ASPIRIN IN PREGNANCY: FOR ALL?

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BACKGROUND

FIGO
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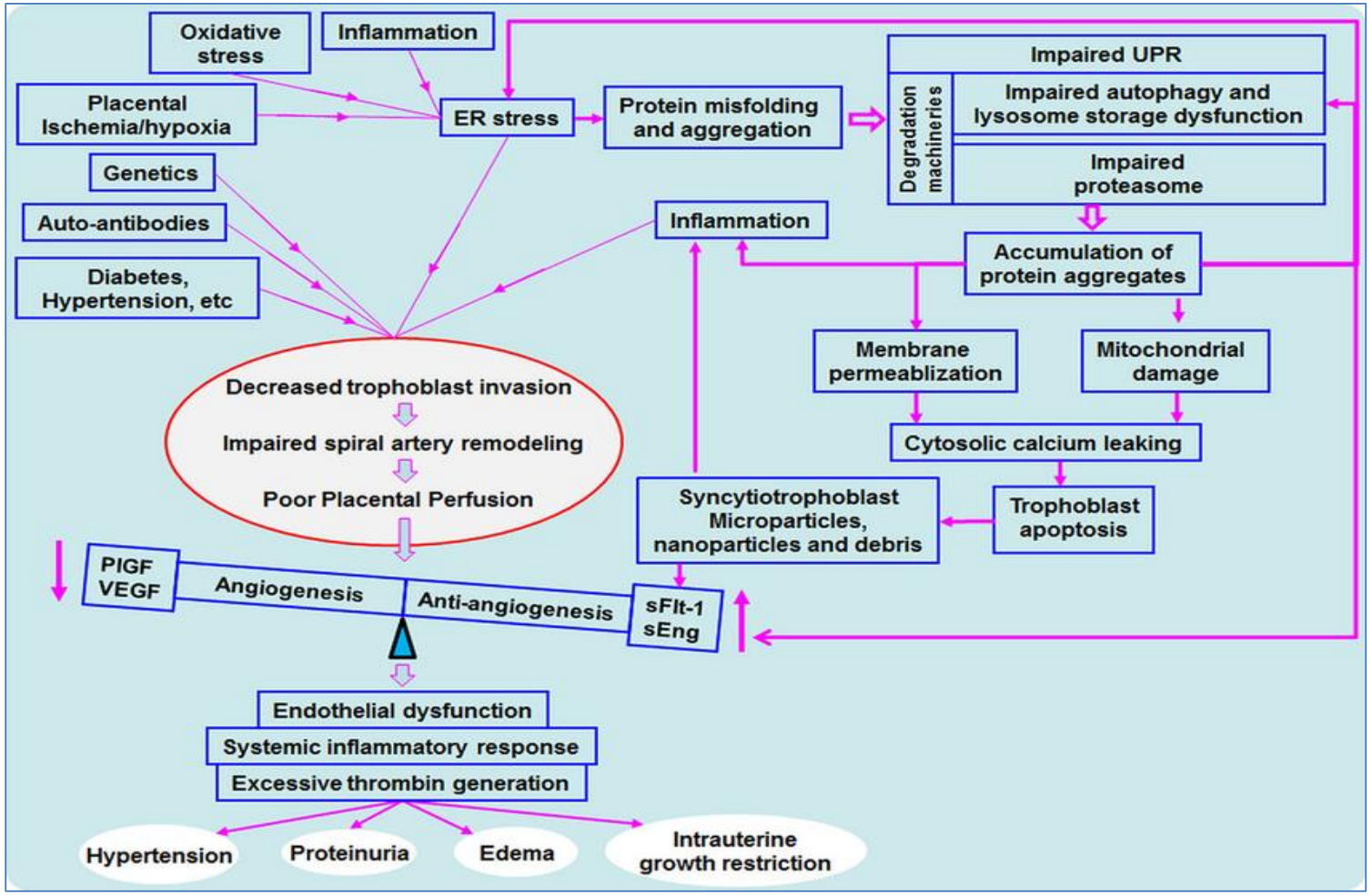
POOR PLACENTATION



FIGO
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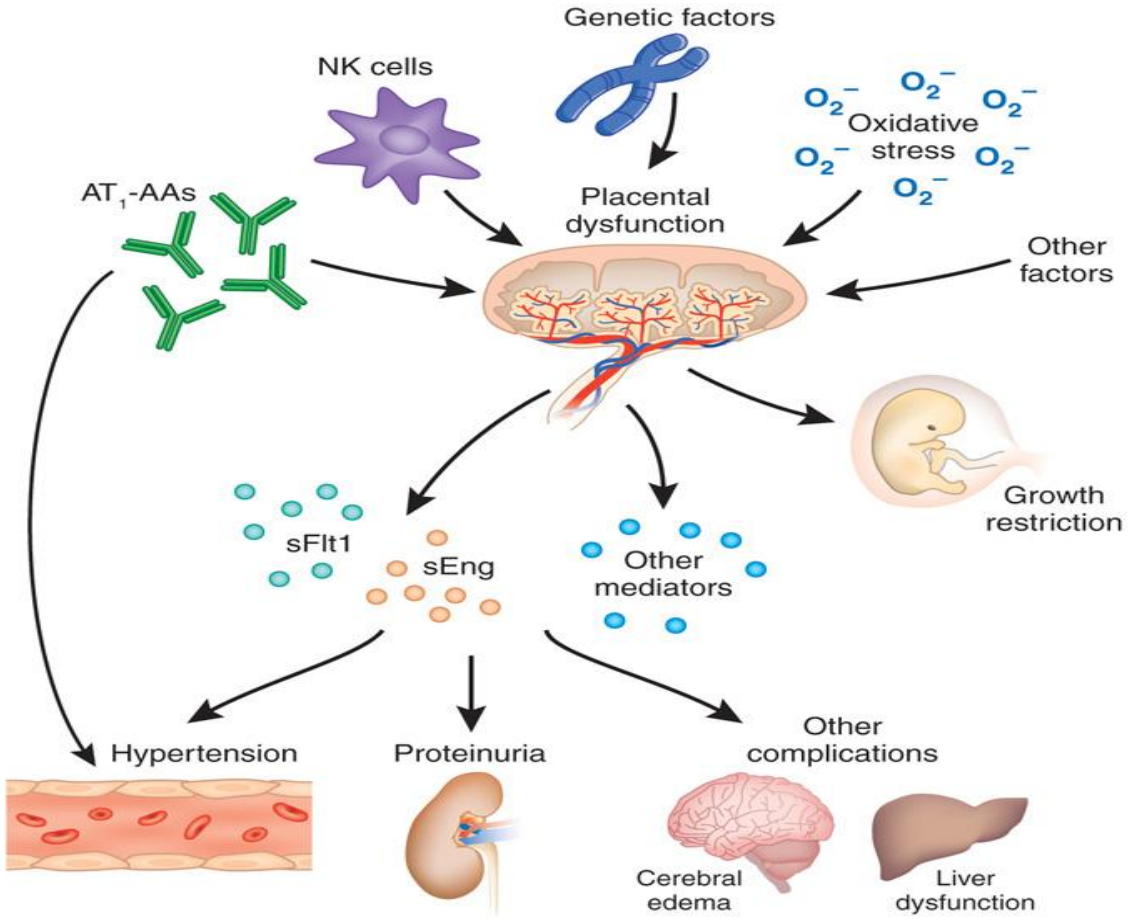
PATHWAYS OF POOR PLACENTATION



