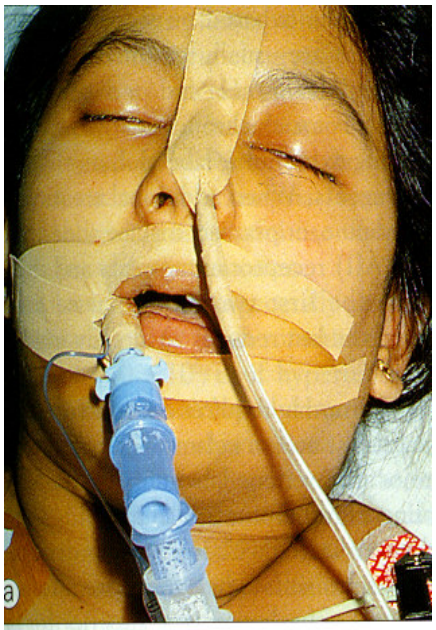
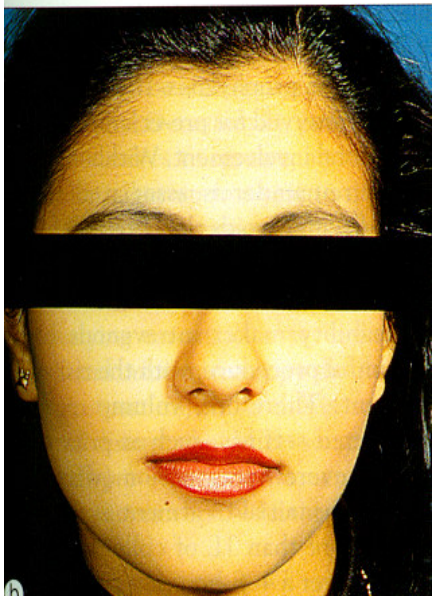




Pre-eclampsia

Sudden onset severe pre-eclampsia
followed by eclampsia
and fetal death in utero,
requiring acute ventilation
and Cesarean section

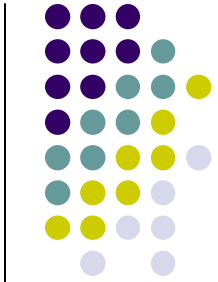
Full resolution of disease
2 weeks post-partum

Mrs PE

- A 29 yr old previously well primigravida - 27 weeks
  asymptomatic BP 150 / 90 mmHg
  - BP 100/60 at 10 weeks gestation
  - Mother had hypertension in pregnancy, now essential hypertension
  - No symptoms, fetal movements plentiful
  - Urinalysis '2+' proteinuria; PCr 50mg/mmol
  - Normal examination, reflexes
  - Fundal height 28cm

