasm for the use of LDA
  - Caritis 1998

LOW-DOSE ASPIRIN TO PREVENT PREECLAMPSIA IN WOMEN AT HIGH RISK

VARIABLE	INCIDENCE OF PREECLAMPSIA		RELATIVE RISK (95% CONFIDENCE LIMITS)
	ASPIRIN	PLACEBO	
	percent		
Risk group			
Pregestational diabetes mellitus (n=462)	18	22	0.9 (0.6, 1.2)
Hypertension (n=763)	26	25	1.1 (0.8, 1.4)
Multifetal gestation (n=678)	12	16	0.7 (0.5, 1.1)
Previous preeclampsia (n=600)	17	19	0.9 (0.6, 1.2)
All groups (n=2503)	18	20	0.9 (0.8, 1.1)

Powered to detect a 50% reduction in preE!!!

Caritis 1998

ACOG 2013 Hypertension in Pregnancy Task Force

- LDA for women with:
  - h/o Pre-E requiring delivery < 34 weeks
  - Pre-E in multiple pregnancies
- What is the expected impact?
- Expected reduction in Pre-E very minimal – 480 cases/year
- Essentially ZERO impact on PTB
  - Werner and Rouse Obstet Gynecol Dec 2015

Time for a reappraisal

- What do the LDA metaanalyses show?
- What can we learn from the variability in LDA trial results?
  - Does it matter when the LDA is started?
  - Does dose matter
  - Does it matter if early vs. late pre-e is the study endpoint? Severe vs. mild?
- Where do we go from here?

Time for a reappraisal Systematic Reviews

Study	Comment	RR (all significant)
Coomarasamy 2003	Historical risk factors (previous pre-e, HTN, DM, renal disease, age)	Pre-e 0.86 Perinatal death 0.79
Askie 2007 (PARIS)	Individual patient data metaanalysis, 61 trials, 32,217 patients	Pre-e 0.90 Composite adverse outcome** 0.90

** Pre-e, maternal death, PTD, SGA, NND

Why the variation in the trial outcomes?

- Does it matter when LDA is started?
- Does the dose of LDA matter (60 vs 81 vs 100mg)?

Does it matter when LDA is started? Meta-analyses

Study	Comparison	Findings
Bujold 2010	Preeclampsia with LDA started before or after 16 weeks	RR 0.47 < 16 wks RR 0.81 > 16 wks (NS)
Roberge 2013	Perinatal death with LDA started before or after 16 weeks	RR 0.41 < 16 wks RR 0.93 > 16 wks (NS)
Roberge 2012	Severe vs. mild pre-e if LDA started < 16 weeks	RR 0.22 severe pre-e RR 0.81 mild pre-e (NS)
Roberge 2012	Preterm vs. term pre-e if LDA started < 16 weeks	RR 0.11 preterm pre-e RR 0.98 term pre-e (NS)

LDA started before vs. after 16 weeks

- Meta-analysis of 27 studies
- Stratified by LDA started < vs. > 16 weeks
- RR Pre-e 0.47 (0.34-0.65) if started < 16 weeks
- RR Pre-e 0.81 (0.63-1.03) if started > 16 weeks
  - Bujold 2010 Obstet Gynecol 116:2010

LDA started before vs. after 16 weeks

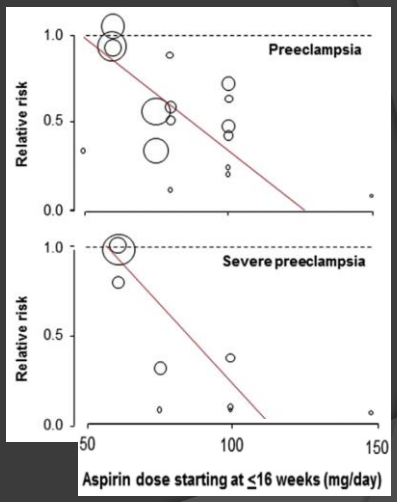
- Problems with study:
  - Inclusion criteria markedly different in various studies
  - Total of 9 studies started < 16 weeks: 4 unpublished, 4 in minor journals, 1 in BJOG
  - No plausible theory offered for why it should matter
  - Multiple studies with LDA started after 20-24 weeks showed benefit

The early vs. late battle continues…

- Roberge, Nicolaides, et al:
  - "Low-dose aspirin initiated at >16 weeks' gestation has a modest or no impact on the risk of preeclampsia" AJOG 2017
- Meher, Askie, et al:
  - "There was no significant difference in the effects of antiplatelet therapy for women randomized before 16 weeks' gestation compared with those randomized at or after 16 weeks" AJOG 2017

How about the dose?

