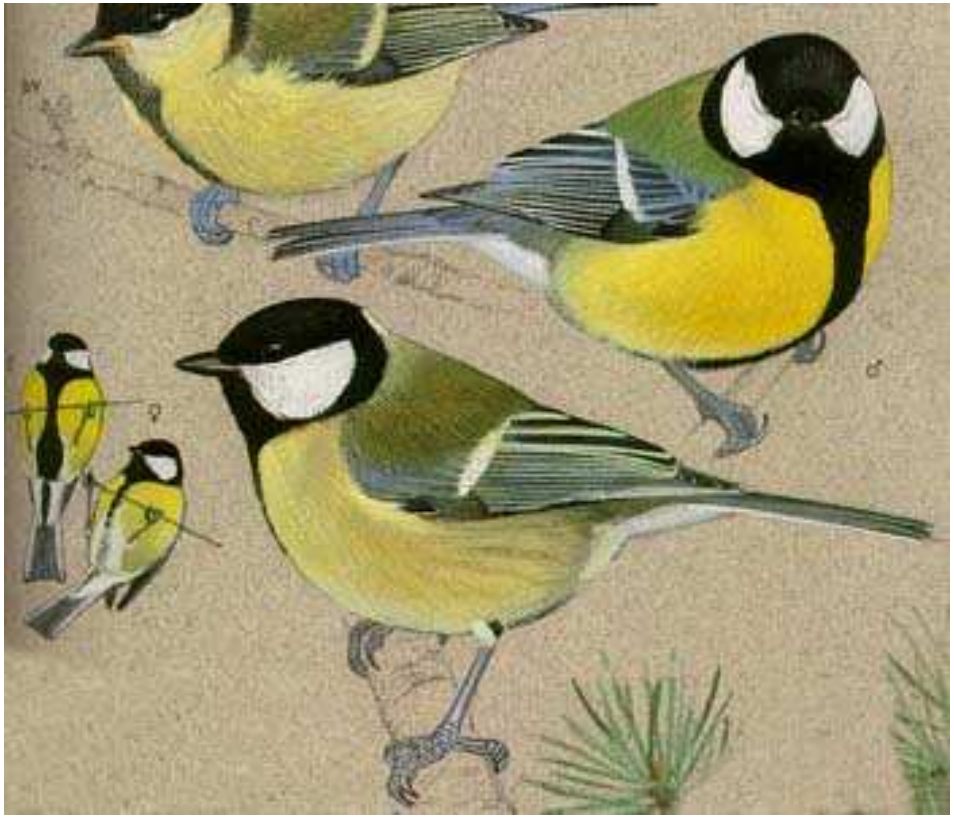
The Role of Oxidative Stress and Antioxidant Supplementation in Pregnancy Disorders

Lucilla Poston

KING'S HEALTH PARTNERS

KING'S College LONDON

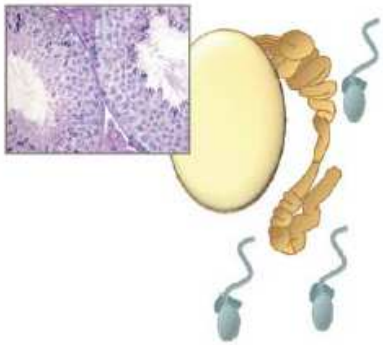
The brightest males have better chance of reproductive success!



Sperm of colourful males are better protected against oxidative stress

Helfenstein et al; Ecology Letters 2010; 12: 213-222.

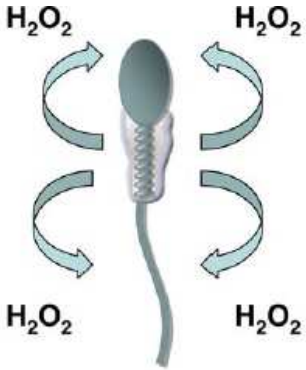
Carotenoid-based colourful trait in the Great Tit (*Parus Major*) associated with resistance to lipid peroxidation in sperm



Release of defective sperm prone to oxidative damage

- Retention of excess residual cytoplasm
- Disrupted chromatin remodelling
- High polyunsaturated fatty acid content

Oxidative Attack



- Apoptosis activates ROS generation
- Mitochondrial H_2O_2 attacks poorly protaminated DNA and PUFAs

Antioxidant Supplements Beneficial?

- In vitro> in vivo

Adapted from ; Aitken and Iuliis :
On the Possible Origins of DNA Damage in Human Spermatazoa.
Molecular Human Reproduction 2010; 16: 3-13

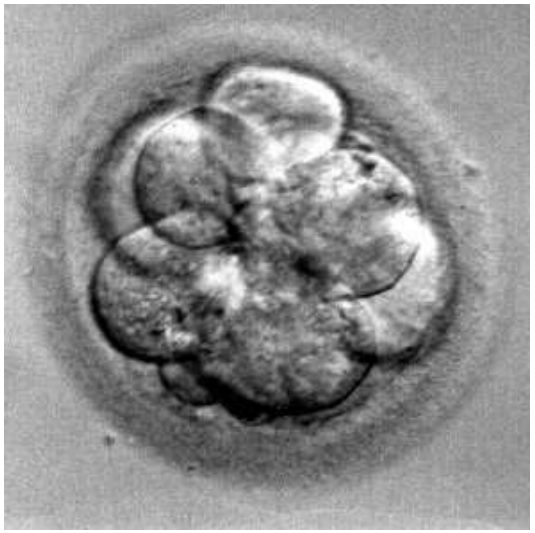
Oxidative stress influences human oocyte development

- Low level ROS generation implicated in *normal* meiosis of primary oocyte (MI) and folliculogenesis
- MII division inhibited by excessive ROS
- Adequate antioxidant defences (eg GSH) required for successful ovulation and fertilisation

Lifestyle and supplements

Oocyte oxidative stress associated with cigarette smoking and alcohol intake *(Ruder Eh et al, Human Repro Update 2008*)

Pre-conceptional multivitamin supplements may enhance fertility *(Chavarro JE et al, Obstet Gynecol 2007)*



IVF

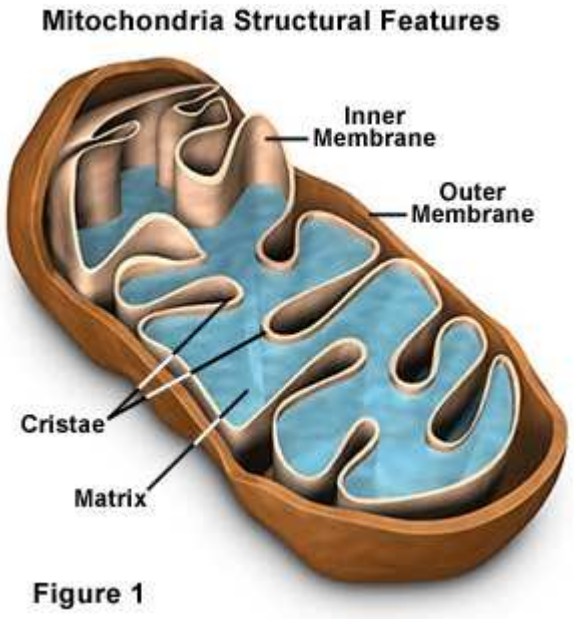
- ROS implicated in embryo arrest
  Reduced oxygen tension improves IVF embryo viability
  (Betts DH et al, Mol Human Reproduction 2008)

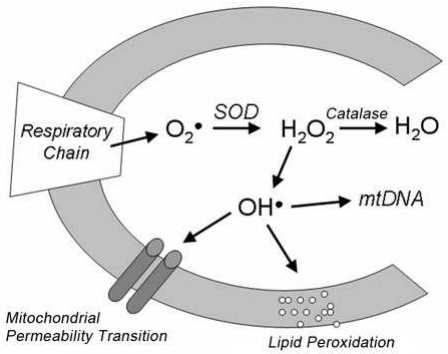
Maternal Obesity affects Fertility and Reproductive Success

- Reduced conception/increased miscarriage rate
- Impaired immediate outcomes of assisted reproductive technologies

Mitochondria in oocyte and embryo

- Maternally inherited.
- Involved in oocyte maturation, fertilization, embryo development.
- Excessive energy substrates perturb mitochondrial metabolism in oocytes and embryos, compromising development.