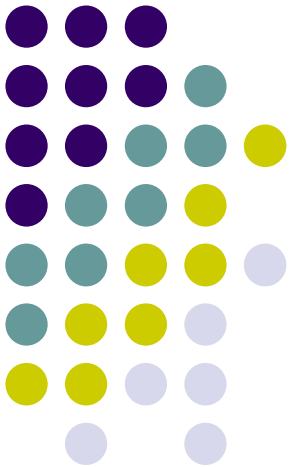
  - ***She has pre-eclampsia***

What we'll consider

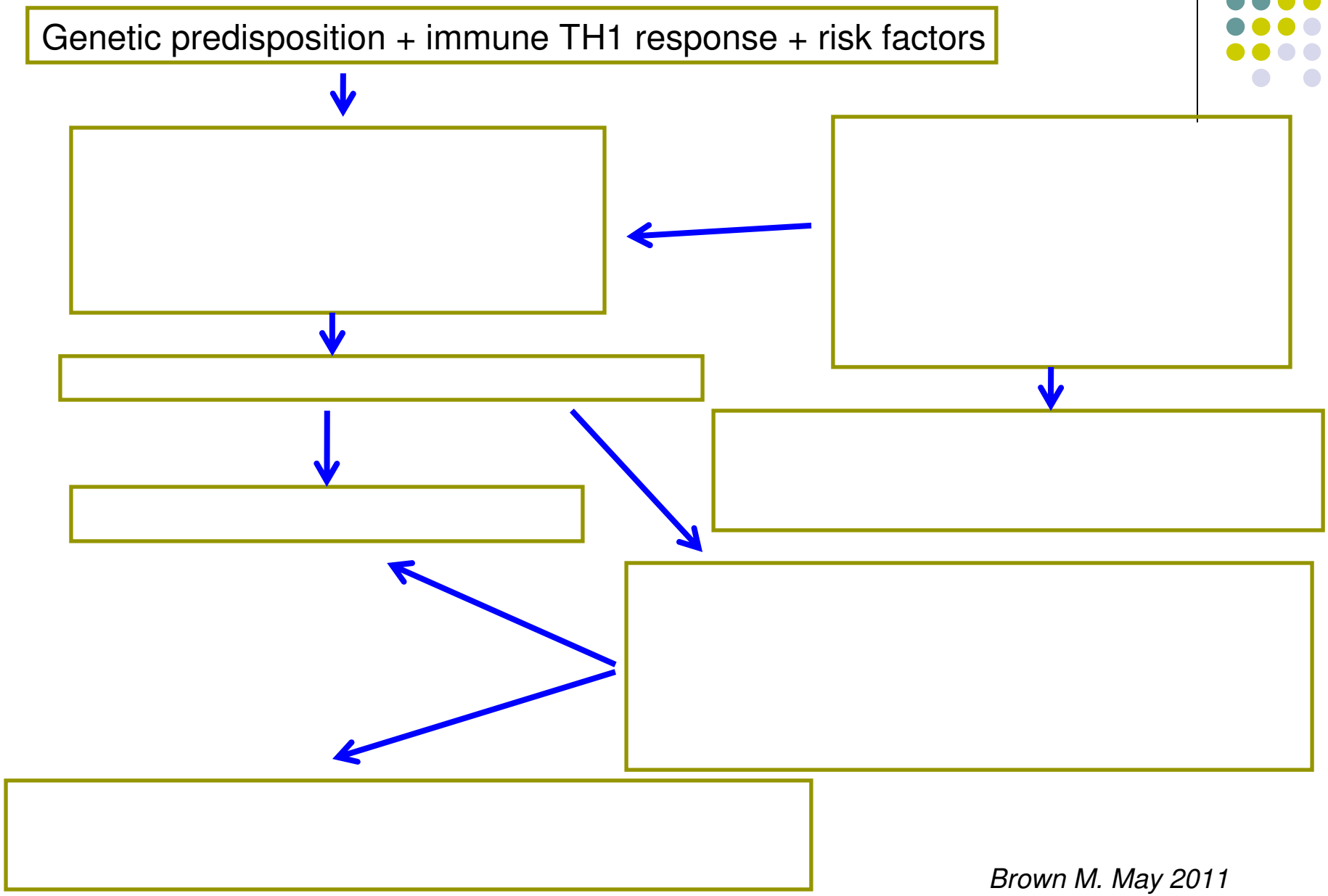


1. Why has this happened?
2. How should she be managed ?
3. What are the long term implications?

Pathogenesis

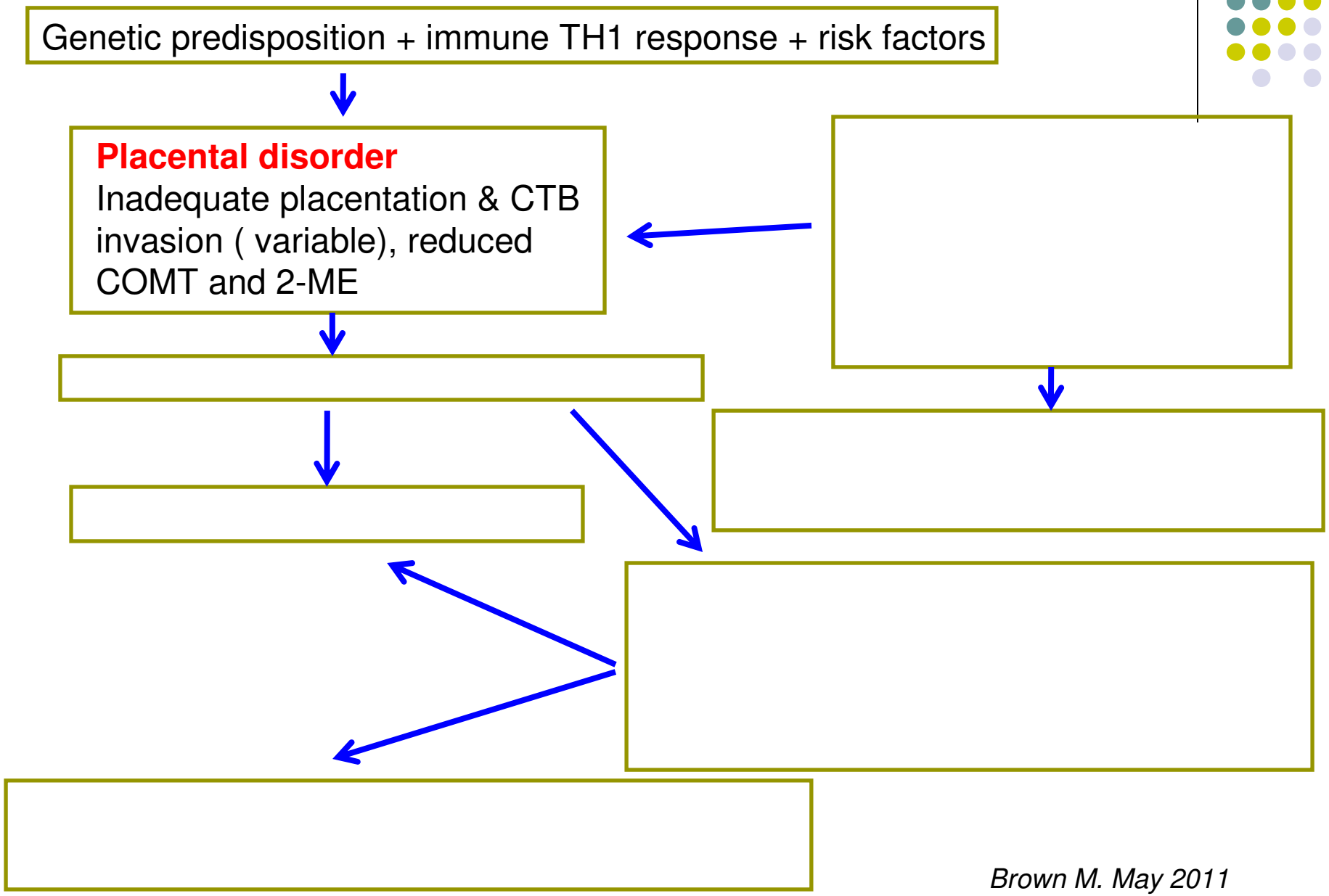


Pathogenesis of Pre-eclampsia



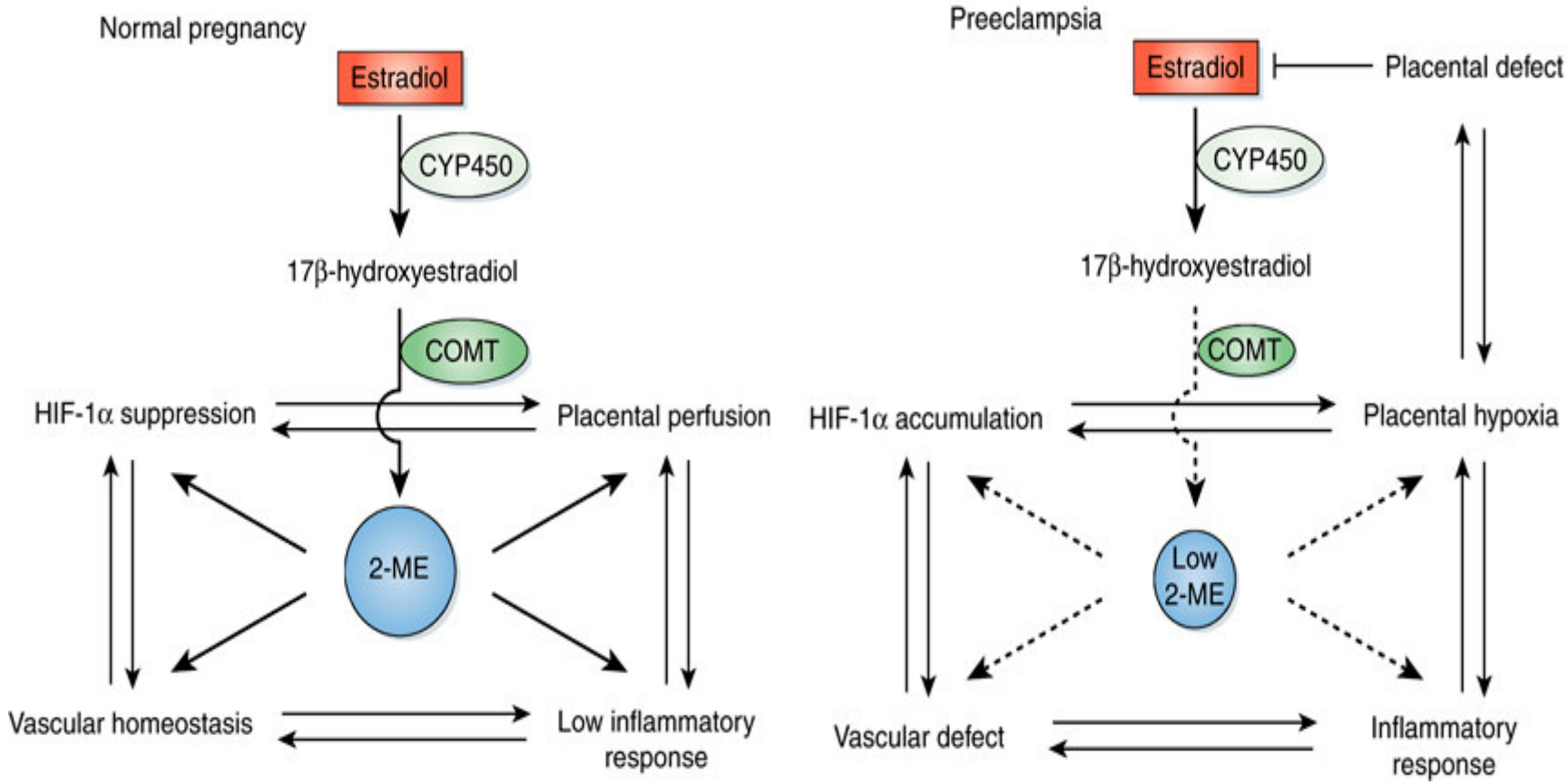
Brown M. May 2011

Pathogenesis of Pre-eclampsia



Brown M. May 2011

Proposed pivotal role for Estradiol, COMT and Estradiol metabolite in pre-eclampsia



The putative role of COMT/2-methoxyestradiol (2-ME) in pregnancy.

Keizo Kanasaki and Raghu Kalluri. Kidney International (2009) **76,** 831–837

Q. Which one of the following is NOT a risk factors for developing pre-eclampsia ?

A. Primigravida

B. Twin pregnancy

C. Essential hypertension

D. Smoking

E. Obesity

A. Which one of the following is NOT a risk factors for developing pre-eclampsia ?

A. Primigravida

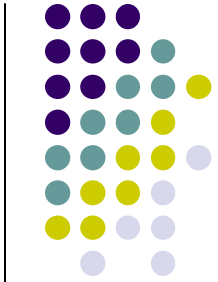
B. Twin pregnancy

C. Essential hypertension