FIGO
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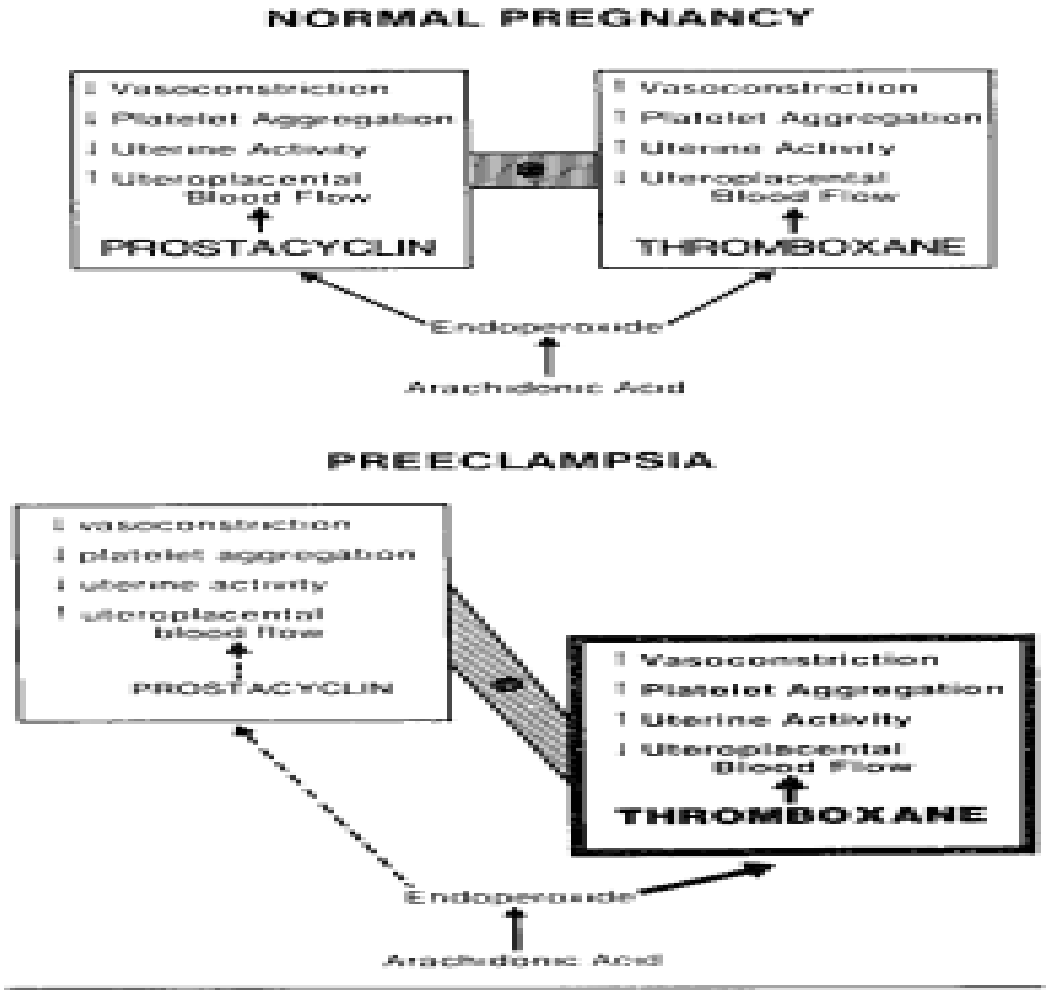
POOR PLACENTATION



FIGO
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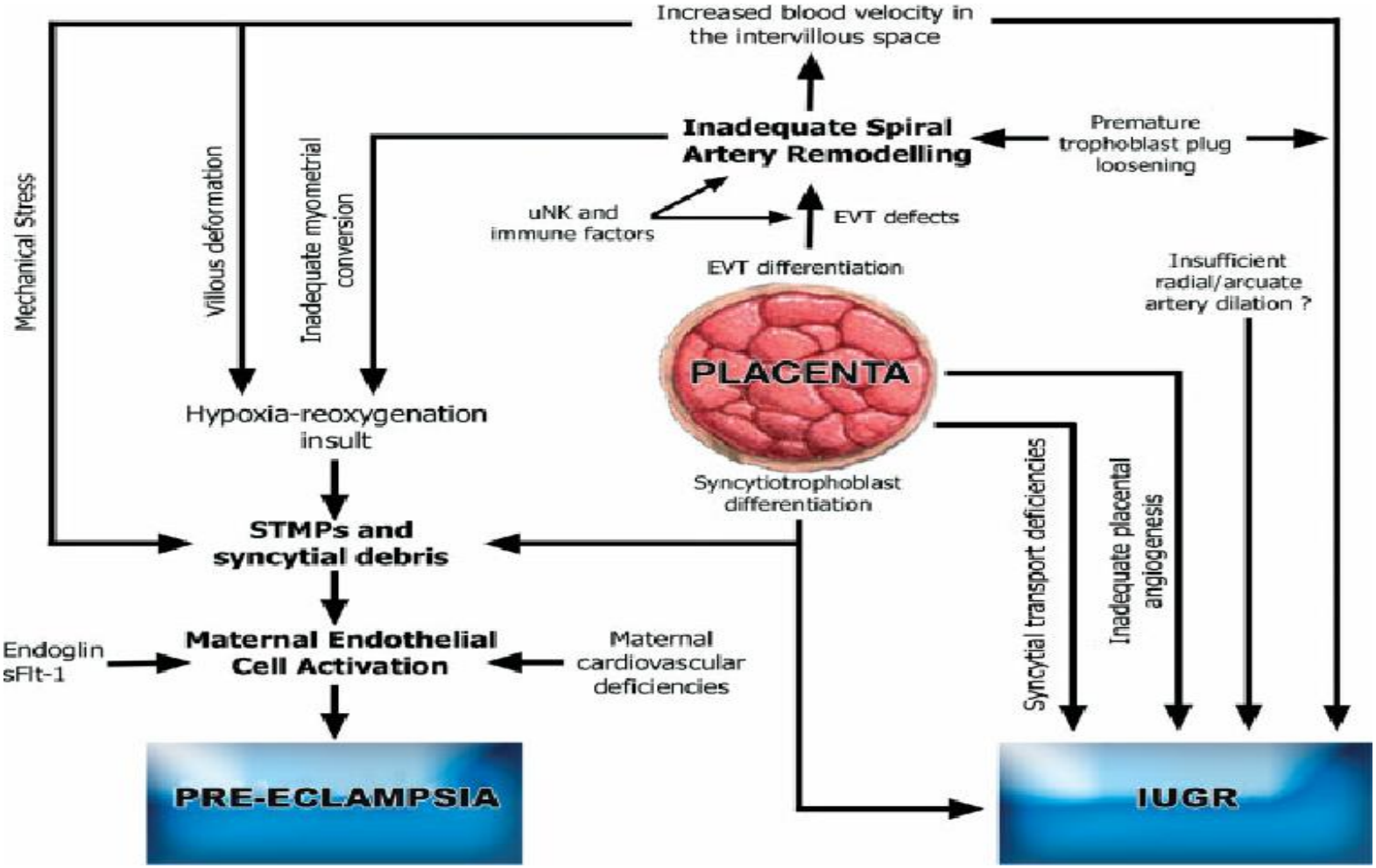
PREGNANCY OUTCOMES DUE TO POOR PLACENTATION