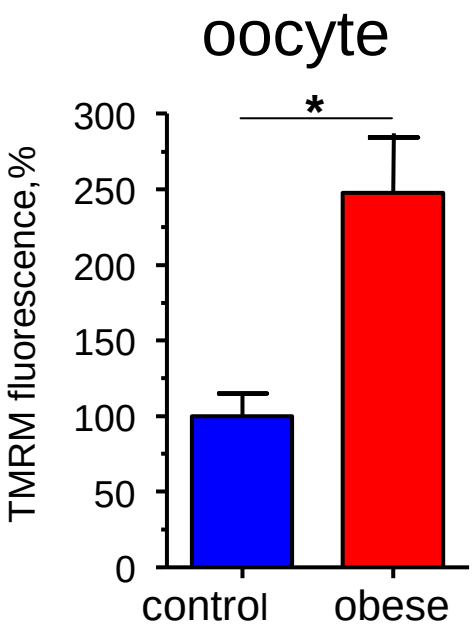


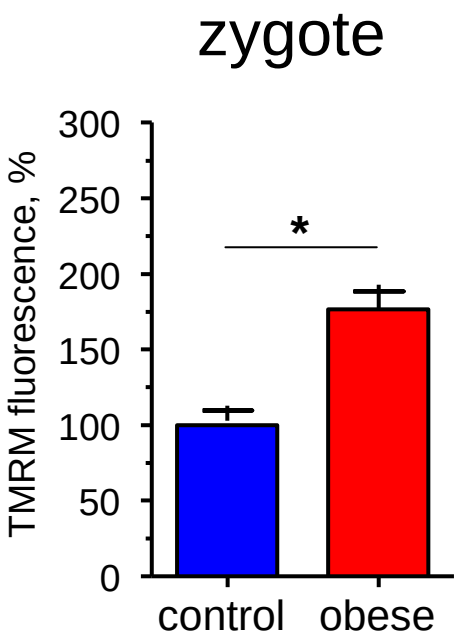


Maternal Diet Induced Obesity in Mice

Increased mitochondrial activity (membrane potential↑) and altered distribution in oocytes and zygotes

A





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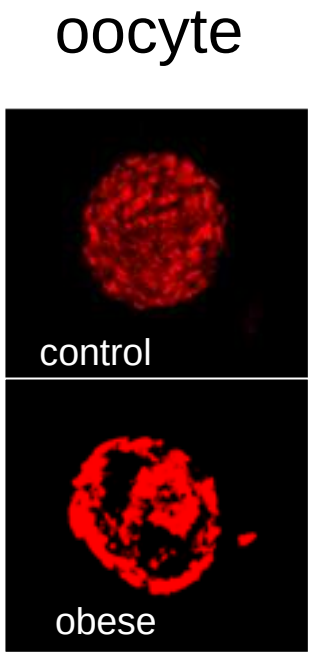
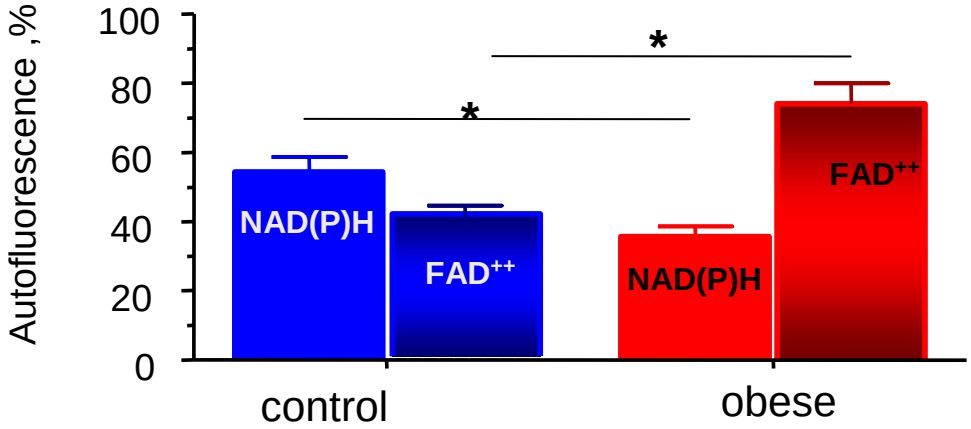


Igosheva N et al, PLosOne 2010

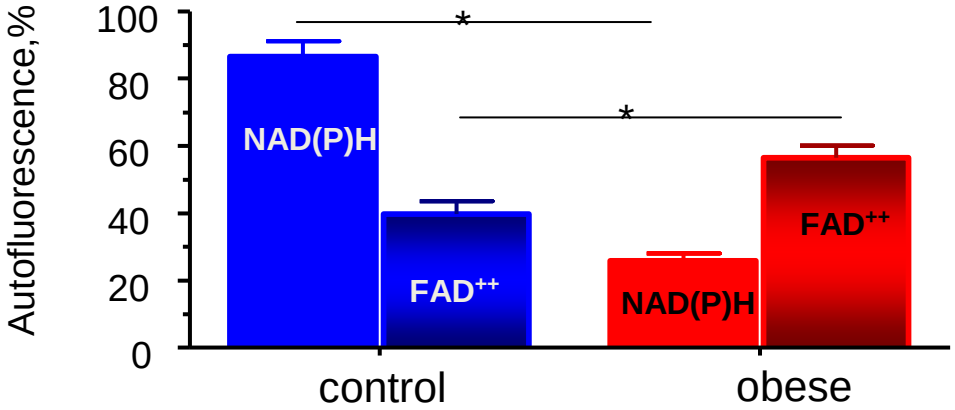
Maternal Diet-Induced Obesity in Mice

Intracellular redox potential shifts towards oxidation in oocytes and zygotes

(NAD(P)H & FAD^{++} autofluorescence)



oocytes

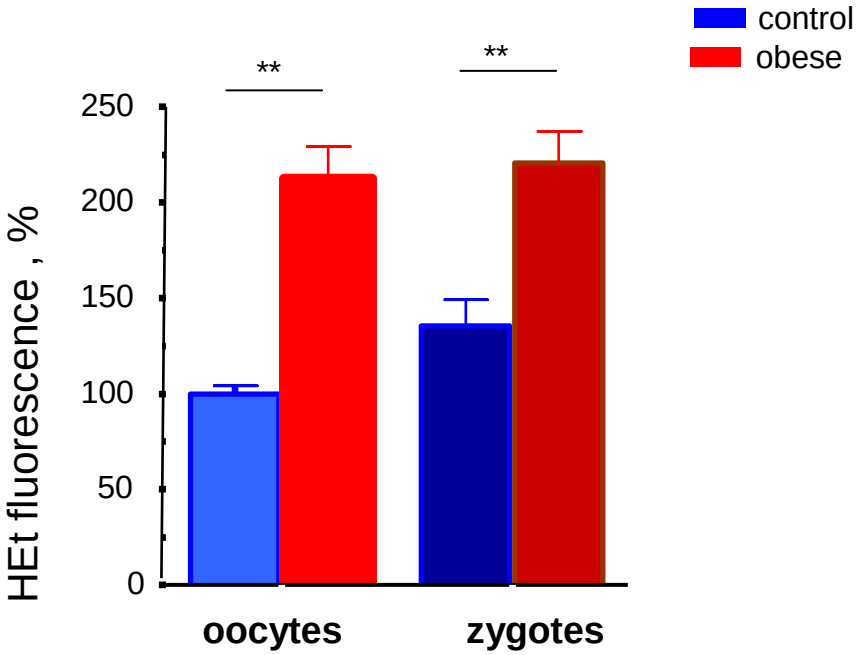


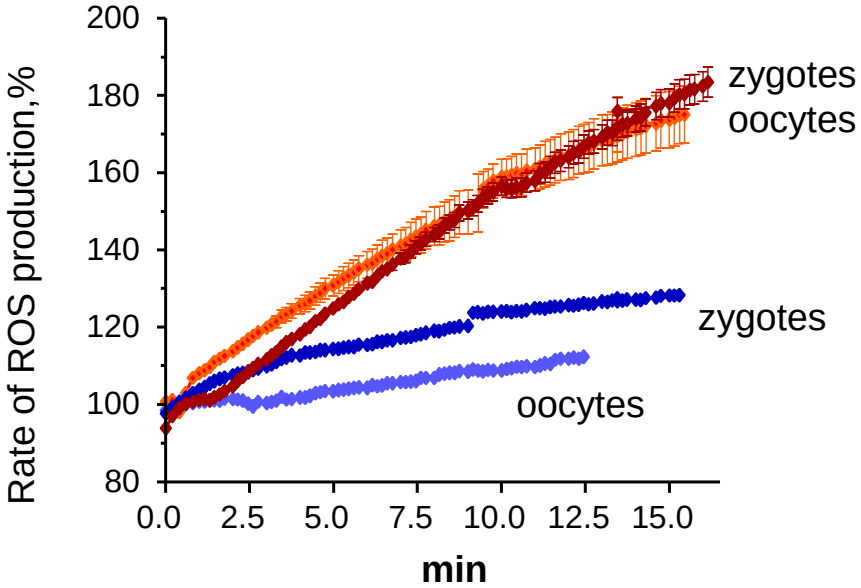
zygotes

Igosheva N et al, PLosOne 2010

Maternal diet-induced obesity
increased oxidative stress in oocytes and zygotes

(Het fluorescence)