D. Smoking

E. Obesity

Pathogenesis of Pre-eclampsia



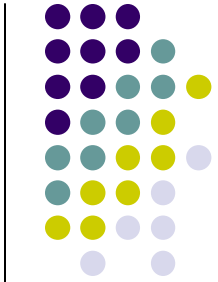
Genetic predisposition + immune TH1 response + risk factors

Placental disorder
Inadequate placentation & CTB invasion (variable), reduced COMT and 2-ME

Risk factors:
Obesity, primigravida, diabetes
CKD, prior pre-eclampsia,
Multiple pregnancy, chronic hypertension, SLE
? APL ?Thrombophilias

Brown M. May 2011

Obesity and Early vs. late-onset pre-eclampsia



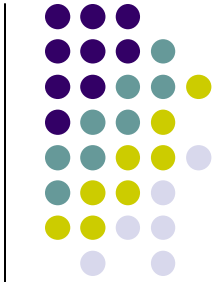
- **Adipose tissue produces**
  - TNFa
  - Leptin – modulates satiety & energy homeostasis,
    - Placental production also – may modulate fetal growth
  - Adiponectin – anti-diabetic, anti-atherogenic, anti-inflammatory

- **Early (≤32 weeks) (n=17)**
  - Elevated leptin cf controls corrected for obesity
  - No increase in adiponectin

- **Late (n=38)**
  - Elevated leptin cf controls corrected for obesity
  - Increased adiponectin – may be a protective response

Masuyama H, et al. BJOG 2010;117:314–320.

