

Low-dose aspirin & Antioxidants in Prevention of Pre-eclampsia: A literature review

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Introduction

- Pre-eclampsia is 'The Disease of Theories'
- Classified as PIH
- It occurs in : 2-8 % of all pregnancy
- Characterized : vasoconstriction,
- cell damage and coagulation abnormality
- Maternal mortality/morbidity

Prevention

- Poses greater implication
- Maternal/perinatal outcomes
- Low dose aspirin & antioxidants
- Good results in preventing preeclampsia
- High-risk group of pregnant women
- Prevent unnecessary sequelae

Plan

- Search & Selection Criteria
- Pathophysiology of pre-eclampsia
- Role of low dose aspirin & antioxidants in preventing pre-eclampsia
- The effect of low dose aspirin
- Previous trials of low dose aspirin
- The effect of antioxidants
- Discussion
- Conclusion

Search strategy & selection criteria

- A MEDLINE SEARCH 1980-2000
- Search term: pre-eclampsia, prevention, low dose aspirin and antioxidant
- Manual search of bibliographies
- Ten RCTs
- 18.892 patients

Physiology

- Cell endothelial normal
- -prevent intravascular coagulation by activating protein C
- -produce prostacyclin that inhibites platelete adherence
- Regulate function of thromboxane (vasoconstriction)

Pathophysiology of pre-eclampsia

- Placental ischaemia ----> EC Dysfunction
- Very LDL vs Toxicity-preventing activity
- Immune maladaptation
- Genetic imprinting
- Vasospasm is a basic pathophysiology in PE (C.Alberd 1918)

Pathophysiology PE

- Vascular constriction
- Resistance in blood flow
- Thromboxan A₂ increased
- Vascular sensitive to angiotensine AII
- Inter endothelial cell leaks