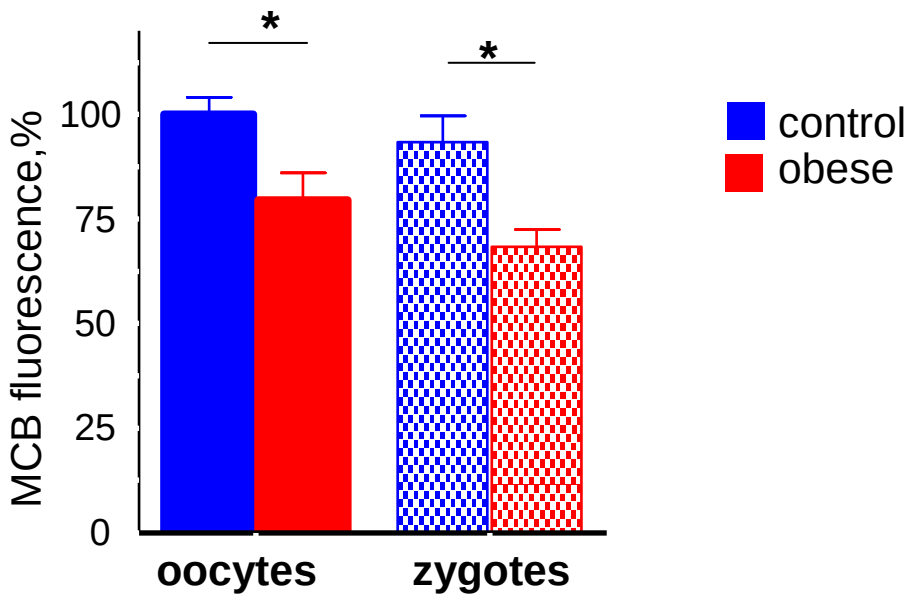


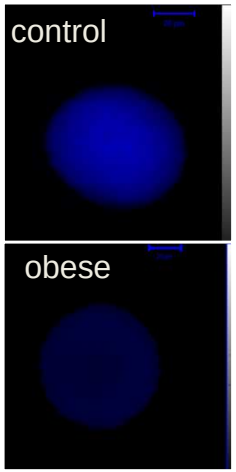
Igosheva N et al, PLosOne 2010

Maternal Diet-Induced Obesity

Attenuated antioxidant defence in oocytes and zygotes

(Glutathione by MCB fluorescence)