Pathogenesis of Pre-eclampsia



Genetic predisposition + immune TH1 response + risk factors

Placental disorder
Inadequate placentation & CTB invasion (variable), reduced COMT and 2-ME

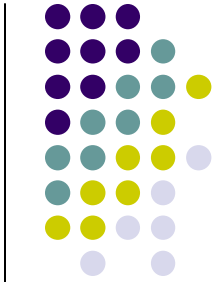
Risk factors:
Obesity, primigravida, diabetes
CKD, prior pre-eclampsia,
Multiple pregnancy, chronic hypertension, SLE
? APL ?Thrombophilias

Utero-placental ischemia and/or hypoxia

Fetal growth restriction / hypoxia

Brown M. May 2011

Q. Factors mediating the genesis of pre-eclampsia include:



A. Elevated levels of circulating VEGF

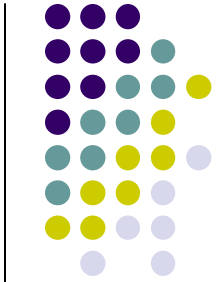
B. Reduced levels of circulating soluble endoglin

C. Elevated levels of circulating sFlt-1

D. Elevated levels of circulating angiotensin II

E. Plasma volume expansion

A. Factors mediating the genesis of pre-eclampsia include :



A. Elevated levels of circulating VEGF

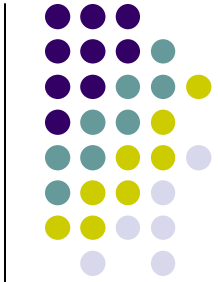
B. Reduced levels of circulating soluble endoglin

C. Elevated levels of circulating sFlt-1

D. Elevated levels of circulating angiotensin II

E. Plasma volume expansion

Pathogenesis of Pre-eclampsia



Genetic predisposition + immune TH1 response + risk factors

Placental disorder
Inadequate placentation & CTB invasion (variable), reduced COMT and 2-ME

Risk factors:
Obesity, primiparity, diabetes
CKD, prior pre-eclampsia,
Multiple pregnancy, chronic hypertension, SLE
? APL ?Thrombophilias