FIGO
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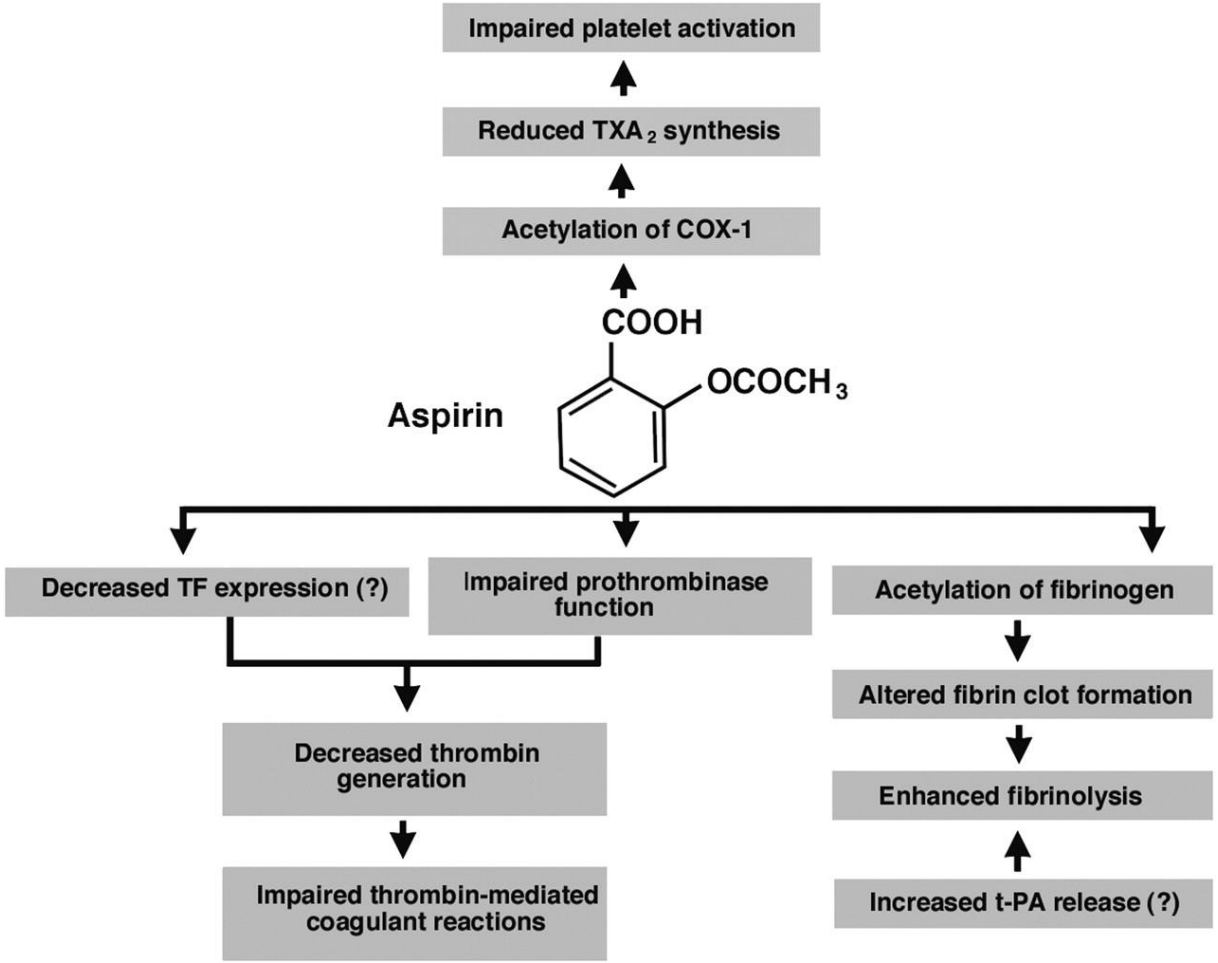
ASPIRIN ACTIONS



ASPIRIN FOR MANAGING POOR PLACENTATION

- Haapsamo et all demonstrated that LDA could improve uterine artery blood flow by transforming the spiral arteries
- Trophoblastic invasion starts at 8-10 weeks, mostly completed by 16- 18 weeks but can continue up to 22 weeks
- Imbalance of TXA_2 (produced by platelets)and PGI_2(produced by endothelial cells) has been implicated in early pregnancies that are destined to develop pre eclampsia
- Rationale is platelets do not have DNA genome to regenerate COX unlike endothelial cells
- **Interventions should ideally start at 8-10 weeks and certainly before 16 weeks to be effective**

FIGO
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Sneak peek at Aspirin in Pregnancy

- 21 systematic reviews since 1991
- PARIS collaboration IPD
- ASPRE trial

Prevention of PE

Low-dose aspirin: background

Prevention of pre-eclampsia by early antiplatelet therapy
Beaufils M et al Lancet 1985

- Randomized study: 102 patients at high risk of PE and / or FGR
- **Aspirin 150 mg** and dipyridamole 300 mg / day **from 12 weeks** (group A) vs no treatment (group B)
- Preeclampsia: **Group A n = 0** vs. **Group B n = 6**
- Fetal death or severe FGR: **Group A n = 0** vs. **Group B n = 9**

Aspirin from early in pregnancy in high-risk patients may protect against PE, FGR, IUD

ASPIRIN FOR POOR PREGNANCY OUTCOMES

Antiplatelet agents for preventing pre eclampsia and its complications: A meta-analysis of individual patient data

Askie LM PARIS collaborative group Lancet 2007

- 32,217 women, 31 randomised controlled trials of pre eclampsia
- **Antiplatelet agents vs controls;**
  - **Relative risk of developing pre eclampsia 0.90 (95%CI 0.84-0.97)**
  - **Relative risk of delivery before 34 weeks 0.90 (95% CI 0.83-0.98)**
  - **Relative risk of serious adverse outcome 0.90 (95% CI 0.85-0.96)**
  - **NNT to prevent one case of serious adverse outcome : 67**
- **Antiplatelet agents had no significant effect on the risk of bleeding events for women or their babies**

Cochrane Database of Systematic Reviews

Antiplatelet agents for preventing pre-eclampsia and its complications

Review | Intervention

Lelia Duley ✉,David J Henderson-Smart,Shireen Meher,James F King

First published: 18 April 2007

59 trials (37,560 women)

- **17% reduction in PRE ECLAMPSIA** (*46 trials, 32,891* ***RR 0.83*** *95% CI 0.77-0.89, NNT 72)*

- **8% reduction in preterm birth** (*29 trials, 31,151* ***RR 0.92*** *95% CI 0.88-0.97, NNT 72)*

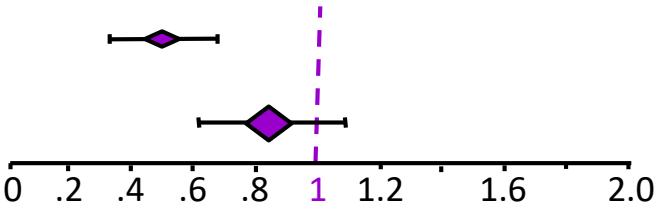
- **14% reduction in fetal/neonatal deaths** (*40 trials, 33,098* ***RR 0.86****, 95% CI 0.76-0.98, NNT 243)*

- **10% reduction in SGA babies** (*36 trials, 23,638* ***RR 0.90*** *95% CI 0.83-0.98 , NNT150)*

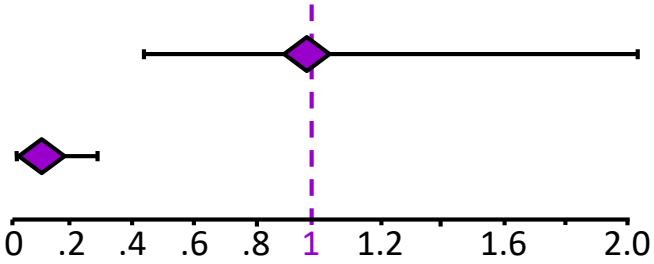
Prevention of PE

Low-dose aspirin: background

Gestation at start of aspirin



In the group with aspirin at <16 w



Bujold et al., 2010; Roberge et al., 2012; 2013

FIGO
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Obstet Gynecol. 2010 Aug;116(2 Pt 1):402-14. doi: 10.1097/AOG.0b013e3181e9322a.

Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis.

Bujold E[1], Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest JC, Giguère Y.

34 RCTs of 11,384 pregnant women at risk of pre eclampsia, given aspirin or placebo

OUTCOMES	Aspirin initiated before 16 weeks	Aspirin initiated after 16 weeks
Pre eclampsia	RR 0.47 (95% CI 0.34- 0.65) 9.3% vs 21.3% control	RR 0.81(95% CI 0.63-1.03) 7.3% vs 8.1% control
Severe pre eclampsia	RR 0.09 (95%CI 0.02-0.37) 0.7% vs 15% control	
IUGR	RR 0.44 (95%CI 0.3-0.65) 7% vs 16.3% control	RR 0.98 (95%CI 0.87- 1.10) 10.3% vs 10.5% control
Gestational hypertension	RR 0.62 (95%CI 0.45-0.84) 16.7% vs 29.7% control	
Preterm Birth	RR 0.22 (95%CI 0.10-0.49) 3.5% vs 16.9% control	

Prevention of PE

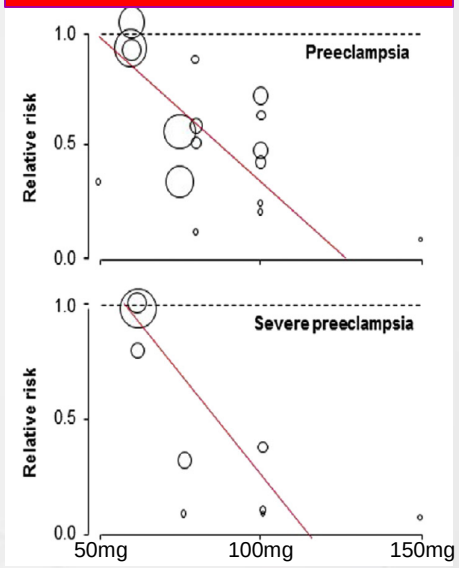
Low-dose aspirin: dose response

Objective To estimate the impact of aspirin dosage on the prevention of PE and FGR

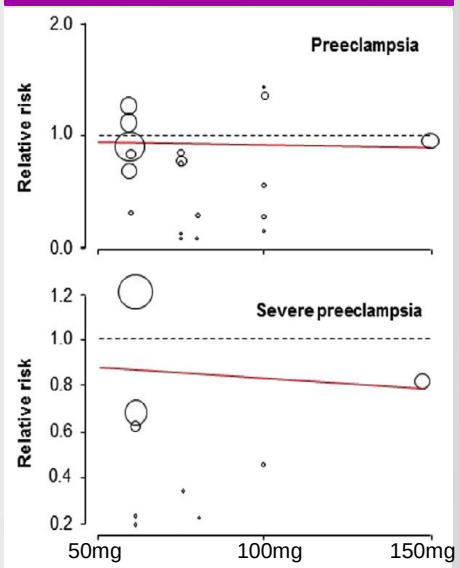
Study design

- Systematic review and meta-analysis of RCTs of ASA vs placebo or no treatment
- Dose response relationship (GA at initiation of ASA ≤16w and > 16w)
- 45 studies; 20,909 participants
- **Aspirin initiated at <16w**
  - 21 studies, 5130 participants

ASA ≤16w



ASA >16w



Aspirin, when given at ≤16w, was associated with a significant reduction in prevalence of PE, with a significant dose response relationship.

Roberge S, Nicolaides K, Demers S et al, AJOG 2017

Chronobiol Int. 2013 Mar;30(1-2):260-79. doi: 10.3109/07420528.2012.717455. Epub 2012 Sep 24.

Chronotherapy with low-dose aspirin for prevention of complications in pregnancy.

Ayala DE[1], Ucieda R, Hermida RC.

Prospective double blind, placebo controlled randomised controlled trial
350 high risk women
Randomised to 6 groups – ASA 100 mg or placebo
Timing : on awakening 8 hours after awakening Bedtime
Intervention at 12-16 weeks continued to delivery
BP measured for 48 hours at baseline, every 4 weeks until 7 months, fortnightly-delivery

RESULTS

- No effect on BP when ingested on awakening
- **Highly statistically significant reduction at 8 hours and more so at bedtime**
- **Significantly lower hazard ratios of composite of PE, PTB, IUGR, stillbirth (0.35 95% CI 0.22-0.56 p<0.001)**

FIGO

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OF
GYNECOLOGY & OBSTETRICS

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~~ASPIRIN AT ANYTIME~~

- **Needs to be started as early as possible and before 16 weeks for it to be effective**

- **Timing of administration in the evening shows better efficacy**

Prevention of PE

Aspirin: platelet aggregation

Aim

To compare the effects of different doses of aspirin on platelet aggregation and PGI_2 production by vessel wall after ischaemia.

Methods

- 25 young healthy volunteers
- Subjects were allotted to the various dosage groups of aspirin (2, 2.5, 3.5, 5, 8 and 10 mg/Kg).
- PGI_2 production and platelet aggregation were investigated before and after aspirin administration.

Results

- A dose of 2.5 mg/Kg reduced platelet aggregation by 25-35%.
- The inhibition of platelet aggregation was almost at maximum 2h after administration of 3.5 mg/Kg of aspirin. Further increase in the dose (5, 8 and 10 mg/Kg) only provoked a slight increase in inhibition, which was not proportional to the increase in dose.
- **PGI_2 production induced by ischaemia was affected by aspirin only at doses higher than 2.5mg/kg.**

Average weight 50 Kg = 175 mg/day

Masotti et al, Lancet, 1979

Aspirin resistance: Clinically relevant in pregnancy?

- Concept of suboptimal platelet response to aspirin well documented in cardiovascular and stroke research in 20 years

  Krasopoulos G at al .*BMJ 2008*

- Suboptimal platelet response –
  - a biochemical failure to inhibit platelet activation in aspirin-treated individuals, assessed in the laboratory or with point-of-care tests.
  - described clinically as recurrence of ischaemic events despite aspirin treatment at the recommended dose.
- **Reported prevalence 5-65% depending on population studied**

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Aspirin resistance: Clinically relevant in pregnancy?

- **30% at 81 mg**
- **10% at 121mg**
- **5% at 160 mg**

Caron et al: J Obstet Gynaecol Can 2009

ASPRE: Prevention of preterm PE

Study design

DOSE: **150 mg / day**

Aspirin resistance: 30% at 81mg and 5% at 160 mg
Caron et al: J Obstet Gynaecol Can 2009;31:1022-7

START: **11-13 weeks**

FINISH: **36 weeks**

Avoid potential hemorrhage for neonate

TIME: **Bed time**

RCT aspirin 100 mg vs placebo morning, afternoon, night
Aspirin at night: lower incidence of PE, FGR, PTB or IUD
Ayala DE, Ucieda R, Hermida RC: Chronobiol Int 2013; 30:260-279

OUTCOME:

Preterm PE

STUDY POPULATION:

High-risk group defined by FMF algorithm

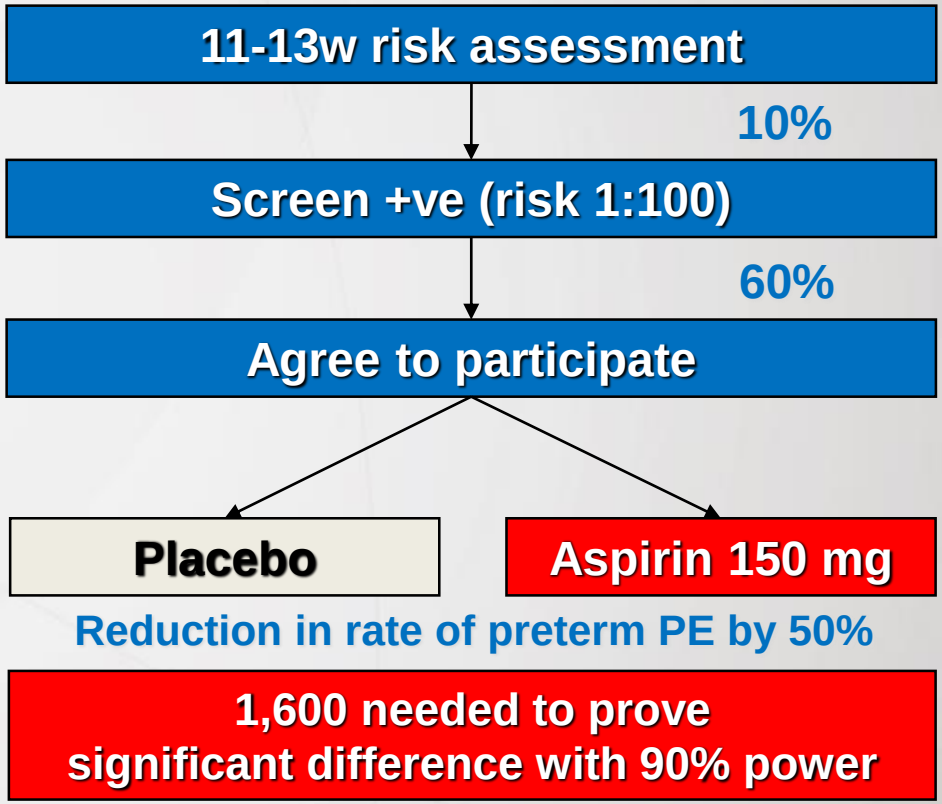
ASPRE: Prevention of preterm PE

Study design

Virgen de la Arrixaca, Murcia, Spain
San Cecilio Hospital, Granada, Spain
Hospiten Sur, Tenerife, Spain
Chu Brugmann Brussels, Belgium
Attikon University Hospital, Greece
Ospedale Maggiore Policlinico, Italy
Rabin Medical Centre, Israel
King's College Hospital, UK
Medway Maritime Hospital, UK
Lewisham University Hospital, UK
North Middlesex Hospital, UK
Southend University Hospital, UK
Homerton University Hospital, UK

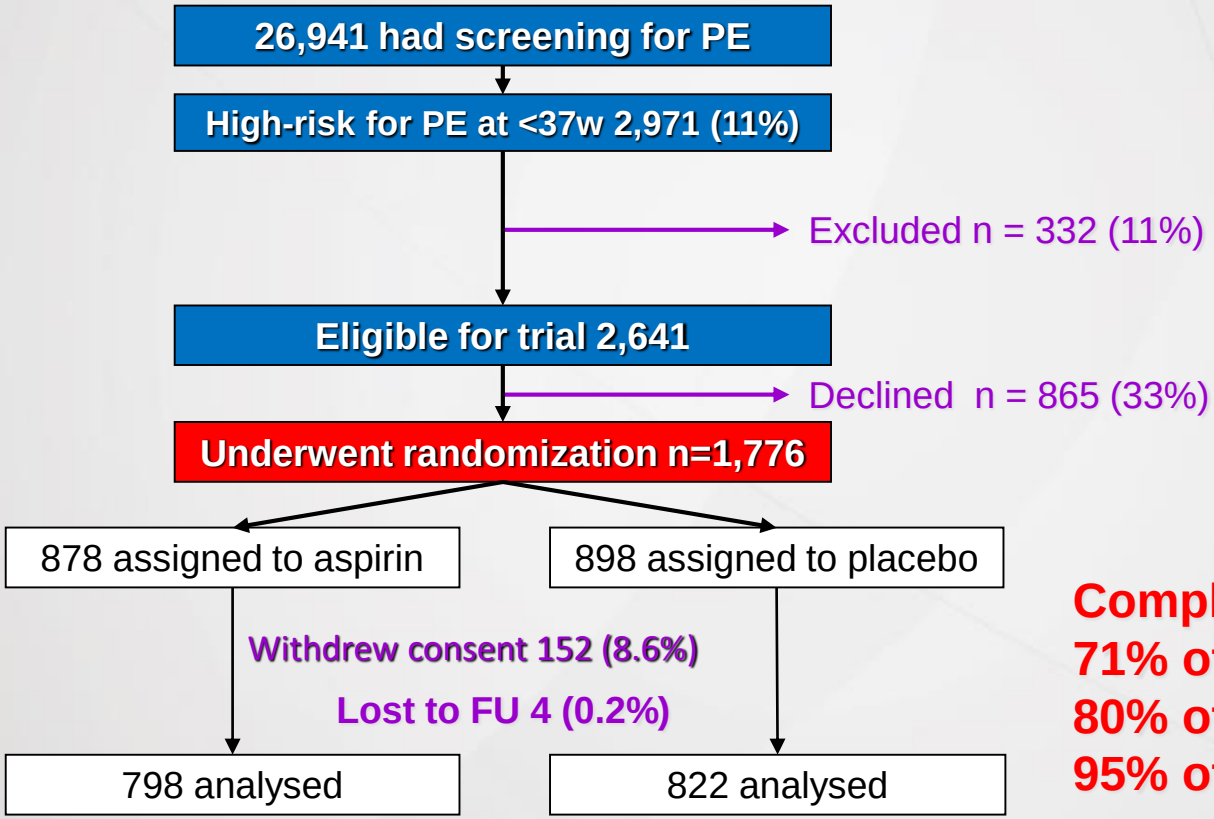
Statistical analysis: D Wright, A Wright
Clinical Trials Unit: UCL, London

Companies: Perkin Elmer, Astraia, Viewpoint, HyLabs Diagnostics, Hananja ehf



ASPRE: Prevention of preterm PE

Screening, randomization, follow-up



253	Receiving aspirin
47	Hypersensitivity to aspirin
17	Peptic ulcer, bleeding disorders
10	Participation in another drug trial
2	Miscarriage before randomization
3	Termination before randomization

Compliance:

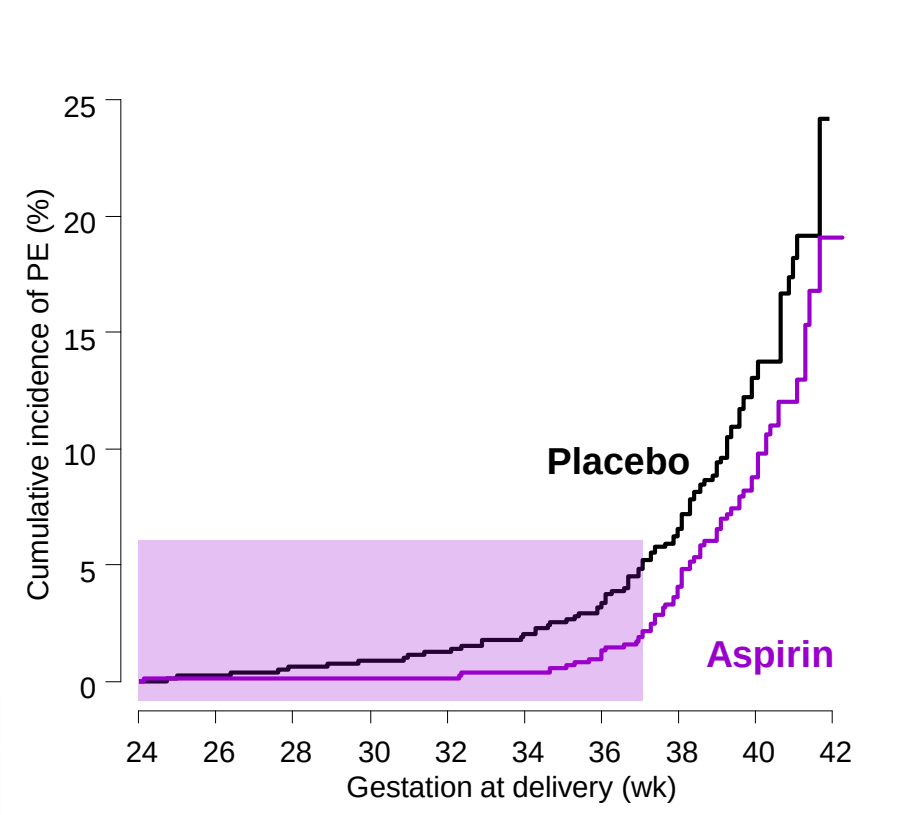
71% of women took >90% of tablets

80% of women took >85% of tablets

95% of women took >50% of tablets

ASPRE: Prevention of preterm PE

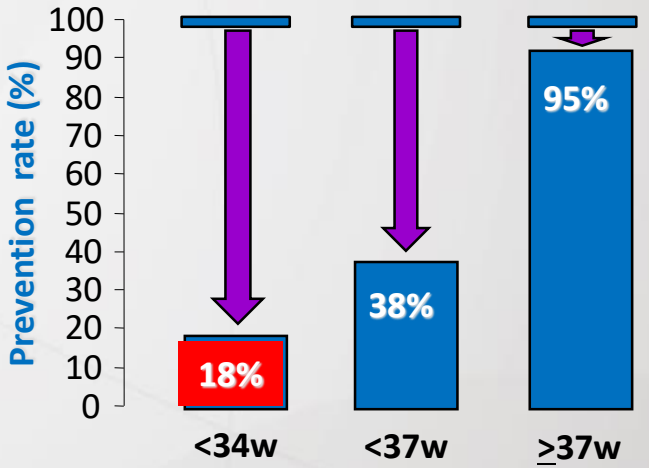
Results: effect on rate of PE



PE <34 w: 1.8% vs 0.4% 82% drop

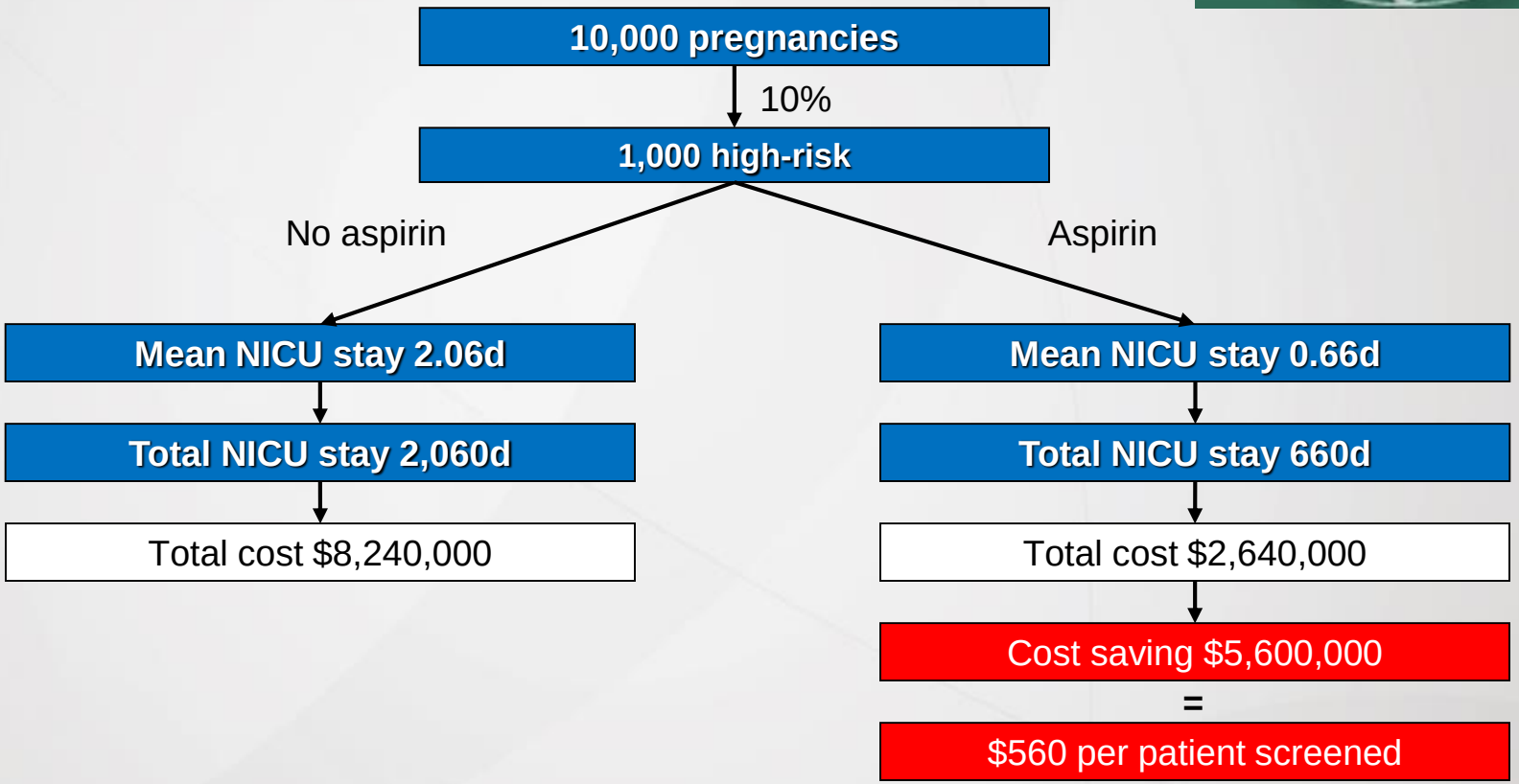
PE <37 w: 4.3% vs 1.6% 62% drop

PE ≥37 w: 7.2% vs 6.6% 5% drop



ASPRE: Prevention of preterm PE

Results: potential cost saving



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ASPIRIN FOR EVERYONE

Obstet Gynecol. 2015 Dec;126(6):1242-50. doi: 10.1097/AOG.0000000000001115.

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

Werner EF[1], Hauspurg AK, Rouse DJ.