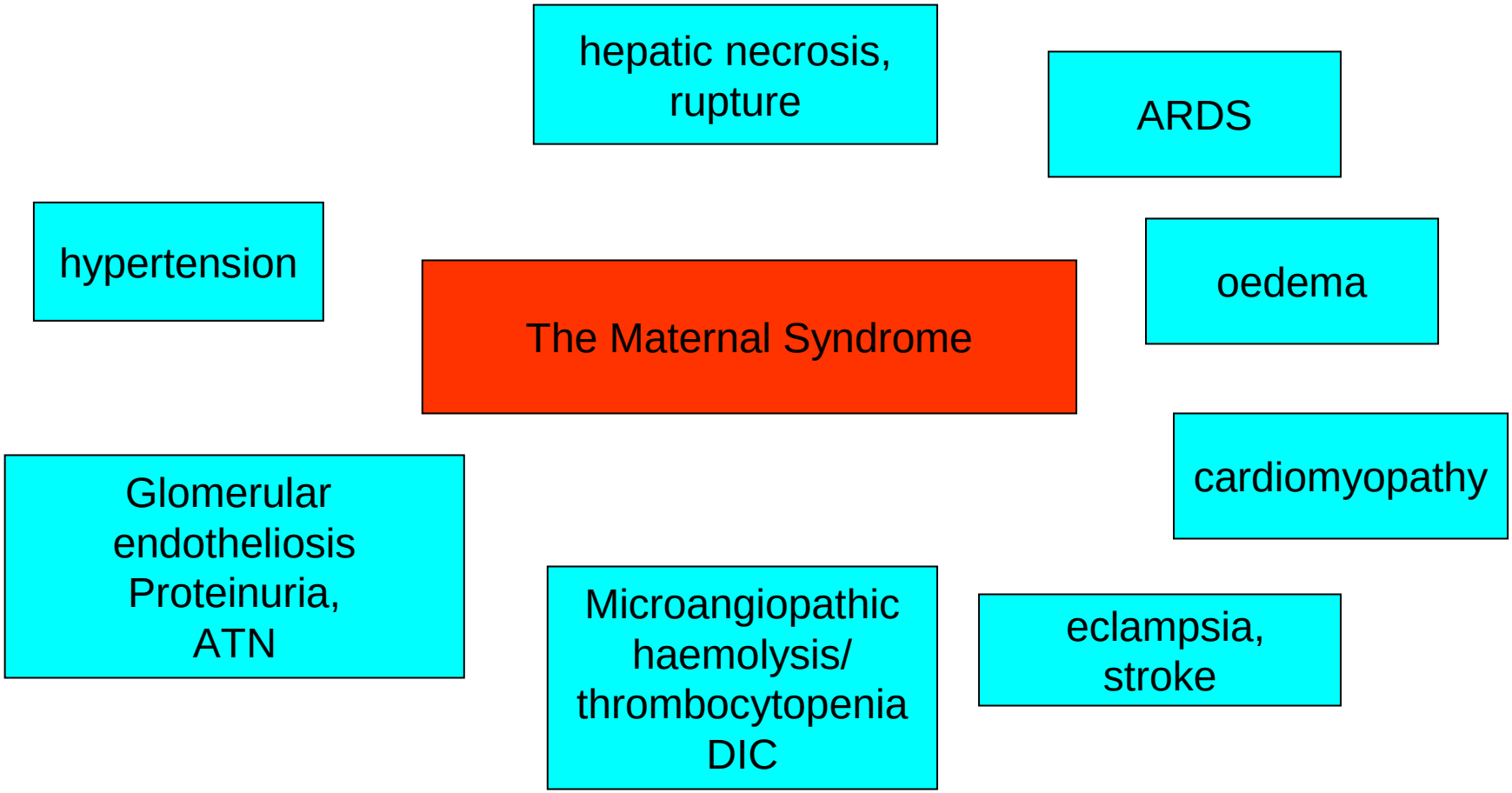


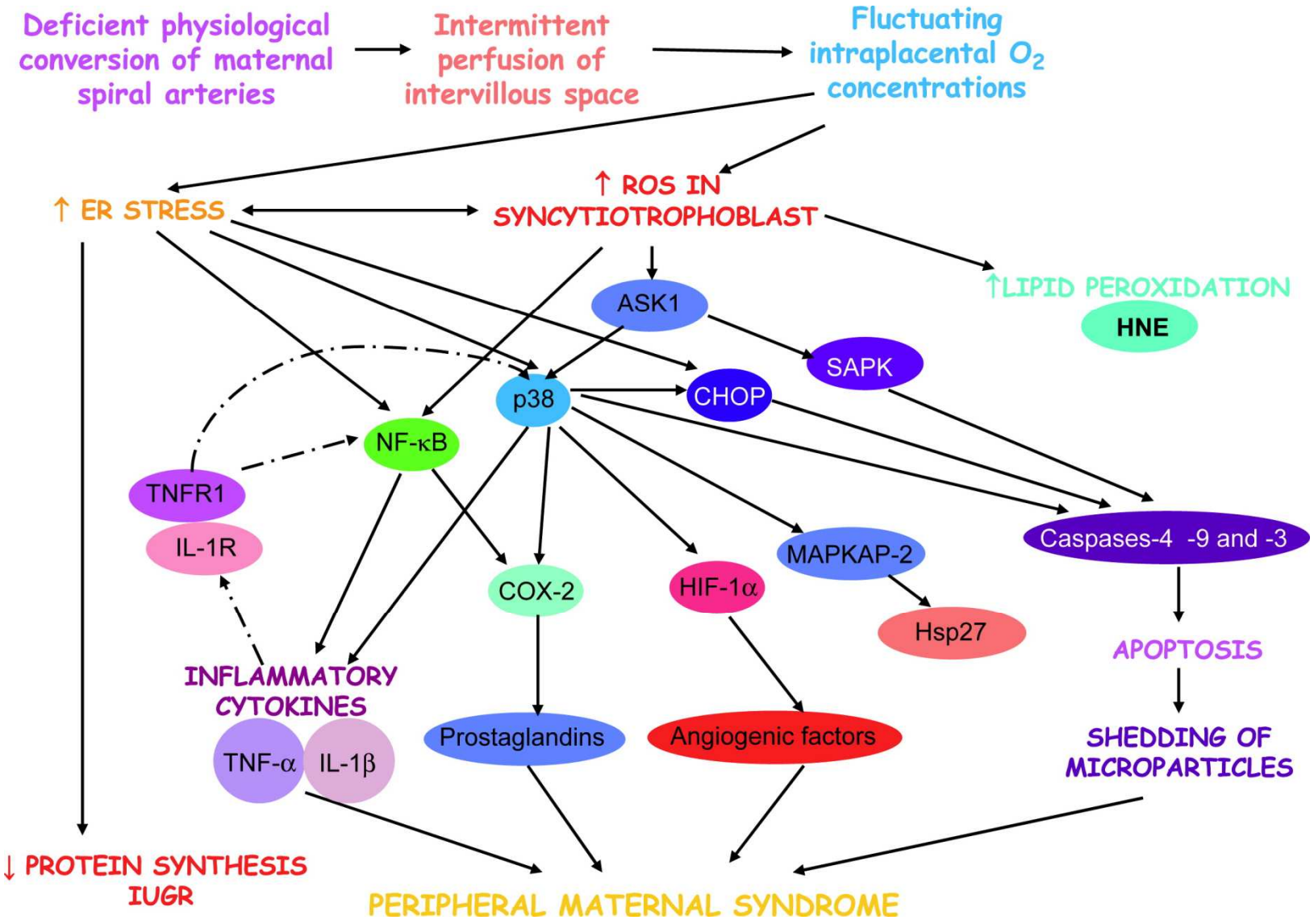


oocyte

Igosheva N et al, PLosOne 2010

Pre-eclampsia

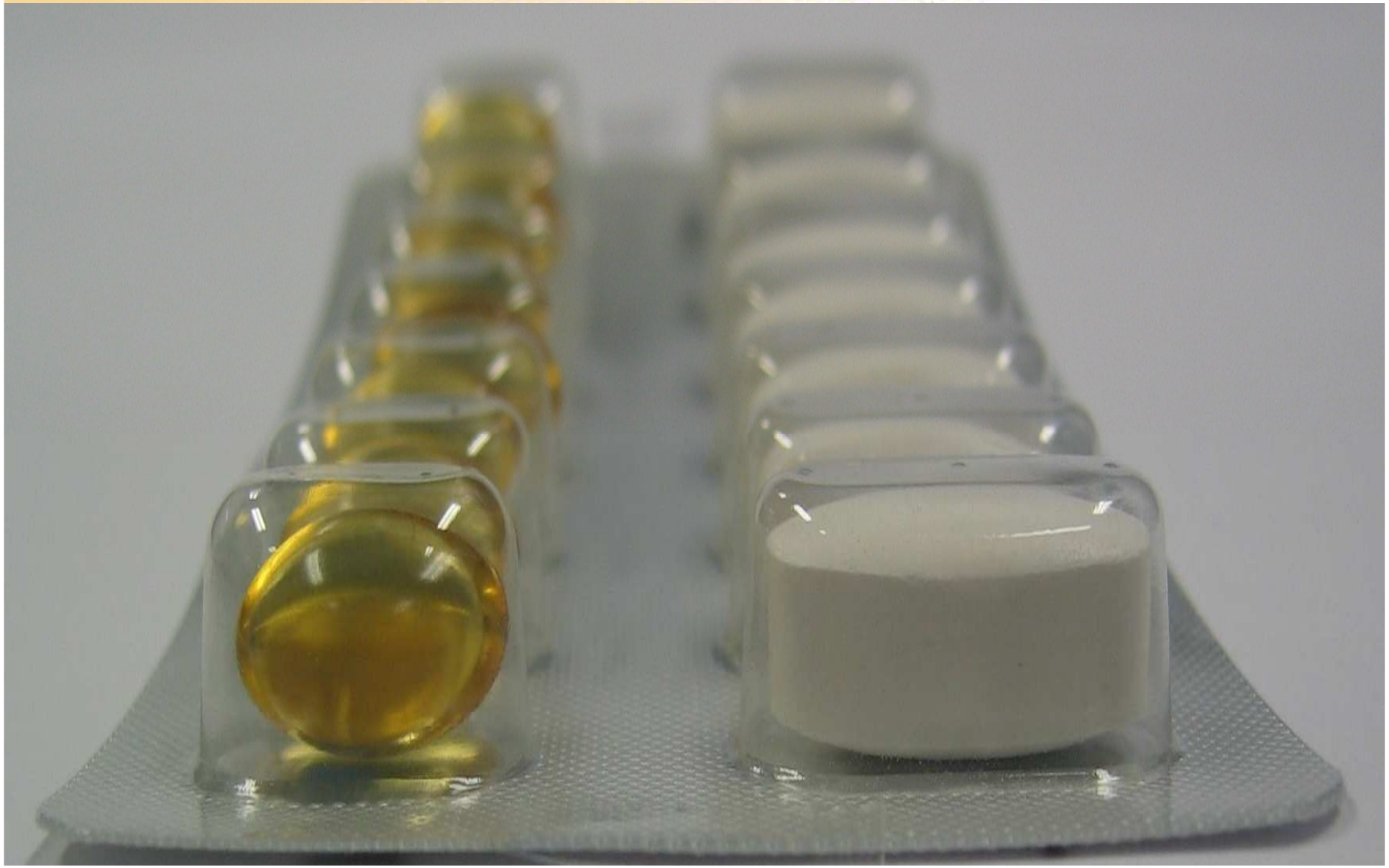




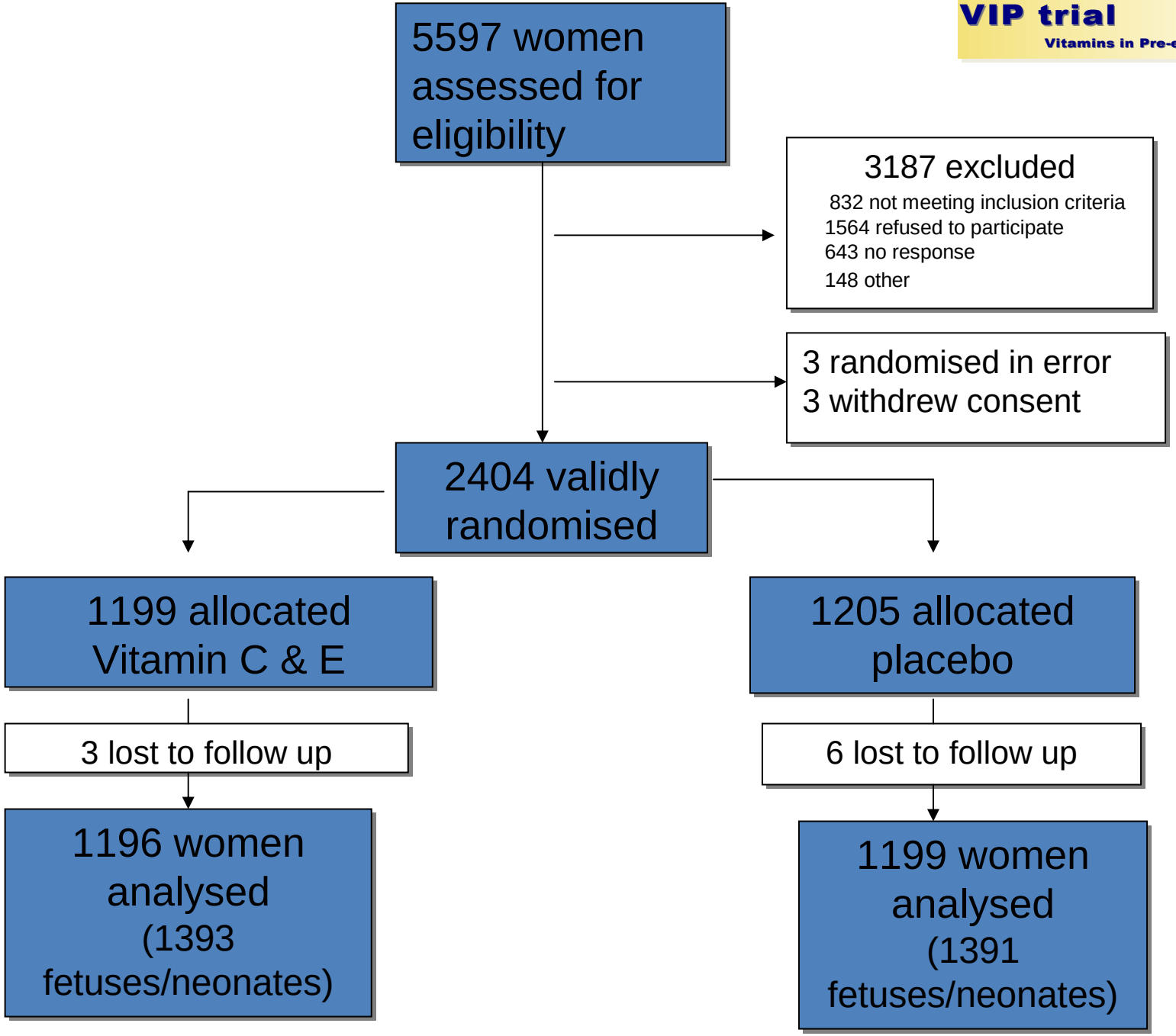
From Cindrova-Davies T. Gabor Than Award Lecture: Pre-eclampsia- From placental oxidative stress to maternal endothelial dysfunction. Placenta 2009.

