ANTIOXIDANTS SUPPLEMENTATION IN PREVENTION OF PREECLAMPSIA

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Introduction

- Pre-eclampsia affects 10% of pregnant women.
- Indonesia : prevalence 4.1% to 14.3%; contributes to 30%-50% of maternal deaths.
- Possibility of preventing pre-eclampsia through antioxidant supplementation.
- Benefit for high risk women
  - what dose to use?
  - when to start the treatment ?
- relatively inexpensive and feasible for nutritional interventions during pregnancy

Scientific Background

Placental events:

Abnormal placentation

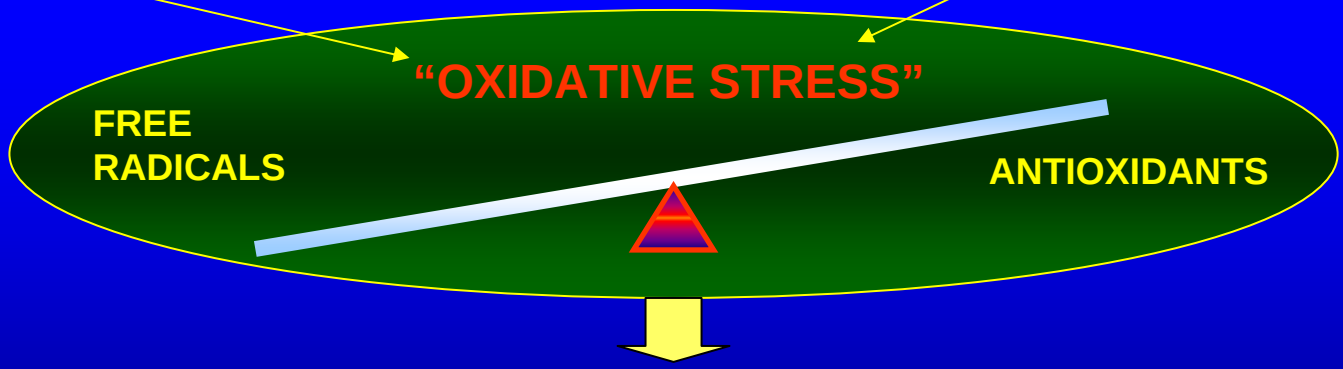
Placental hypoperfusion

STAGE I

Maternal constitution:

Environment; Nutritional status, behaviour, genetics

Adaptation to pregnancy



ENDOTHELIAL DYSFUNCTION

STAGE 2

PREECLAMPSIA

Objectives

To review the existing data on the effectiveness and safety of antioxidants supplementation, when given to women at risk of developing pre-eclampsia

METHODS

- Search Strategy:
  All relevant articles from 1993 to 2004.
- Studies were identified by performing a MEDLINE search.
- Manual searches of relevant journals, reference lists of retrieved articles.
- Direct communication with other researchers in the field made it possible to get unpublished data.

RESULTS

Table 1. Characteristics of studies

Study	Country	Methods	Sample size	Subjects	Interventions	Timing	duration
Gülmezoglü, 1997	South Africa	RCT	56	Severe PE	Vit C 1000 mg, E 800 IU allopurinol 200 mg	24-32 weeks' gestation	14 days
Chappell, 1999	UK	RCT	283	High risk	Vit C 1000mg,E 400 IU	16-20 weeks' gestation	20-24 weeks
Chappell 2002	UK	RCT	193	Low & high risk	Vit C 1000mg,E 400 IU	16-20 weeks' gestation	20-24 weeks
Pressman 2003	USA	RCT	20	elective SC patients	Vit C 500mg,E 400 IU	35 weeks' gestation	2-4 weeks
Sharma, 2003	India	RCT	251	primigravidas	Lycopene 4 mg	16-20 weeks' gestation	20-24 weeks
Han L, 1993	China	RCT	100	High risk	Selenium 100 mg	32-34 weeks gestation	6-8 weeks
Wibowo 2004	Indonesia	RCT	25	Severe PE	N-acetyl cysteine (NAC) 40 mg/kgBW vs 10 IU vitE	Not mentioned	5 days
Lumbanraja, 2004	Indonesia	RCT	28	Mild PE	NAC 600 mg	32-37 weeks' gestation	15 days
Ziaei, 2001	Iran	RCT	100	High risk	Garlic 800 mg	28-32 weeks' gestation	8 weeks
Mose, 1999	Indonesia	RCT	50	High risk	Garlic1050 mg	26-32 weeks' gestation	2 weeks