- Possible dose-response effect of LDA
  - Roberge 2017
- Perhaps the MFMU trial used too small a dose?



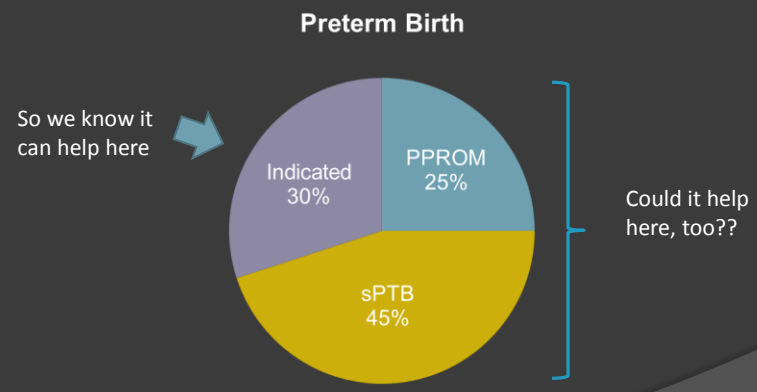
Timing and dose: Summary

- Start as early as possible after 12 weeks
- Do not hesitate to start later – initiate as late as 28 weeks depending on initiation of care, recognition of risk factors, etc.
- Use 81 mg/day
- Stay tuned!

Impact of USPSTF recommendations on preE prevention

- Recall trivial impact of "old" ACOG recs – 480 cases prevented
- Estimated additional 13,500 preE cases prevented
- Precise impact on PTB uncertain but likely significant
- Also reduces PTB due to IUGR…
- Will asses overall impact of aspirin shortly…

Might aspirin prevent PTB due to sPTB or PPROM?

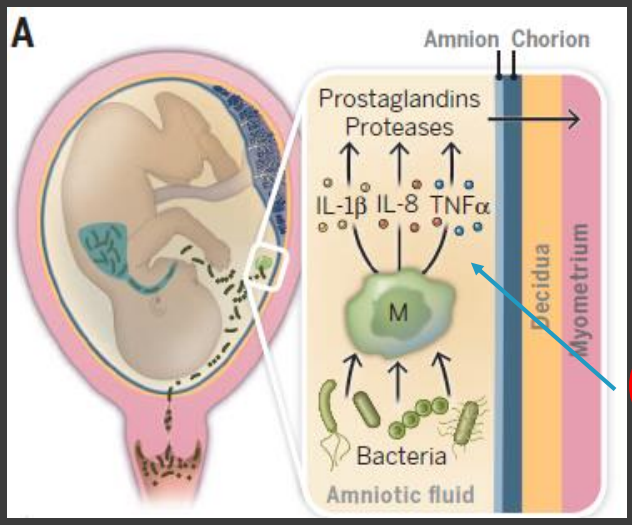


Can Low-dose Aspirin Prevent sPTB or PPROM PTB?

- Is this a plausible hypothesis?
  - Preterm birth as an inflammatory state
  - Other anti-inflammatories and preterm birth
  - Is there a reason to hope that this could work?
- What do the data show?

PTB as an inflammatory state

- PubMed search of “preterm birth” & “inflammation” yields 2786 results
- There is a tendency to equate inflammation and infection
- PTB related to infection fairly well understood
- PTB related to inflammation without infection less well studied
- Inflammatory stimulus -> cytokine release -> prostaglandin release



Romero 2014 Science

PTB Phenotypes

- We classically think of PTB as occurring due to:
  - sPTB
  - PPROM PTB
  - Indicated PTB
- Turns out that the occurrence of one increases the risk of the others in subsequent pregnancies
- Turns out experts can't always agree on what the indication was!
  - Laughon AJOG 2014
  - Ananth AJOG 2006
  - Stout AJOG 2014

Dose ASA Prolong Pregnancy?

- Lancet 1973
- Case-control study
  - 103 women taking > 3250 mg ASA/day (!!) for at least 6 months
  - 52 women matched for dz (RA, CV dz, etc.), not on ASA
  - 50 women with no risks, not on ASA
    - Lewis and Schulman, 1973 Lancet

COMPARISONS IN THE THREE STUDY GROUPS (MEAN ±S.D.)