Utero-placental ischemia and/or hypoxia

Mediators:
sFlt-1, endoglin, PlGF, AT-1AA & TNFa, uric acid, SNS stimulation

Fetal growth restriction / hypoxia

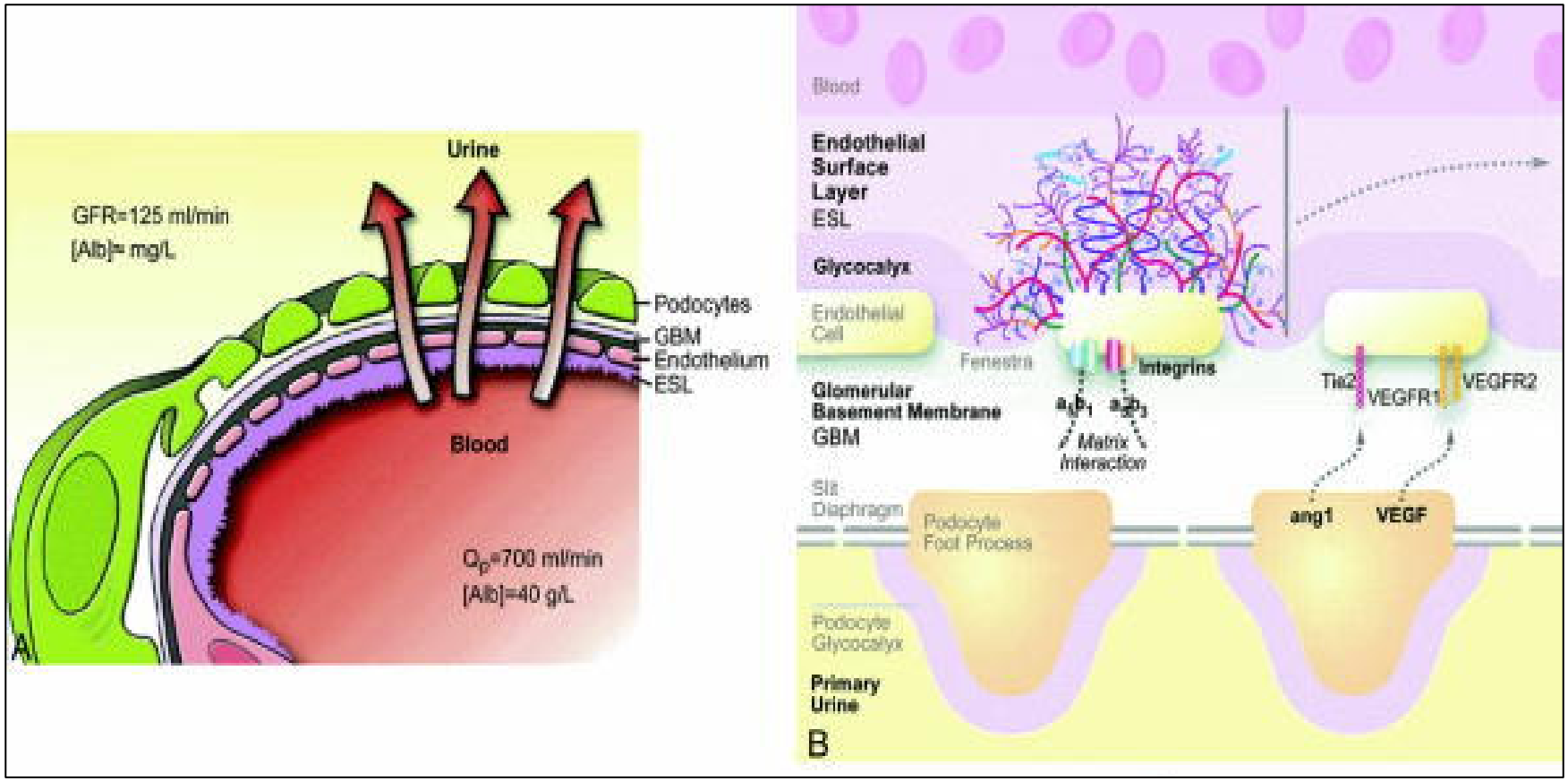
Brown M. May 2011

Soluble FMS- like Tyrosine kinase 1 (sFlt1)

- Variant of VEGF receptor
- increased placental production in PE
  - mops up circulating VEGF and PlGF
  - leads to decreased circulating VEGF & PlGF
- VEGF depletion or antagonism known to lead to proteinuria
- sFLT1 given to pregnant rats caused proteinuria, hypertension, endotheliosis, fibrin deposits

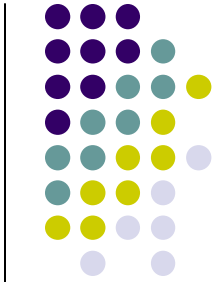
Maynard et al.JCI 2003;111:649-658

How proteinuria happens



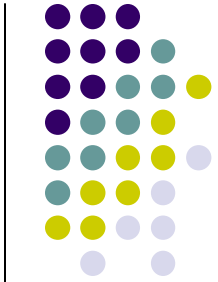
Interpreting Abnormal Proteinuria in Pregnancy: The Need for a More Pathophysiological Approach.
Lindheimer, Marshall; Kanter, David. Obstetrics & Gynecology. 115(2, Part 1):365-375, February 2010.

Endoglin in Pre-eclampsia



- Human endoglin (CD105),
  - dimeric membrane glycoprotein expressed on vascular endothelial cells
  - anti-angiogenic factor
    - Binds TGFβ-1 and TGFβ-3 proteins
  - Expressed in human decidua & upregulated in PE
    - sEng may be a truncated form
    - Possible role in integrin-switching as part of normal trophoblast invasion
  - Mutations on Eng gene linked to HHT
    - Disordered vasculogenesis

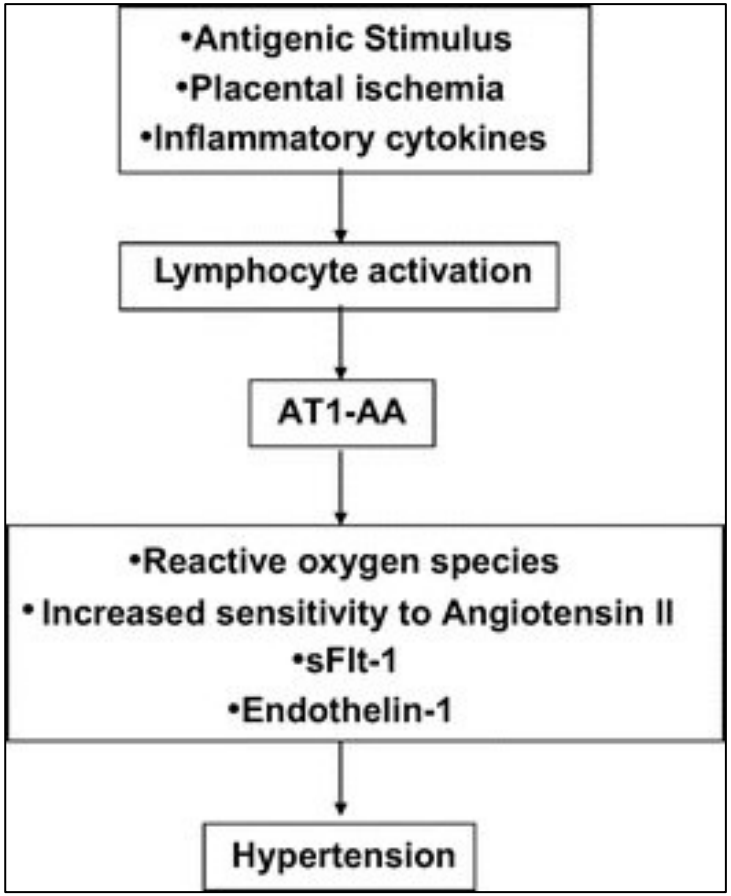
AT1-AA in pre-eclampsia



- AT1-AA from pre-eclamptic women induces
  - sFlt-1 production via AT1R and calcineurin/nuclear factor activated T-cell signalling.
- injecting the IgG or affinity-purified AT1-AA from women into pregnant mice caused
  - hypertension,
  - proteinuria, glomerular endotheliosis,
  - placental abnormalities, intrauterine growth restriction,
  - elevated sFlt

Zhou CC, et al. Angiotensin receptor agonistic auto-antibodies induce pre-eclampsia in pregnant mice. Nat Med. 2008;14:855–862