VIP trial

Vitamins in Pre-eclampsia

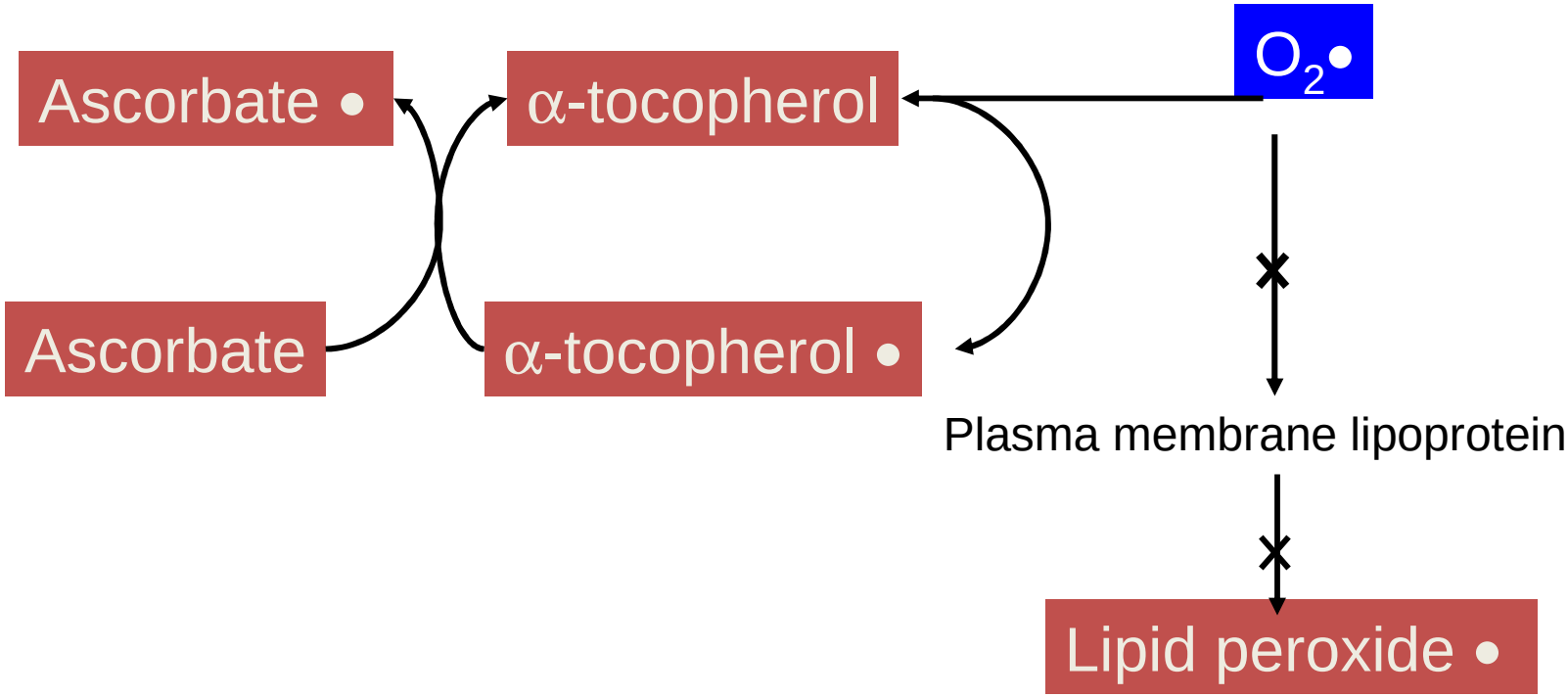


VIP trial
Vitamins in Pre-eclampsia



Synergy between ascorbic acid and α tocopherol

Ascorbate regenerates α-tocopherol



VIP trial
Vitamins in Pre-eclampsia

Vitamin C and E Supplements Do Not Prevent Pre-eclampsia in High Risk Women

	Treatment	Placebo	Risk Ratio (95% CI)	p
Pre-eclampsia	181 (15%)	187 (16%)	0.97 (0.80 to 1.17)	0.754
Low birthweight (<2.5Kg)	387 (28%)	335 (24%)	1.15 (1.02 to 1.30)	0.023
SGA (<5th centile)	294 (21%)	259 (19%)	1.12 (0.96 to 1.31)	0.161

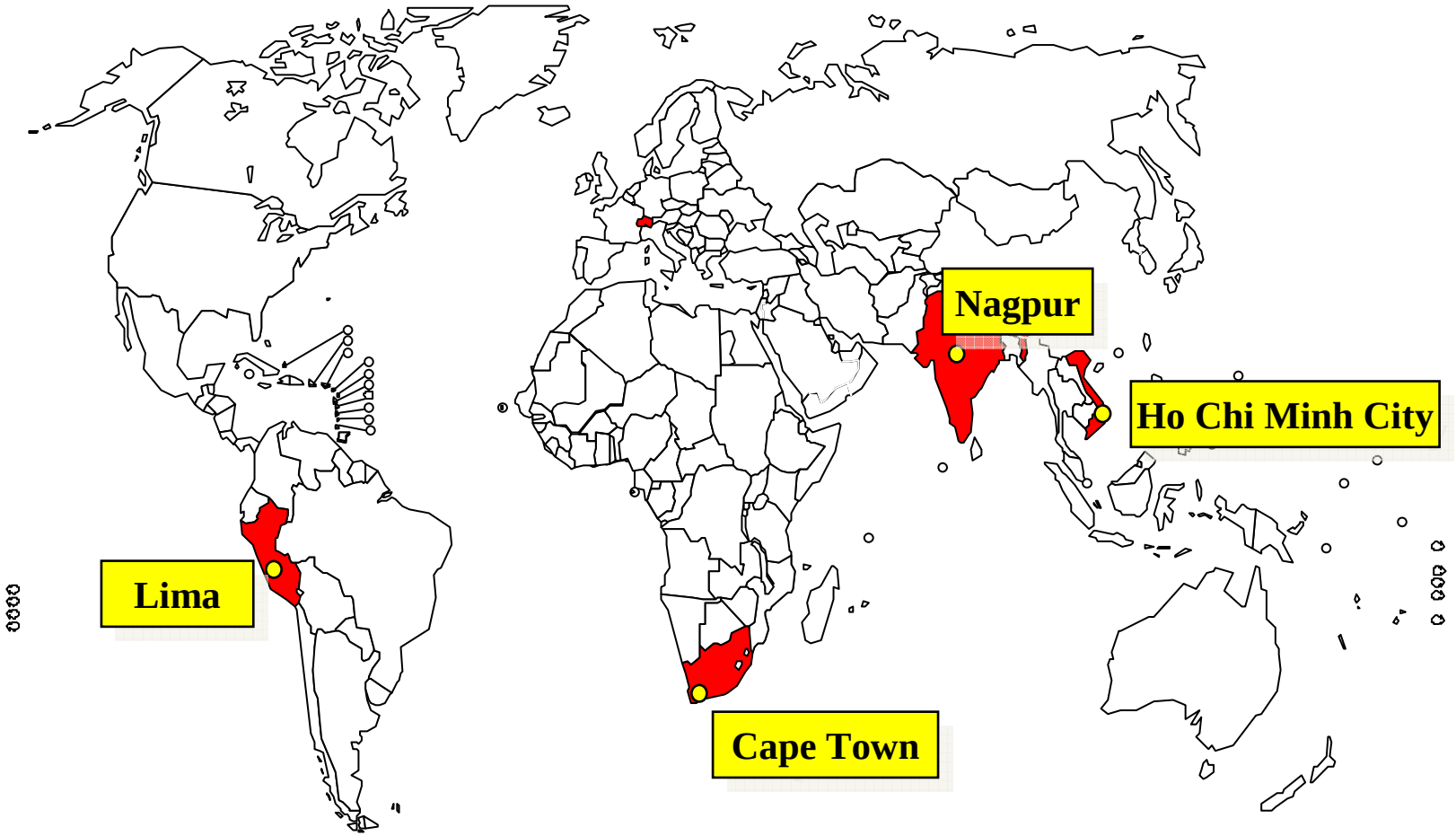
Poston et al, Lancet 2006

WHO multicentre randomized trial of Vitamin C and E supplementation among pregnant women at high risk for preeclampsia and low nutritional status

Villar J, Purwar M, Merialdi M, Zavaleta N,
Ngoc NTN, Anthony J, Poston L, Shennan A
on behalf of the WHO Vitamin C and Vitamin E trial group

Villar et al BJOG 2009

Study populations



Villar et al BJOG 2009

NO evidence for protection against pre-eclampsia by Vitamins C and E

- Poston et al, Lancet 2006 (high risk women)
- Rumbold et al , NEJM 2006 (nulliparous women)
- Villar et al, BJOG 2009 (high risk, developing countries)
- Roberts et al, NEJM 2010 (low risk women).