Variable	Group I (103)	Group II (52)	Group III (50)
Age (yr.)	26·0±5·68	26·7±5·05	26·3±5·18
Gravidity ..	2·55±1·69	2·69±1·34	2·52±1·60
Parity	1·37±1·52	1·50±1·43	1·62±1·40
Length of gestation (days)	286·1*±13·3	275·2±10·6	278·6±6·91
Length of labour (hr.)	12·1*±10·6	7·30±4·11	6·96±4·96
Birth-weight (g.)..	3077±597	2972±538	3379*±460
Blood-loss estimated (ml.)	340*±155	244±114	235±97

* Mean different ($P < 0·05$) from other two groups. Otherwise, differences between groups were not significant at this level.

Anti-inflammatories and preterm birth

- Cochrane review of COX inhibitors
- 13 trials (10 with indomethacin), 713 women
  - Decreased risk PTB < 37 weeks (RR .21) vs placebo
  - Decreased risk PTB < 37 weeks (RR .53) vs other tocolytics
  - Increased EGA at delivery (3.5 weeks)
- Safety concerns remain (increased gr III/IV IVH, PVL and NEC in recent metaanalysis)
  - Hammers 2014 AJOG

LDA and PTB
MFMU HRA Study

Outcome	Incidence		Relative Risk (95% Confidence Limits)
	Aspirin (N=1254)	Placebo (N=1249)	
	percent		
Postpartum hemorrhage	6	6	0.9 (0.7, 1.3)
Abruptio placentae	1	2	0.7 (0.4, 1.3)
Preterm delivery	40	43	0.9 (0.9, 1.0)
Infant small for gestational age	10	9	1.2 (0.9, 1.5)
Perinatal death	3	5	0.8 (0.5, 1.1)
Neonatal intraventricular hemorrhage	2	1	1.5 (0.8, 2.8)

Caritis 1998 NEJM

LDA and PTB
Low risk nulliparas

	Aspirin (N = 302)	*Placebo (N = 302)*
Indicated preterm delivery	12 (4%)	13 (4.3%)
Spontaneous preterm delivery	8 (2.7%)	11 (3.7%)
Preterm premature rupture of membranes	9 (3%)	8 (2.7%)
Labor induced	66 (22%)	84 (28%)
Cesarean delivery	72 (24%)	66 (22%)

Differences between groups were not significant.

Hauth 1993 AJOG

Time for a reappraisal
Systematic Reviews

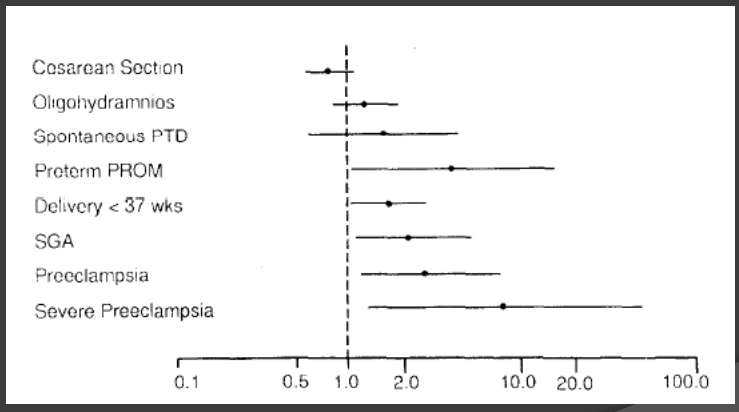
Study	Comment	RR (all significant)
Coomarasamy 2003	Historical risk factors (previous pre-e, HTN, DM, renal disease, age)	Pre-e 0.86 Perinatal death 0.79 Preterm birth 0.86
Askie 2007 (PARIS)	Individual patient data metaanalysis, 61 trials, 32,217 patients	Pre-e 0.90 Composite adverse outcome** 0.90 PTB < 34 weeks 0.90

** Pre-e, maternal death, PTD, SGA, NND

LDA and PTB
Is there any evidence?

- Consistent evidence that LDA reduces PTB in women at high risk of preE!
- Data suggest reduction in PTB may be related to factors other than preeclampsia prevention alone
- Is it plausible that LDA reduces sPTB and PPROM PTB in women at risk of preE?
- How about women not at risk of preE?

Does correction of the abnormal TXA/PGI2 ratio correlate with the prevention of preeclampsia?