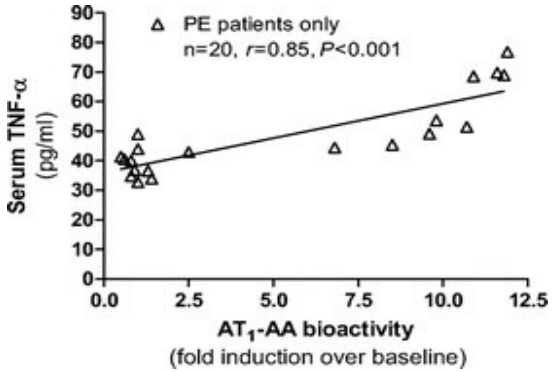
AT 1 AA in Pre-eclampsia



Progress Toward Identifying Potential Markers for Preeclampsia: Role of Agonistic Autoantibody to the Angiotensin II Type I Receptor.
LaMarca, Babbette
Hypertension. 55(2):236-237, February 2010.
DOI: 10.1161/HYPERTENSIONAHA.109.141465

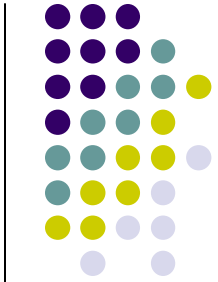
Relationship between AT1R-AA and TNFa in pre-eclampsia

- AT1R AA found prominently in 20 severe pre-eclamptics
- AT1R AA correlated with TNFa in human pre-eclampsia
- In mice : At1R AA increased BP and induced proteinuria
  - Partly mediated via stimulation of TNFa
    - TNFa response attenuated by Losartan
    - BP & proteinuria response partially blocked by TNFa inhibition
    - TNFa increases sFlt-1 release
    - Not seen in non-pregnant mice



Irani et al. Hypertension. Vol 55(5), May 2010, pp 1246-1253

Pathogenesis of Pre-eclampsia



Genetic predisposition + immune TH1 response + risk factors

Placental disorder
Inadequate placentation & CTB invasion (variable), reduced COMT and 2-ME

Risk factors:
Obesity, primiparity, diabetes
CKD, prior pre-eclampsia,
Multiple pregnancy, chronic hypertension, SLE
? APL ?Thrombophilias

Utero-placental ischemia and/or hypoxia

Mediators:
sFlt-1, endoglin, PlGF, AT-1AA & TNFa, uric acid, SNS stimulation

Fetal growth restriction / hypoxia

Maternal endothelial dysfunction:
Reduced NO, PGI2, increased Tx and ET
vasoconstriction
platelet activation
capillary leak

Brown M. May 2011

Putative mechanisms of impaired uric acid handling in pre-eclampsia

Table 1 | Putative mechanisms of impaired uric acid handling in pre-eclampsia

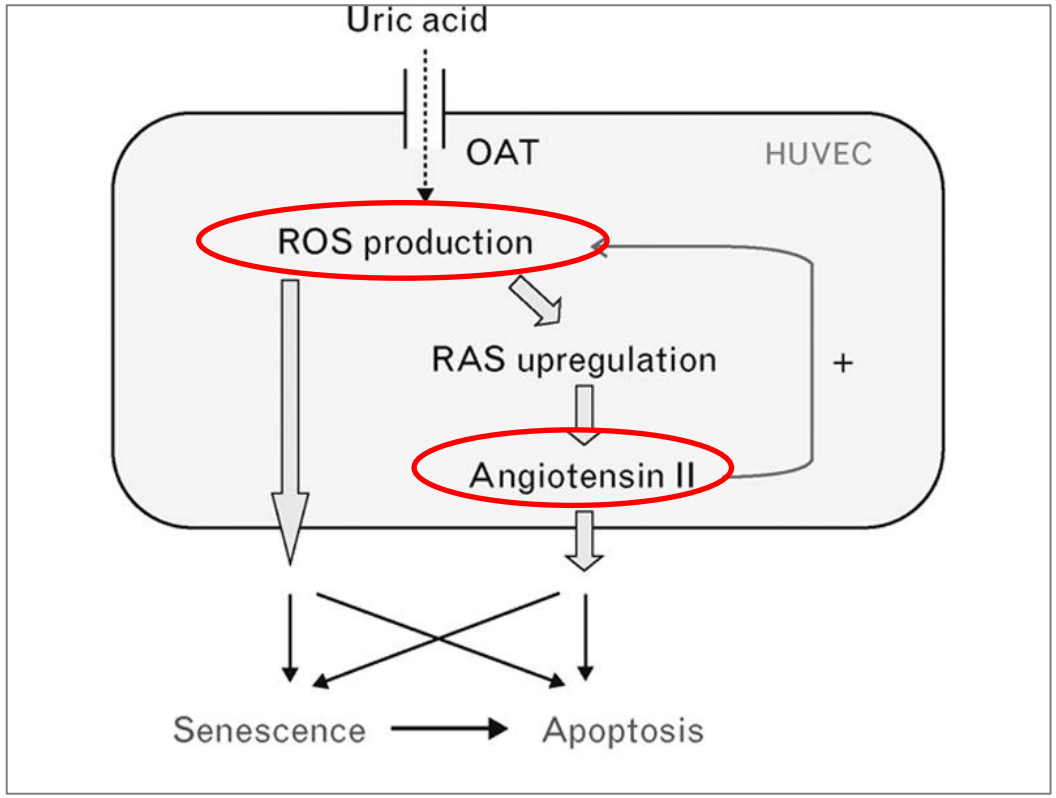
Putative mechanism	Factors that reduce plasma urate levels in normal pregnancy	Factors that increase plasma urate levels in pre-eclampsia
Dilution	Plasma volume expansion	Plasma volume contraction
Impaired filtration	Increased GFR	Reduced GFR
Altered tubular response	Uricosuric action of estrogen; plasma volume expansion	Relative hypovolemia, which stimulates urate reabsorption; insulin or angiotensin II stimulation of urate reabsorption; impaired excretion owing to competition by lactate for tubular transporter
Tissue ischemia mechanisms	Not applicable	Metabolism of purines into uric acid, superoxide anions and hydrogen peroxide; oxidative stress; increased turnover of trophoblast tissue, which provides substrate for further purine metabolism; cytokine release; increased xanthine oxidase levels and activity in cytotrophoblast tissue[45]

Abbreviation: GFR, glomerular filtration rate.