DOI: 10.1111/j.1471-0528.2009.02150.x
www.blackwellpublishing.com/bjog

Epidemiology

Intake of vitamin C and E in pregnancy and risk of pre-eclampsia: prospective study among 57 346 women

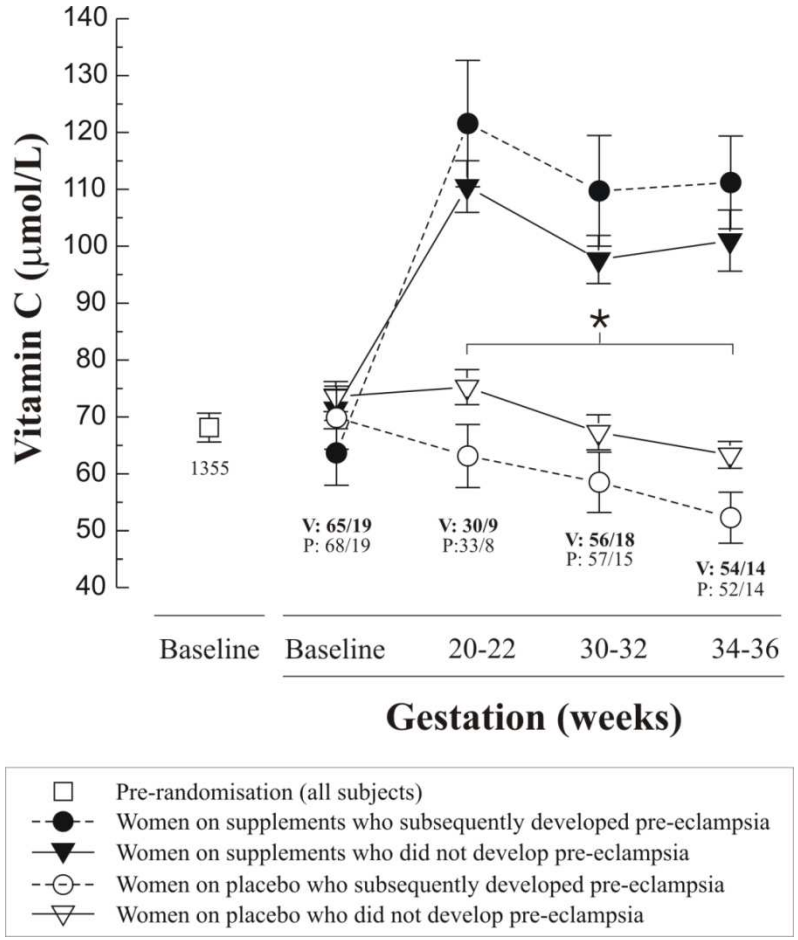
ÅK Klemmensen,[a,b] A Tabor,[c] ML Østerdal,[a] VK Knudsen,[a] TI Halldorsson,[a] TB Mikkelsen,[a] SF Olsen[a,d]

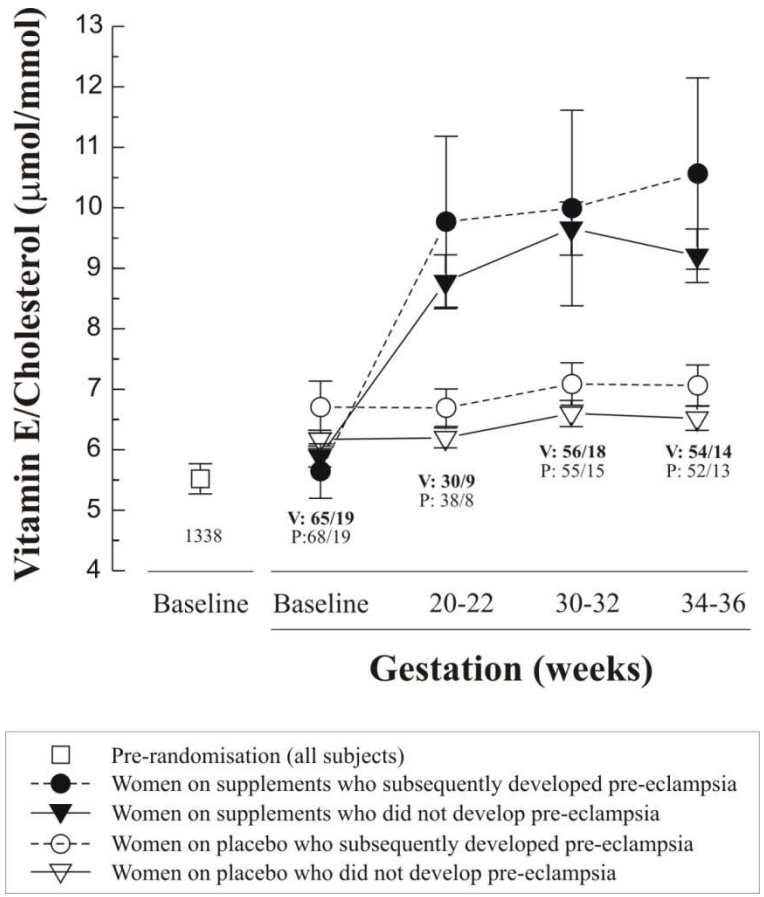
No association with vitamin C intake and pre-eclampsia.

Trend ($p<0.01$) towards protection against severe pre-eclampsia, eclampsia and HELLP

BJOG 2009; 116: 964-974

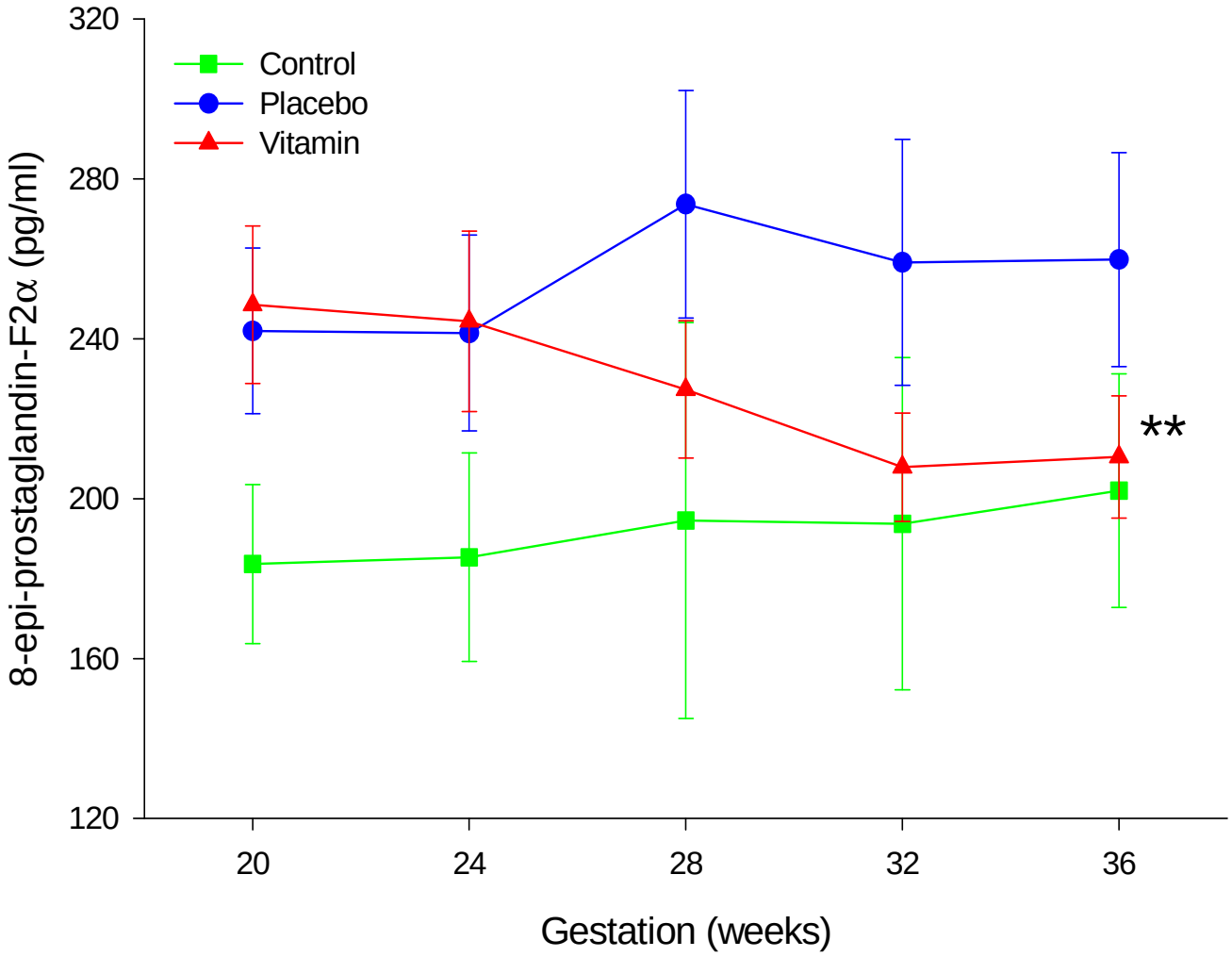
Antioxidant Status is Improved by Vits C and E