Schéma

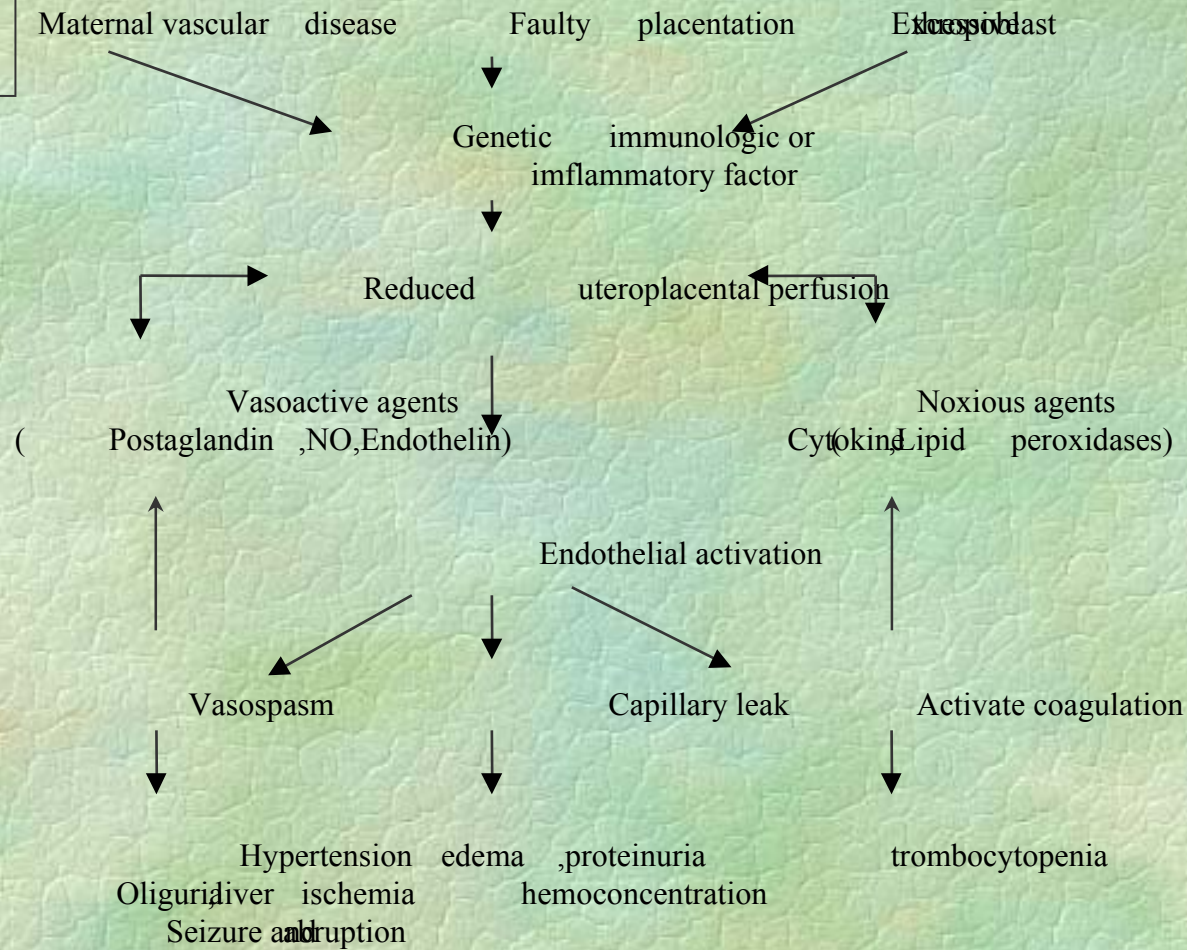


Figure I. Pathophysiological hypertensive due to pregnancy

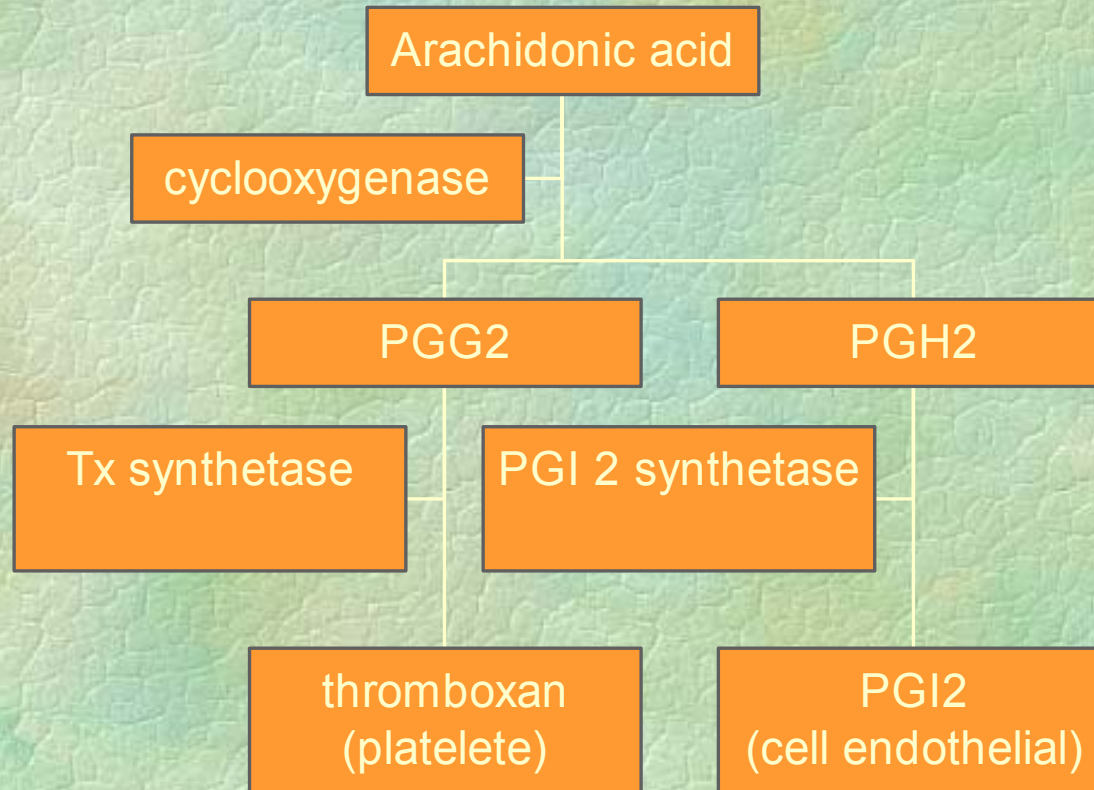
Acetylsalicylat acid (aspirin)

- Most commonly used in the 19th century
- 20-30 billion tablets/year in USA
- Hydrolyzed to sodium salicylat
- Half-life: 2.7 minutes
- Rapidly absorbed by stomach/ intestine

Aspirin

- Anti platelet drug
- Inhibites cyclooxygenase in pre-systemic (portal) circulation
- Blockes synthesis of thromboxane A₂
- Tx A₂: vasoconstriction and platelet aggregation
- Dose 1 - 1,6 mg/kg

Action of low dose aspirin



James A.