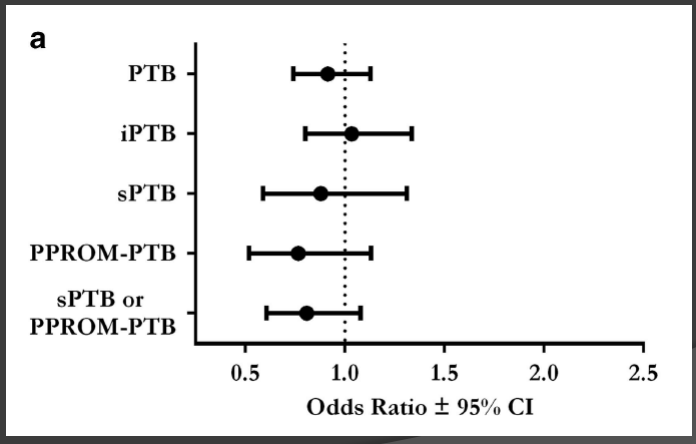
RR of adverse outcome with < 2-fold reduction in TXA
Hauth 1995

ORIGINAL ARTICLE

The impact of low-dose aspirin on preterm birth: secondary analysis of a randomized controlled trial

AA Allshouse[1], RH Jessel[2] and KD Heyborne[2,3]

MFMU HRA Trial



Review

Antiplatelet Agents and the Prevention of Spontaneous Preterm Birth

A Systematic Review and Meta-analysis

Elvira O. G. van Vliet, MD, PhD, Lisa A. Askie, PhD, Ben W. J. Mol, MD, PhD, and Martijn A. Oudijk, MD, PhD

Outcome	RR (all significant)
sPTB < 37 wks	0.93
sPTB < 34 wks	0.86

Is there any other evidence? EAGeR Secondary Analysis

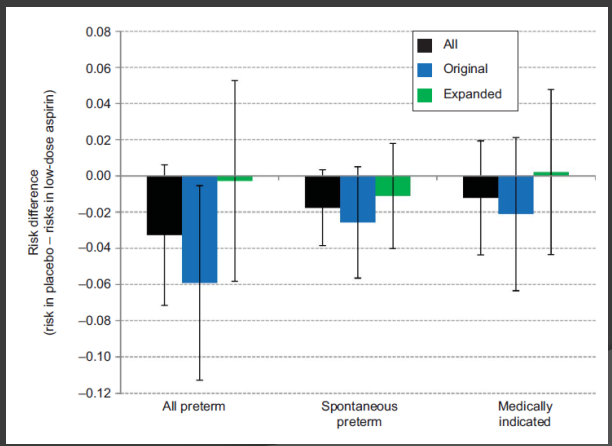
- EAGeR (Effects of Aspirin in Gestation and Reproduction) Study
- Multi-center RCT, 1228 women, 2007-11
  - Two strata:
    - Original – exactly one loss < 20 weeks during last 12 months
    - Any women with 1 or 2 losses regardless of gestation or timing
      - Schisterman Lancet 2014

Original Research

Low-Dose Aspirin and Preterm Birth

A Randomized Controlled Trial

Robert M. Silver, MD, Katherine Ahrens, PhD, Luchin F. Wong, MD, Neil J. Perkins, PhD, Noya Galai, PhD, Laurie L. Lesher, MBA, David Faraggi, PhD, Jean Wactawski-Wende, PhD, Janet M. Townsend, MD, Anne M. Lynch, MD, Sunni L. Mumford, PhD, Lindsey Sjaarda, PhD, and Enrique F. Schisterman, PhD



Is there any other evidence? EAGeR Secondary Analysis

- Summary
  - Trend for reduction in PTB in all groups
  - Statistically significant reduction in PTB in original cohort with confirmed pregnancies in EAGeR
  - Primary effect is on sPTB, not iPTB in all studies!

USPSTF

Level of Risk	Risk Factors
High risk† *Single risk factors consistently associated with the greatest risk of preeclampsia*	Prior preeclampsia Multiple gestation pregnancy Chronic hypertension Type 1 or 2I diabetes Renal disease Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)
Moderate risk‡ *The presence of multiple moderate risk factors may be used by clinicians to identify women at high risk of preeclampsia*	Never having borne children Obesity (i.e., BMI >30 kg/m^2) Family history of preeclampsia (i.e., mother, sister) Sociodemographic characteristics (i.e., black race, low socioeconomic status) Age ≥35 years Personal history factors (e.g., born low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)
Low risk	Prior uncomplicated term delivery

Henderson 2014

LDA and PTB
Is there any evidence?