Poston et al, Lancet 2006

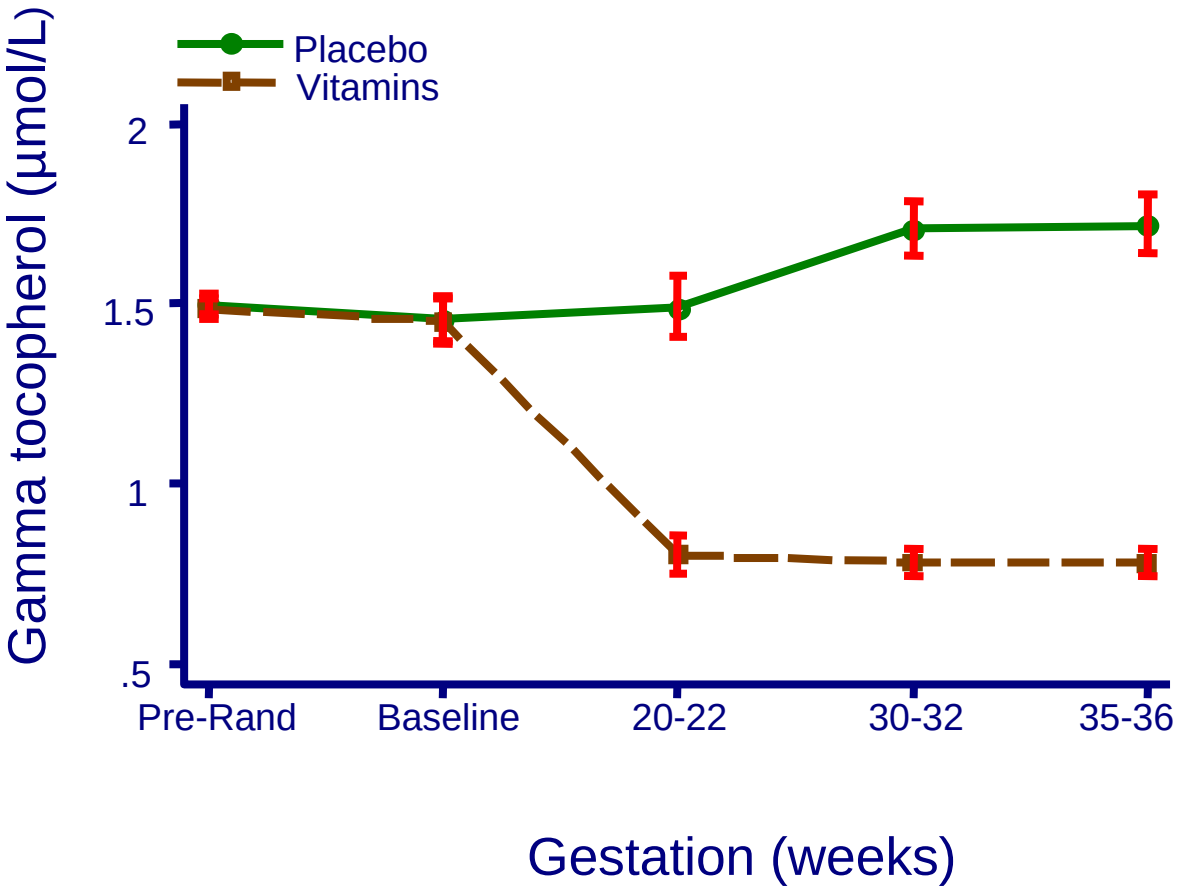
Effect of antioxidants on plasma isoprostane concentrations: 8-epi PROSTAGLANDIN $F_{2\alpha}$



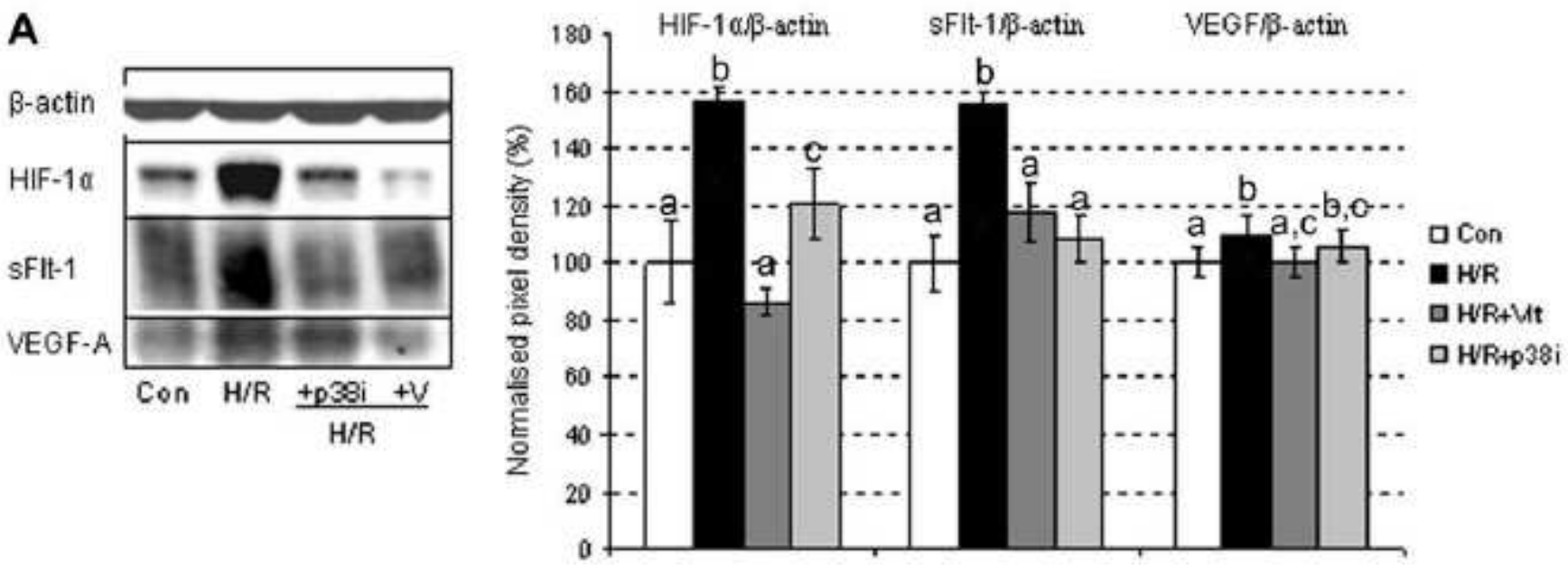
Chappell et al, AMJOG 2002

VIP trial
Vitamins in Pre-eclampsia

Vitamins C and E reduced γ Tocopherol in Women at Risk of PE



In vitro hypoxia-reperfusion in Trophoblast increases HIF-1α and sFlt-1; prevented by vitamin C and E



Cindrova-Davies T Placenta 2009.

Are we giving antioxidants too late?

American Journal of Epidemiology Advance Access published June 13, 2006

American Journal of Epidemiology

DOI: 10.1093/aje/kwj218

Original Contribution

Periconceptional Multivitamin Use Reduces the Risk of Preeclampsia

Lisa M. Bodnar[1,2,3,4], Gong Tang[5], Roberta B. Ness[1,2,3], Gail Harger[1,2], and James M. Roberts[1,2,3]

After adjustment in multiple regression model, regular use of multivitamins associated with 45% reduction in pre-eclampsia risk compared with non-use (odds ratio 0.32-0.95)

A Dietary Pattern Characterized by High Intake of Vegetables, Fruits, and Vegetable Oils Associated with Reduced Risk of Preeclampsia in Nulliparous Pregnant Norwegian Women

23,423 nulliparous pregnant women in Norwegian Mother and Baby Cohort Study.

	Preeclampsia	
	Yes, n = 1267	No, n = 22,156
Vegetable	−0.122 ± 0.027	0.007 ± 0.007
Processed food	0.160 ± 0.027	−0.010 ± 0.007
Potato and fish	0.049 ± 0.029	−0.003 ± 0.007
Cakes and sweets	−0.013 ± 0.028	0.001 ± 0.007

[1] Values are means ± SEM. The scores are not adjusted for confounders (Mann-Whitney U-test).

Brantsaeter Al et al, Journal of Nutrition 2009

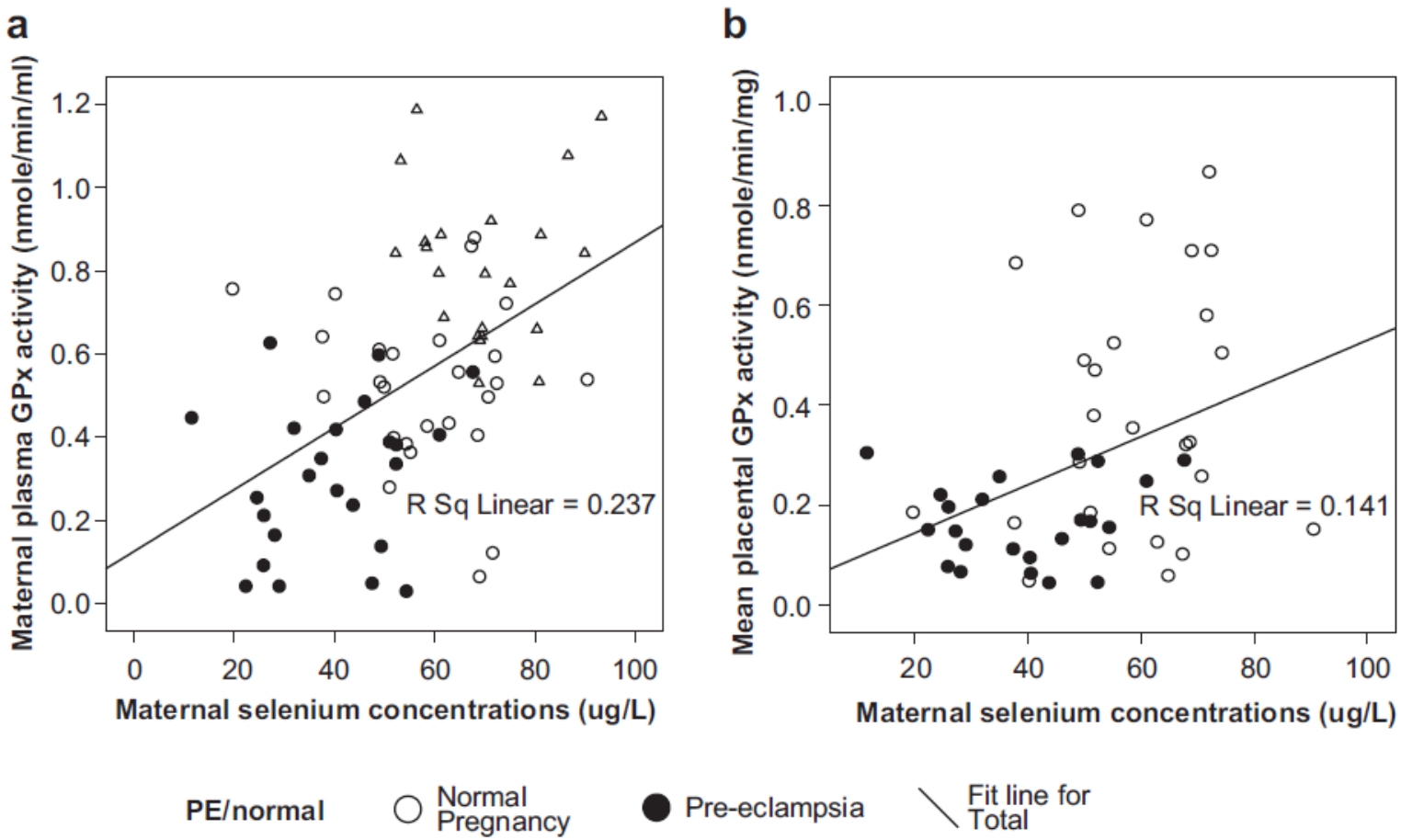
Are we giving wrong antioxidants ?