Martin, A. C. & Brown, M. A. (2010) Could uric acid have a pathogenic role in pre-eclampsia?
Nat. Rev. Nephrol. doi:10.1038/nrneph.2010.125

nature REVIEWS NEPHROLOGY

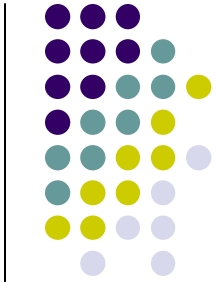
Mechanism(s) for Uric acid endothelial dysfunction



Yu, Min-A; Sánchez-Lozada, Laura G; Johnson, Richard J; Kang, Duk-Hee

Journal of Hypertension. 28(6):1234-1242, June 2010.

Pathogenesis of Pre-eclampsia



Genetic predisposition + immune TH1 response + risk factors

Placental disorder
Inadequate placentation & CTB invasion (variable), reduced COMT and 2-ME

Risk factors:
Obesity, primiparity, diabetes
CKD, prior pre-eclampsia,
Multiple pregnancy, chronic hypertension, SLE
? APL ?Thrombophilias

Utero-placental ischemia and/or hypoxia

Mediators:
sFlt-1, endoglin, PlGF, AT-1AA & TNFa, uric acid, SNS stimulation

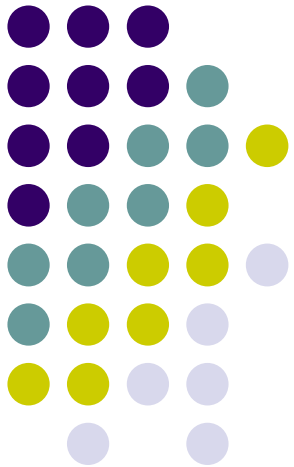
Fetal growth restriction / hypoxia

Maternal endothelial dysfunction:
Reduced NO, PGI2, increased Tx and ET
vasoconstriction
platelet activation
capillary leak

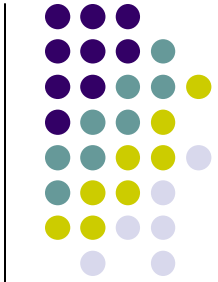
Maternal hypertension & organ hypoperfusion
Brain, kidneys, liver, placenta

Brown M. May 2011

Management



Mrs PE – day 2



- Reflexes remain normal; feels well
- Ultrasound shows appropriate growth, dopplers & AFI
- Maternal assessment
  - Spot protein 220 mg/mmol
  - Liver transaminases normal
  - Platelets 130,000; hematocrit 0.42
  - Creatinine 80 umol/L; uric acid 0.40 mmol/L
- Decision to prolong pregnancy – in hospital
- Betamethasone given
- Oxprenolol commenced day 2

Q. Regarding the management of pre-eclampsia which of the following is correct?

A. Pre-eclampsia can not be diagnosed unless proteinuria is present

B. All women should be given magnesium to prevent convulsions

C. Antihypertensives are associated with improved fetal growth

D. There is RCT evidence that delivery should be effected immediately if presenting at $\geq$37 weeks

E. ACE inhibitors are first line therapy

A. Regarding the management of pre-eclampsia which of the following is correct?

A. Pre-eclampsia can not be diagnosed unless proteinuria is present

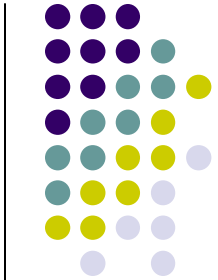
B. All women should be given magnesium to prevent convulsions

C. Antihypertensives are associated with improved fetal growth

D. There is RCT evidence that delivery should be effected immediately if presenting at ≥37 weeks

E. ACE inhibitors are first line therapy

At which phases can we intervene?



Genetic predisposition + immune TH1 response + risk factors

Placental disorder
Inadequate placentation & CTB invasion (variable), reduced COMT and 2-ME

Risk factors:
Obesity, primiparity, diabetes
CKD, prior pre-eclampsia,
Multiple pregnancy, chronic hypertension, SLE
? APL ?Thrombophilias

Utero-placental ischemia and/or hypoxia

Mediators:
sFlt-1, endoglin, PlGF, AT-1AA & TNFa, uric acid, SNS stimulation

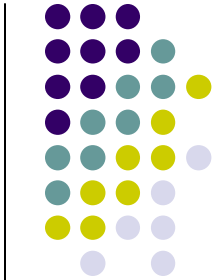
Fetal growth restriction / hypoxia

Maternal endothelial dysfunction:
Reduced NO, PGI2, increased Tx and ET
vasoconstriction
platelet activation
capillary leak

Maternal hypertension & organ hypoperfusion
Brain, kidneys, liver, placenta

Brown M. May 2011

Principles of management



- Maternal
  - Convulsion prophylaxis
  - Antihypertensive therapy
  - Monitoring disease progression
  - Volume expansion?
  - ***Timing delivery***
- Fetal
  - Corticosteroids
  - Monitoring growth & wellbeing
  - ***Timing delivery***

Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension

Caroline S.E. Homer[a], Mark A. Brown[b,c,d], George Mangos[b,c,d] and Gregory K. Davis[b]

Table 3 Clinical outcomes more likely in non-proteinuric PE vs. proteinuric PE and gestational hypertension N=1348