Study	Populations	Finding
Coomarasamy (2003)	Historical risk factors (previous pre-e, HTN, DM, renal dz, age)	Pre-e 0.86 Preterm birth 0.86
Askie 2007 (PARIS)	Individual patient metaanalysis (61 trials, 32,217 patients, high and low risk)	Pre-e 0.90 PTB < 37 weeks 0.93 PTB < 34 weeks 0.90
Recommendation		Projection
US Preventive Services Task Force (2014)	Systematic review – high risk patients	Pre-e 0.76 Preterm birth 0.86

NNT: USPSTF Recs

Outcome	Risk of outcome	RR	Absolute change in risk	Risk after change	NNT Benefit (95% CI)
Preeclampsia	0.10	0.76	-0.02	0.08	42 (26, 200)
	0.18	0.76	-0.04	0.14	23 (15, 111)
	0.23	0.76	-0.06	0.17	18 (11, 87)
IUGR	0.07	0.80	-0.01	0.06	71 (41, 1429)
	0.13	0.80	-0.03	0.10	38 (22, 769)
	0.24	0.80	-0.05	0.19	21 (12, 417)
Preterm birth	0.11	0.86	-0.02	0.09	65 (38, 455)
	0.19	0.86	-0.03	0.16	38 (22, 263)
	0.31	0.86	-0.04	0.27	23 (13, 161)

NICE and WHO

Organization	Guideline	Definition of treatment population
National Institute for Health and Clinical Excellence (NICE), 2011	NICE advises that women at high risk of preeclampsia or with more than one moderate risk factor take 75 mg of aspirin daily from 12 weeks until the birth of the baby.	*High risk if any:* • Hypertensive disease during prior pregnancy • Chronic kidney disease • Autoimmune disease • Type 1 or type 2 diabetes • Chronic hypertension *High risk if >1 of the following moderate risks:* • First pregnancy • Age ≥40 years • >10-year pregnancy interval • BMI ≥35 kg/m^2 • Family history of preeclampsia (mother, sister) • Multiple pregnancy
World Health Organization (WHO), 2011	WHO recommends that women at high risk of preeclampsia take 75 mg of aspirin daily, initiated before 20 weeks of pregnancy.	*High risk:** • Previous preeclampsia • Diabetes • Chronic hypertension • Renal disease • Autoimmune disease • Multiple pregnancy

*The WHO guidelines note that this is not an exhaustive list of high-risk factors.

Original Research

A Cost–Benefit Analysis of Low-Dose Aspirin Prophylaxis for the Prevention of Preeclampsia in the United States

Erika F. Werner, MD, Alisse K. Hauspurg, MD, and Dwight J. Rouse, MD

Outcome	No Aspirin	Per the College	Per the USPSTF‡	Universal
No. of women treated	0	14,000	940,800	4,000,000
Aspirin costs ($)	0	70,000	4,704,000	20,000,000
Preeclampsia (n)	167,200	166,720	153,160	152,240
Incremental cases avoided‡	—	480	13,560	920
Incremental NNT‡	—	29	68	3,325
Related costs ($)	564,374,160	562,682,280	516,946,400	513,790,680
Preterm birth (n)	452,360	451,800	435,160	433,800
Incremental cases avoided‡	—	560	16,640	1,360
Incremental number needed to treat‡	—	25	56	2,249
Related costs ($)	8,868,234,720	8,856,711,440	8,522,864,920	8,495,785,120

Impact of adoption of USPSTF on PTB

- "Old" ACOG recommendations would be expected to prevent 560 PTB per year in US
- USPSTF recommendations would be expected to prevent 16,640 PTB per year in US
- This would lead to a 4% reduction in PTB, larger than the effect of 17OHP-C!!
  - Werner and Rouse Obstet Gynecol Dec 2015

Summary: ASA for PTB prevention

- Given LDA's anti-inflammatory effects and the inflammatory nature of PTB, there is biologic plausibility to this concept
- Empiric link between LDA administration and PTB prevention is strong
- Paradoxically, impact is larger on sPTB than on iPTB

Summary

- Effect more established in “high-risk” than “low-risk” women
  - ? Implicates placental hypoxia, hemorrhage, etc.
- Strong consensus that expanded criteria for LDA will prevent large number of PTBs
- Study of other groups of women at risk for PTB ripe for study

Summary

DENVER HEALTH
Level One Care for ALL

- Its time to incorporate the new USPSTF/ACOG criteria into your practice!!

Risk Assessment	Pregnant women are at high risk for preeclampsia if they have 1 or more of the following risk factors: • History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (i.e., systemic lupus erythematosus, the antiphospholipid syndrome)
Preventive Medication	Low-dose aspirin (60 to 150 mg/d) initiated between 12 and 28 weeks of gestation reduces the occurrence of preeclampsia, preterm birth, and IUGR in women at increased risk for preeclampsia. The harms of low-dose aspirin in pregnancy are considered to be no greater than small.

Kent Heyborne
Chief of Obstetrics
Associate Director of OB/GYN
Denver Health Hospital
Associate Professor of OB/GYN
University of Colorado