TOENAILS and Oxidative Stress

Median *toenail* selenium concentrations in preeclamptic subjects significantly lower than in matched controls (P=.001). Being in the *bottom tertile of toenail selenium* was associated with a 4.4-fold (95% CI 1.6-14.9) greater incidence of the condition.

Rayman, Bode and Redman, AmJOG 2003.

Selenium Deficiency in Pre-eclampsia



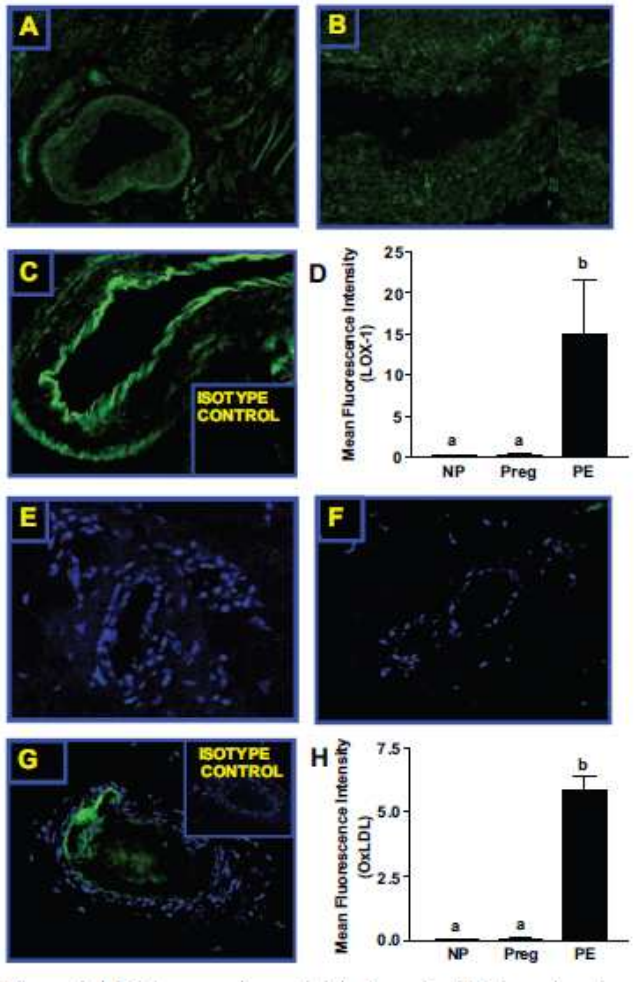
Mistry et al, Hypertension 2008

Inhibition of LOX-1 expression- by scavenging peroxynitrite- a novel approach?

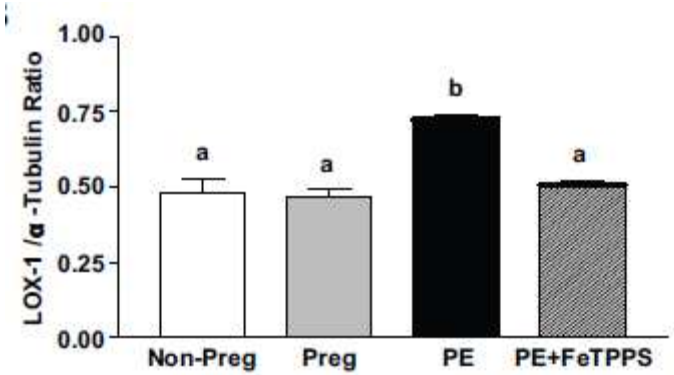
Non-pregnant

pregnant

Pre-eclampsia



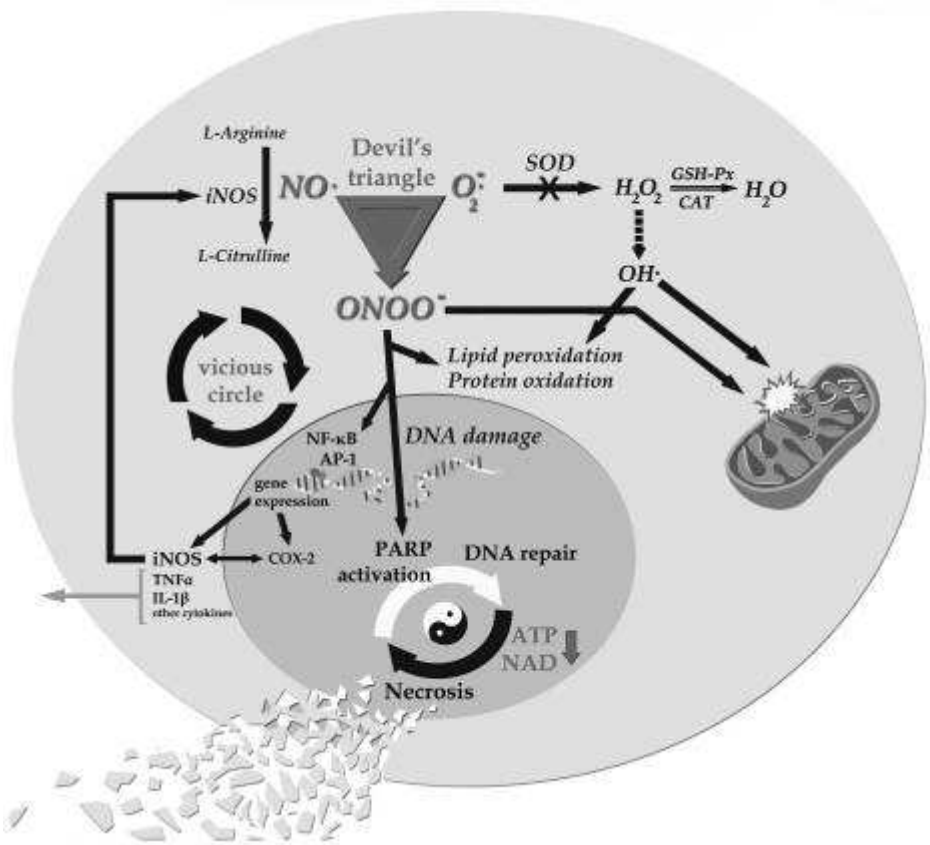
LOX-1 expression in small omental arteries



Inhibitor of peroxynitrite prevents PE serum induced increase in LOX-1

Sankaralingam S et al, Hypertension 2009

Peroxynitrite (ONOO-) as a target in pre-eclampsia?



Antioxidant vitamins do not scavenge ONOO-

Melatonin scavenges ONOO-, Reduces NFκB and AP-1 translocation to nucleus, And inhibits iNOS and COX-2

Novel antioxidant strategies for prevention of pre-eclampsia?

- Start earlier in pregnancy?
- Melatonin
- Selenium
- NADPH oxidase inhibitors

Summary

- Oxidative stress strongly implicated in fertility and pregnancy outcome
- Antioxidant supplementation requires more vigorous testing in sub-optimal fertility
- Vitamin C and E supplemention in pregnancy does not prevent pre-eclampsia
- Other strategies should be explored
- *or* is oxidative stress and ‘innocent bystander’?

Thanks to

Researchers

- Natalia Igosheva
- Josie McConnell
- Tom Fleming
- Michael Duchen
- Andrey Abramov
- Annette Briley
- Andrew Shennan
- Lucy Chappell
- The VIP team
- Jose Villar
- Mario Merialdi and the WHO team

Funders

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- BBSRC
- Tommy's Baby Charity
- World Health Organisation