AJOG 1988;158:1381

- Low dose aspirin (60 mg), significantly decreases the production of thromboxan but not PGI₂ in placental arteries

Fritzgerald,MB et al

AJOG 1987;157:325

- Cyclooxygenase was selectively inhibited with 120 mg aspirin
- 97 % ----> inhibites serum thromboxan B2 & urinary 2.3 dinor thromboxane A2

Previous trials of low dose aspirin in prevention of pre-eclampsia

- CLASP (Lancet 1994), 9354 women 24-28 weeks of pregnancy, 60 mg/day
- Shift et al. 100 mg/day
- Ylikorkala & Makila 1985, 60 mg/day
- Wallenburg et al. 60 mg/day
- In high risk groups of pregnancy: significant reduction of Pre-eclampsia

Table I. Trial with high-risk nulliparous subjects.

Incidence of preeclampsia (%)							
Series	No	Inclusion criteria	Exclusion criteria	Screening technique	Control	Low-dose aspirin	Statistical significance
Wallenberg et.al 1986	46	Healthy nulliparous	Hypertension, Renal disease	Angiotensin infusion	30	9	P<0.1
Shiff et.al 1989	65	Nulliparous,twin gestation,previous preeclampsia	Hypertension,proteinuria (+)	ROT	35.5	11.8	P= .024
McParland et al 1990	100	Nulliparous	Diabetes,lupus	Uterine artery doppler scan	19	2	P<.02
Brown et al,1990	22	NP +ROT +	Hypertension:diabetes	Angiotensin II infusion	63	27	P<.01
Wenstrom et,al 1995	48	Nulliparous	Hp:renaldisease,twins,diabetes	HCG>2.0 multiple of the median	10.7	0	NS
Bower et al, 1996	60	Any	None	Uterine artery doppler scan	41	29	NS(P=.03)

Adapted from Heyborne.KD, AJOG 2000: 183

High risk with underlying disease

Series	No	IC	Control	Inciden of pe Ld asp	Sta sign
Italian study 1993	896	Ea,hip. Ppe,tg	2.7	2.9	Ns
CLASP 1994	6929	Ea,hip,crd, ppe,fh,mg, np & dm	6.7	7.6	Ns
EPPA 1996	1900	-	6.7	6.1	Ns
NICD 1998	2539	Ird,hip,crd & mg	22	18	Ns

Effect of anti oxidants in preventing pre-eclampsia

- Free radicals play a part in the genesis Robert et al (Lancet 1999)
- Placental ischemia could trigger lipid peroxydation caused endothelial cell damage
- Lipid peroxidase are formed in 2 ways: from free radicals & enzymatic process involving lypooxygenase and cyclo oxygenase

Epidemiological studies

- Countries intake of fruits & vegetables, incidence of coronary heart disease



Oxidative stress

- Lipid peroxydation marker, malondialdehyde & 8 epiprostaglandin F2 increased, antioxidant low in plasma
Atherosclerosis & preeclampsia
- Vitamin E lipid soluble anti oxidant in LDL

Anti oxidants

- Vitamin E & C
 - ?
- Decrease of oxidative stress
 - ?
- Improvement of vascular endothelial function
 - ?
- Prevention of pre-eclampsia

Cappel et al, Lancet 1999;354:810

- 283 women with highrisk
- abnormal two-stage uterine artery Doppler and previous history
- Vitamin C 1000 mg/day & vit E 400 IU/day or placebo at 16-22 weeks gestation
- significant decrease (21%) PAH1/PAH 2 (CI 95%, $p = 0.015$)
- PAH-1/PAH-2 ratio reflected endothelial & placental function (no LDL oxidation)
- No detrimental effects on preterm delivery &

Discussion

- The empirical research review show both negative and positif effect of low dose aspirin
- Optimal utilization of screening tools
- No significant perinatal effect

Recommendation: Low dose aspirin to prevent Pre-eclampsia (AJOG 2000;183)

Group	Low dose aspirin <u>recommended</u>	Comment
Nulliparous, LR	No	Minimal clinical benefit
Nulliparous,HR	Yes	Group need better screening
Highrisk, Med	No	-
Highrisk, Obst	Yes	-
Highrisk, Mul G	Optional	More studies needed

Discussion

- Free radicals promote maternal vascular malfunction
- Wang.Y, reported PE ---> lipid peroxidation in maternal circulation
- Finding mitochondrial (sources of oxygen radicals) fraction increased in placental PE women
- Nitric Oxide (NO) key role maintenance of normal pregnancy

Conclusion

- There were contradictory findings in relation to effectiveness of low dose aspirin in preventing pre-eclampsia in high risk groups of pregnant women
- Future studies should utilize optimal screening tools to identify high risk groups of pregnancy

Conclusion

- Future studies with multicentre trials in larger groups to assess the benefit of anti oxidants in preventing pre-eclampsia