- Compared 4 strategies No prophylaxis
  - Prophylaxis according to ACOG
  - Prophylaxis according to US Preventative Task Force
  - Universal prophylaxis

- Costs associated with aspirin, preeclampsia, PTB, potential aspirin associated adverse affects
- Rate of pre eclampsia **4.18%** no prophylaxis
  - **4.17%** ACOG 0.35% (n=14,000)women receive aspirin
  - **3.83%** US PSTF 23.5% (n= 940,000)women receive aspirin
  - **3.81%** universal

- **US Preventative Service Task Force – saves $ 377.4 million in direct medical care cost**
- **Universal - saves $ 365 million**

- ***BOTH USPSTF and UNIVERSAL prophylaxis would reduces morbidity, save lives, lower health cost***

ASPIRIN FOR EVERYONE

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The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

NHS
National Institute for Health and Clinical Excellence

Table. Clinical Risk Assessment for Preeclampsia*

Risk Level	Risk Factors
High†	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 erythematous, the antiphospholipid syndrome)
Moderate‡	Nulliparity Obesity (body mass index >30 kg/m^2) Family history of preeclampsia (mother or sister) Sociodemographic characteristics (African American race, low socioeconomic status) Age ≥35 y Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, >10-y pregnancy interval)
Low	Previous uncomplicated full-term delivery

BOX 3-1. Risk Factors for Preeclampsia

- Primiparity
- Previous preeclamptic pregnancy
- Chronic hypertension or chronic renal disease or both
- History of thrombophilia
- Multifetal pregnancy
- In vitro fertilization
- Family history of preeclampsia
- Type I diabetes mellitus or type II diabetes mellitus
- Obesity
- Systemic lupus erythematosus
- Advanced maternal age (older than 40 years)

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

LOW-DOSE ASPIRIN USE FOR THE PREVENTION OF MORBIDITY AND MORTALITY FROM PREECLAMPSIA
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Asymptomatic pregnant women who are at high risk for preeclampsia
Recommendation	Prescribe low-dose (81 mg/d) aspirin after 12 weeks of gestation. Grade: B

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.
Balance of Benefits and Harms	There is a substantial net benefit of daily low-dose aspirin to reduce the risk for preeclampsia, preterm birth, and IUGR in women at high risk for preeclampsia.
Other Relevant USPSTF Recommendations	The USPSTF recommends that all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 μg) of folic acid. This recommendation is available at www.uspreventiveservicestaskforce.org.

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The Fetal Medicine Foundation

Assessment of risk for preeclampsia (PE)

This application allows estimation of risks of early-PE (delivery at <32 weeks gestation), preterm-PE (<37 weeks) and term-PE (≥37 weeks) by a combination of maternal factors and results of various biophysical and biochemical measurements made at different stages in pregnancy.

Risk calculation is provided for the gestational age blocks of 11^{+0} to 14^{+1}, 19^{+0} to 24^{+6}, 30^{+0} to 34^{+6} and 35^{+0} to 37^{+6} weeks. Please note that when using biophysical and biochemical markers the measurements should be obtained within the same gestational age block.

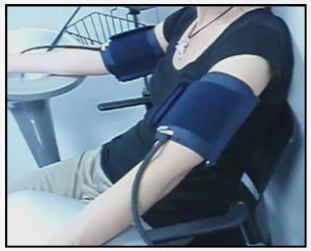
- Useful markers in the first trimester (11^{+0} to 14^{+1} weeks) are MAP, UTPI, PLGF and PAPP-A [1], [2].
- Useful markers in the second trimester (19^{+0} to 24^{+6} weeks) are MAP, UTPI, PLGF and SFLT [3].
- Useful markers in the third trimester are MAP, UTPI, PLGF and SFLT [4], [5].

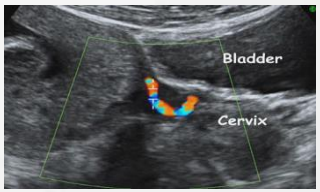
Prediction of PE

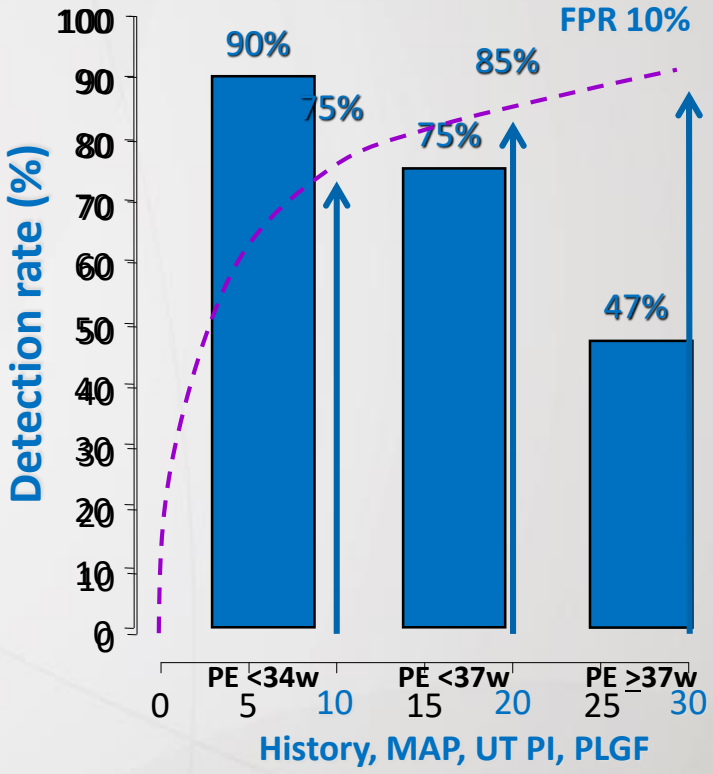
1st trimester combined test

Maternal risk factors

- Age: every 10 years above 30 y
- Weight: every 10 kg above 70 kg
- Racial origin
  Afro-Caribbean
  South Asian
- Obstetric history
  First pregnancy
  Previous preeclampsia
- Family history of preeclampsia
- Conception by IVF
- Chronic hypertension
- Diabetes mellitus
- Autoimmune : SLE / APS





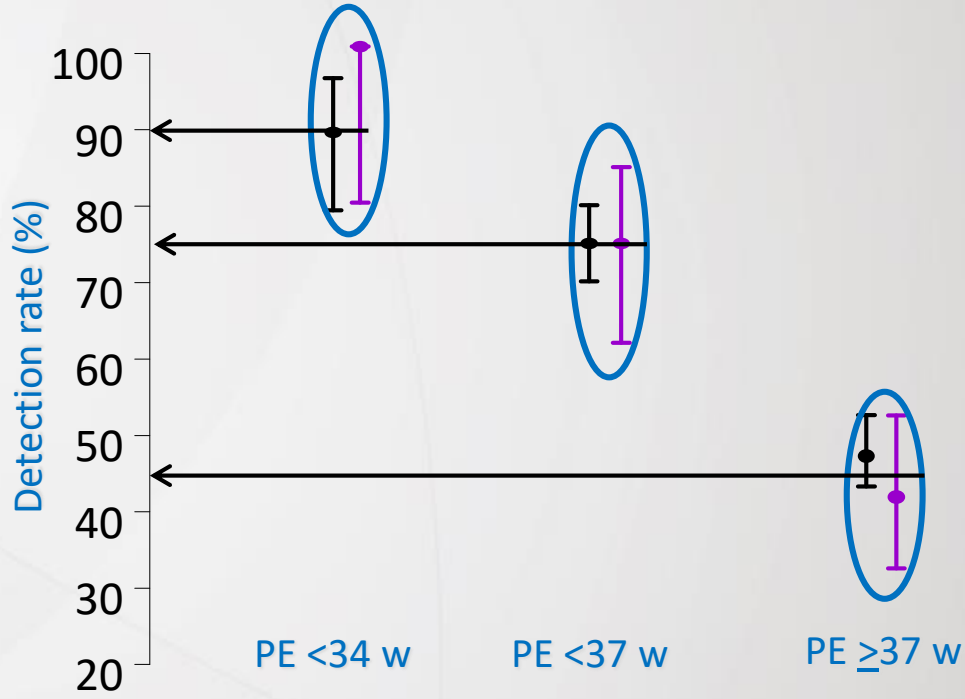


O' Gorman et al. Am J Obstet Gynecol 2016

Screening Quality Study

Validation

funded by EU FP7
ASPRE
project



Screening n = 8,775; PE 239 (2.7%)