Table 2. Results (continued)

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Study	Interventions	Preeclampsia	Hypertension	Obstetric outcome	Perinatal Outcome	Biochemical markers
Gülmezoglü 1997	Vit C 1000 mg, E 800 IU allopurinol 200 mg	1 Eclampsia each group	2 Anti hypertensive drugs (RR 0.74, 95% CI 0.43-1.28)	Delivered within 14 days (RR 0.68. 95% CI 0.45-1.04)	NS in BW Stillbirth RR = 0.84 (0.36-1.93) Neonatal death RR=5.0 (0.64 -39.06) Perinatal death RR=1.29 (o.67 2.48)	NS in LPO Uric acid ↓ Vit E ↑
Chappell, 1999	Vit C 1000mg,E 400 IU	OR= 0.39 (0.17 -0.90, p<0.02)			SGA infants: 32% in placebo 23% in vitamin group.	21% reduction in PA1/PA2 ratio,

Table 2. Results (continued)

Study	Interventions	Preeclampsia	Perinatal Outcome	Biochemical markers
Chappell 2002	Vit C 1000mg,E 400 IU	high risk group: in 26% placebo, 8% vitamin , 0 in low risk	SGA infants: In high risk: 36% placebo, 25% vitamin, 15% in low risk	High risk placebo vs low risk: ↓ vit C,PAI2, PGF ↑ of 8-epi Prostaglandin F2α, leptin, PAI1/2 ratio. High risk-vitamin group vs low risk: Similar in: vitC,8-epi Prostaglandin F2α, leptin, PAI1/2 ratio.
Pressman 2003	Vit C 500mg,E 400 IU			plasma levels of vitamin E ↑ in vitamin group, but not in placebo. No changes in vitamin C levels. vitamin C and E levels correlate with vitamin C in the amniotic fluid and vitamin E in the chorioamnion, respectively.

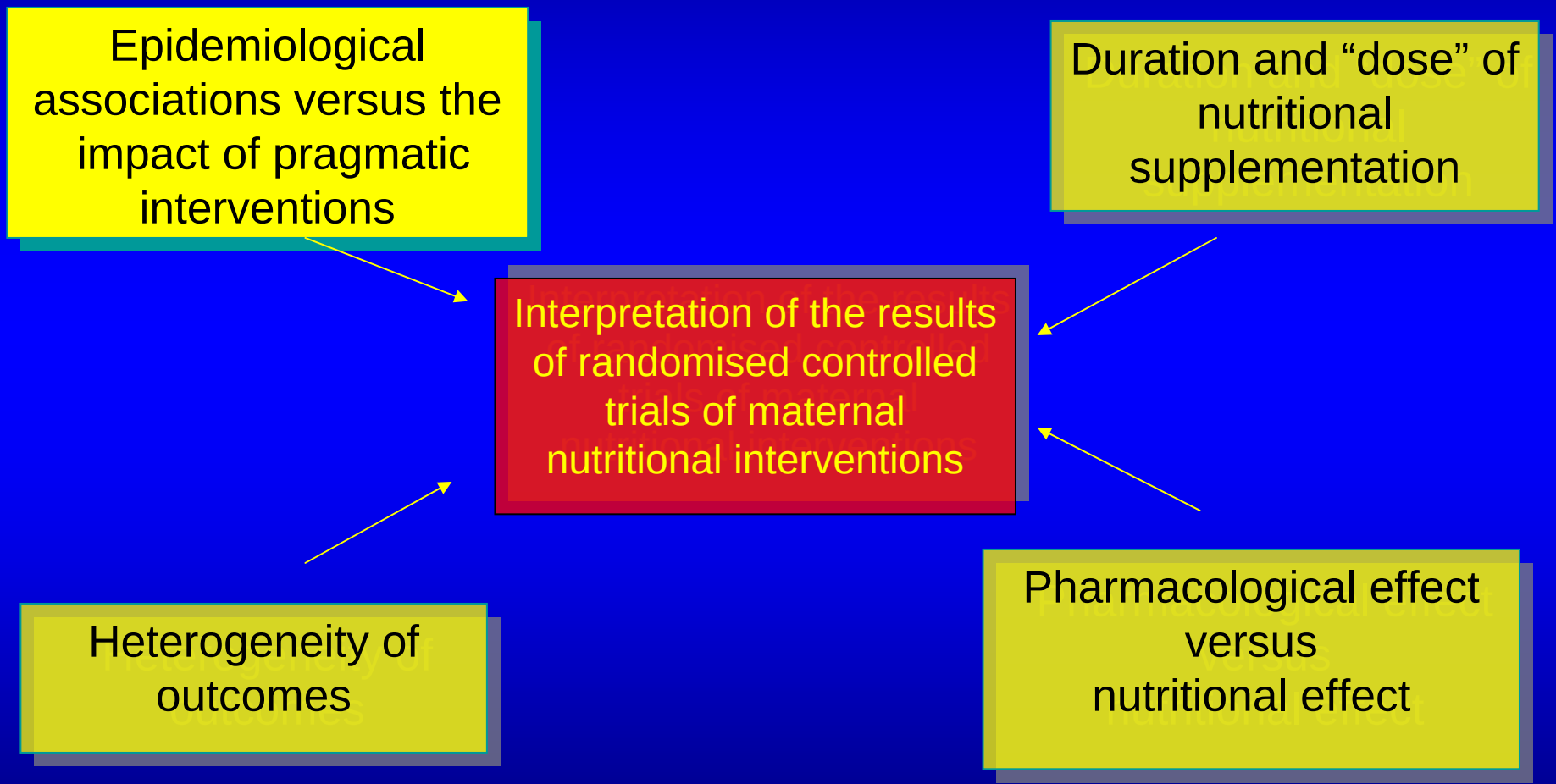
Table 2. Results (continued)

Study	Interventions	Preeclampsia	Obstetric outcome	Blood pressure	Perinatal Outcome	Biochemical markers
Sharma, 2003	Lycopene 4 mg	Preeclampsia in 17.7% placebo and 8.6% lycopene group (54.1% reduction)		Mean diastolic blood pressure in lycopene group < placebo, p = 0.0012	Mean fetal weight in lycopene group, > placebo, p = 0.049 IUGR in 23.7% placebo and 12% lycopene (49.3% reduction)	
Han L, 1993	Selenium 100 mg	prevented and ↓ incidence of PIH and gestational oedema	NS in PPH	.	NS in birthweight	↑ Selenium maternal and umbilical cord
Wibowo 2004	NAC40mg/ kgBW vs 10 IU vitE	↑Length of conservative treatment in NAC group		Systolic & diastolic ↓ after NAC treatment		NS in TNF-alpha, IL-6, fibronectin
Lumbanraja, 2004	NAC 600 mg	33.3% in treatment group, 76.9% in placebo group developed severe preeclampsia (p=0.003).			No asphyxia in treatment group 23% in placebo group.	
Ziaei, 2001	Garlic 800 mg	NS in preventing preeclampsia but preventing hypertension				In Garlic group, ↓total cholesterol after treatment
Mose, 1999	Garlic1050 mg	78.1% in preventing preeclampsia		↓Systolic 7.4% . ↓ Diastolic 15.1%		BW in garlic group >control

Summary of results

- 10 RCTs: vitamin C and E, lycopene, selenium, garlic and N-acetyl cysteine (NAC).
- There was a great variation in the sample size, baseline status of the disease, study participants, time and duration of supplementation, and outcome measures.
- Antioxidant supplementation appears to be a ***promising public health intervention*** for the prevention of pre-eclampsia.

CONCEPTUAL FRAMEWORK



Epidemiological association versus effectiveness of pragmatic intervention

- Pre-eclampsia involves multiple susceptibility genes and environmental influences, these factors can differ from one population to another.
- Oxidative stress in high risk or pre-eclamptic patients consuming more antioxidants is likely to be worsened by low nutritional status.
- It is important to consider whether the high risk or "pre-eclamptic state" populations in different trials are similar regarding their antioxidant status.

Duration and “dose” of antioxidant supplementations

- There are not much data regarding fetal tolerance and safety.
- The positive result may not be achieved if the supplementation dose was too low or administered over a short period of time
- Antioxidant supplementation has been suggested to be initiated earlier, before the disease is clinically established

Pharmacological effect versus nutritional effect

- The protocol should address the question whether the trial should be conducted in a population without deficiency (pharmacological effect), or should it be conducted in a population with some evidence of antioxidant deficiency?