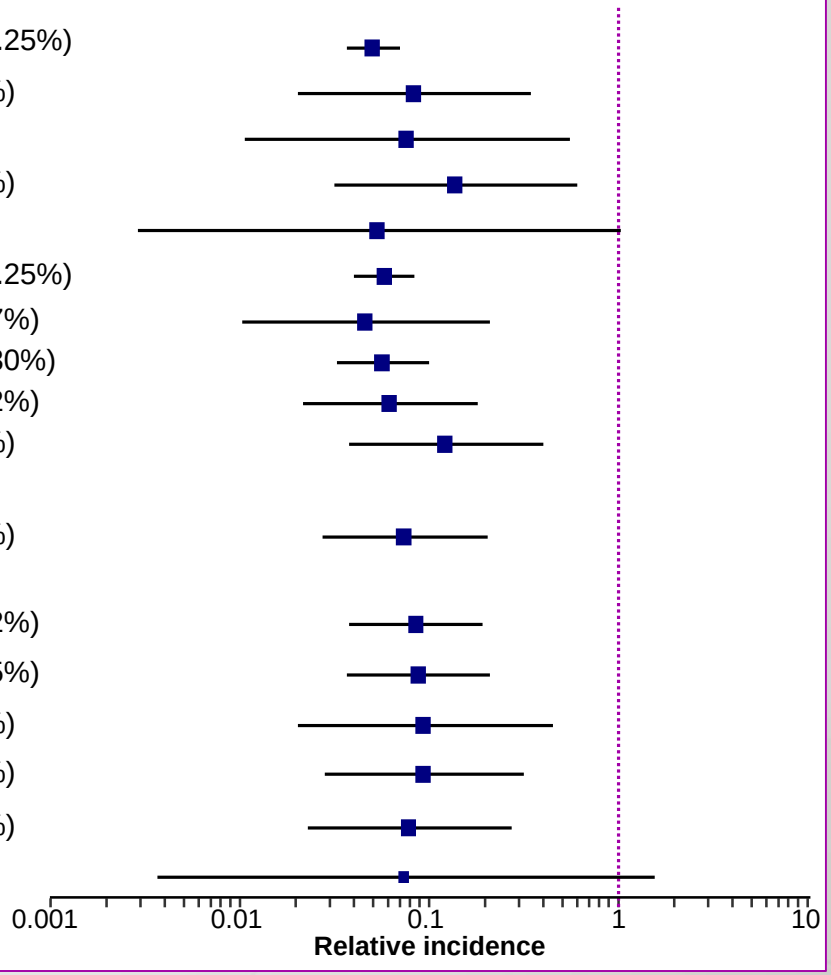
Prediction of PE

NICE & ACOG screened +ve

funded by EU FP7 ASPRE project

Total screened n=34,573

ACOG risk factors	FMF +ve	FMF -ve
Any one risk factor, n=22,287 (64.5%)	171/3,566 (4.80%)	46/18,721 (0.25%)
Previous PE	33/410 (8.05%)	2/298 (0.67%)
Chronic hypertension	43/321 (13.40%)	1/98 (1.02%)
Diabetes Mellitus	12/124 (9.68%)	2/151 (1.32%)
APS or SLE	3/29 (10.34%)	0/78 (0%)
Nulliparity	115/2,686 (4.28%)	36/14,475 (0.25%)
Age >40 yr	11/303 (3.63%)	2/1,183 (0.17%)
BMI ≥30 Kg/m2	66/1,241 (5.32%)	15/4,984 (0.30%)
Family history of PE	19/368 (5.16%)	4/1,245 (0.32%)
In vitro fertilization	8/195 (4.10%)	4/796 (0.50%)
NICE high-risk factors		
Any one factors, n=1,392 (4.0%)	68/781 (8.71%)	4/611 (0.65%)
NICE moderate-risk factors		
Any ≥2 factors, n=2,360 (6.8%)	34/692 (4.91%)	7/1,668 (0.42%)
Nulliparity plus	28/548 (5.11%)	6/1,340 (0.45%)
Age ≥40 yr plus	8/212 (3.77%)	2/556 (0.36%)
BMI ≥35 Kg/m2 plus	17/339 (5.01%)	3/637 (0.47%)
Family history of PE plus	15/263 (5.70%)	3/665 (0.45%)
Pregnancy interval >10 yr plus	2/75 (2.67%)	0/201 (0%)



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Original Research ajog.org

OBSTETRICS

Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11–13 weeks gestation

Neil O'Gorman, MD; David Wright, PhD; Argyro Syngelaki, RM; Ranjit Akolekar, MD; Alan Wright, PhD; Leona C. Poon, MD; Kypros H. Nicolaides, MD

Modality	Detection rate PE/GH (%)	False positive rate(%)
History alone	47/ 35	10
History + MAP 1st trimester	60/40	10
History + MAP + biochemistry (PLGF, PAPPa, s-Flt 1, send)	80(early)/64(late) /39	10
History + MAP + biochemistry + Dopplers UA 11-13 wks	88.5(early)/ 46.7(late) /35.3	10

FIGO
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ASPIRIN FOR EVERYONE

CONTRAINDICATIONS

- Known allergy to the drug
- Use other than as antiplatelet in children/adolescents <16 years(Reye's Syndrome)
- Active peptic ulceration
- History of recent GI bleeding
- History of recent intracranial bleeding
- Bleeding disorders including hemophilia, vWD, severe thrombocytopenia(plts < 30 x 10^{-6}/l
- Severe liver disease with coagulopathy

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~~ASPIRIN FOR EVERYONE~~

Goal of any therapy

Achieve maximum therapeutic effect for the group that benefits most

while

NOT overexposing the majority to potential harm

International Federation of Gynecology and Obstetrics

Working Group on Good Clinical Practice in Maternal-Fetal Medicine

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FIGO Good Clinical Practice Advice

- All women should be assessed in the first trimester through history and mean arterial blood pressure for their risk of developing early pre eclampsia < 34 weeks. Additional tests for screening such as uterine artery Doppler between 11 – 13 weeks and biochemistry can be undertaken to improve sensitivity of screening where available.
- Low Dose Aspirin has been found to reduce the risk of early pre eclampsia, intrauterine growth restriction and preterm birth by improving disordered placentation
- Women who are deemed to be high risk should be offered Low Dose Aspirin (75-150mg) from 12 weeks onwards and before 16 weeks where possible to achieve its intended protection until 28 weeks
- Aspirin should be prescribed in the evening as evidence supports better efficacy during this time

FIGO Good Clinical Practice Advice

- Monitoring of platelet levels or bleeding time on aspirin therapy is not necessary unless the patient develops unexplained bruising or bleeding that may require investigation. Aspirin should be stopped in these circumstances
- Enteric coated preparations delay absorption and should only be considered in women who require this therapy with a history of gastric ulcers.

FIGO Good Clinical Practice Advice

- Aspirin administration will be stopped at 36 weeks' gestation or, in the event of early delivery, at the onset of labour (maximum duration of 25 weeks).

- Mode of delivery , timing of delivery and analgesia requirements should not be influenced by administration of aspirin but by the clinical indications.

- LDA is not associated with increased adverse outcome or bleeding tendencies in mother or neonate.

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CONCLUSION

ASPIRIN FOR EVERYONE

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ISSUES of CONTENTION

- ASPIRIN TO PREVENT POOR PREGNANCY OUTCOMES 
- GIVEN TO EVERY ONE 
- GIVEN AT ANY TIME 

GRAZIE

merci

gracias

thank you

谢谢

DZIĘKUJEMY

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Баярлалаа

hvala

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спасибо

고맙습니다 o 감사합니다.

köszönöm

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