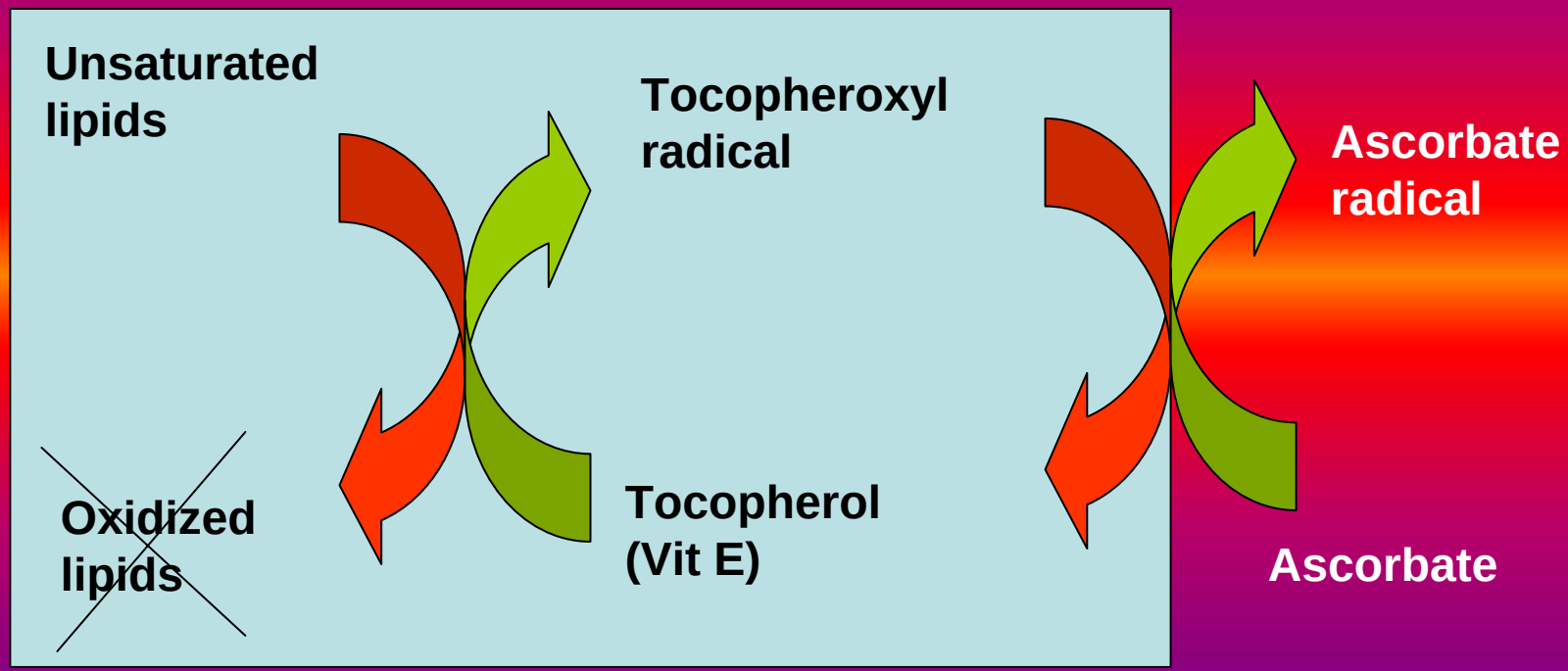
- The baseline nutritional status of antioxidants in the population should be assessed.

Heterogeneity of outcomes

- The outcomes:
  - Clinical outcomes (state of pre-eclampsia, hypertension, blood pressure, perinatal outcomes)
  - Pathological markers (oxidative stress markers, alteration of endothelial dysfunction markers, cytokines, placental function, cholesterol).
- Different antioxidants may act at different levels in the pathophysiological chain => different outcomes.

- Vitamin C
  - scavenging ROS and nitrogen species
  - protects NO* from oxidative destruction
- Vitamin E
  - Peroxyl radical scavenger
  - Protects PUFA & lipoproteins from peroxidation

Vitamin C & E


Unsaturated lipids
Tocopheroxyl radical
Ascorbate radical
Oxidized lipids
Tocopherol (Vit E)
Ascorbate

Conclusions

- Although very encouraging results, the benefit of antioxidant supplementation still needs to be confirmed
- ***Implication for practice:*** The available evidence does not justify to recommend antioxidant supplementation as a public health intervention on a large scale.

Implication for research

- Future successful treatment will require the initiation of treatment before the disease becomes clinically evident.
- Extending the duration of antioxidant supplementation.
- To conduct a follow-up of women and infants to observe long term outcomes.
- Combination of various kinds of antioxidants might be more effective than single nutrient supplementation.