Non-proteinuric PE compared to proteinuric PE	
More common in *Non-proteinuric PE*	• Thrombocytopenia • Liver Disease
Less common in *Non-proteinuric PE*	• Severe hypertension • Pre-term (<37 weeks) birth • Perinatal mortality
Non-proteinuric PE compared to gestational hypertension	
More common in *Non-proteinuric PE*	• Multiple pregnancy • Pre-term delivery • Severe hypertension • Small for gestational age
No difference	• Perinatal mortality

Journal of Hypertension 2008, 26:295–302

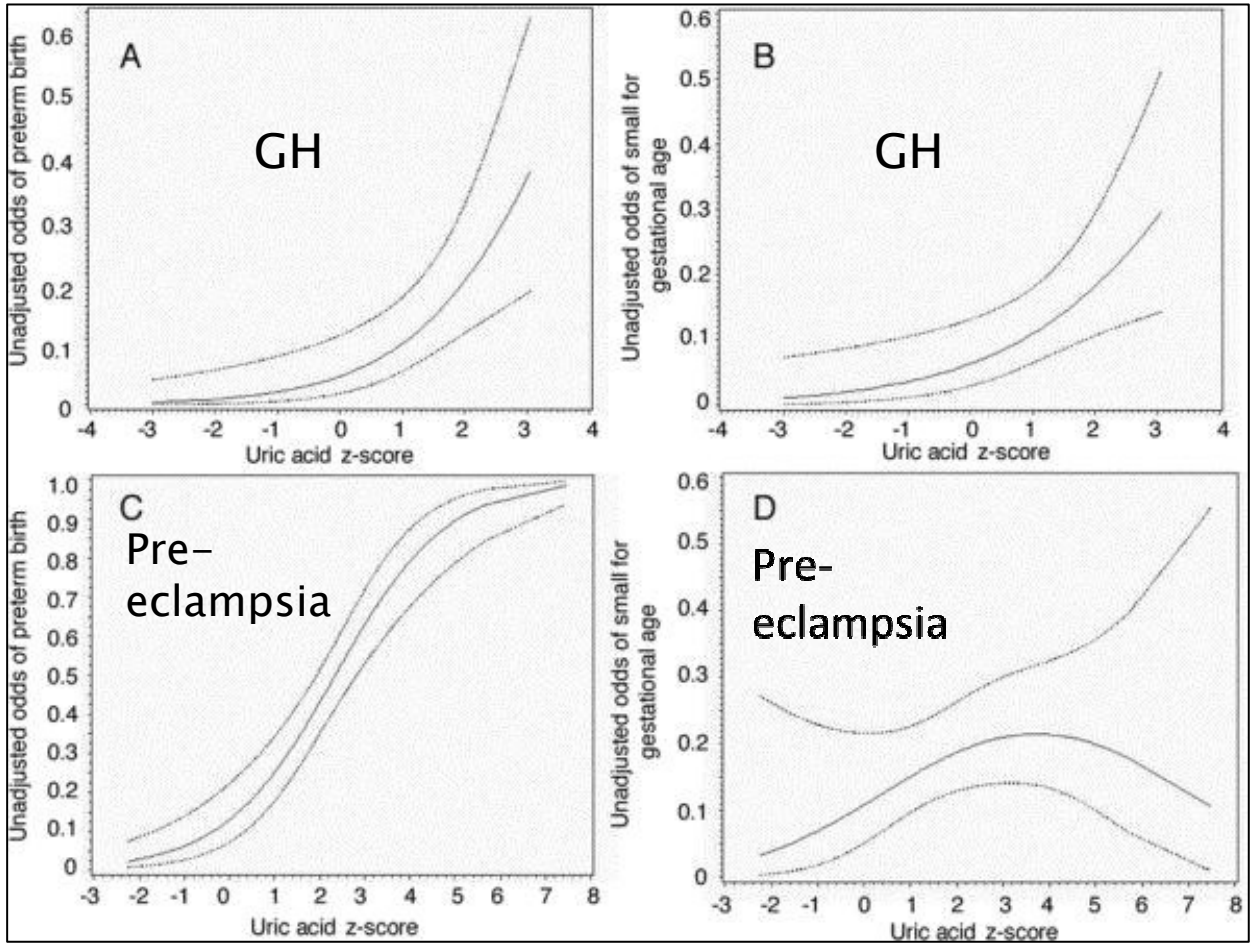
Which women with pre-eclampsia will have poor outcomes?

Factors stratifying maternal risk

1. gestational age
2. maternal chest pain & dyspnoea
3. SaO2 < 90%
4. serum creatinine
5. platelet count
6. AST

- Von Dadelzen et al. PIERS study. 2011. Lancet
- 2023 women with pre-eclampsia – 4 countries – severe maternal outcomes

Uric acid predicts fetal risk



Uric Acid Is as Important as Proteinuria in Identifying Fetal Risk in Women With Gestational Hypertension. Roberts, James et al. Hypertension. 46(6):1263-1269, December 2005.

Gestation corrected Uric acid in pre-eclampsia and gestational hypertension

Significant associations (adjusted for parity):

1. Pre-term birth
2. SGA : especially in ‘benign’ gestational hypertension
3. Thrombocytopenia
4. Impaired GFR

Hawkins et al. Unpublished data. St George hospital. Sydney. 1610 hypertensive pregnant women.

Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial

Corine M Koopmans, Denise Bijlenga, Henk Groen, Sylvia M C Vijgen, Jan G Aarnoudse, Dick J Bekedam, Paul P van den Berg, Karin de Boer, Jan M Burggraaff, Kitty W M Bloemenkamp, Addy P Drogtrop, Arie Franx, Christianne J M de Groot, Anjoke J M Huisjes, Anneke Kwee, Aren J van Loon, Annemiek Lub, Dimitri N M Papatsonis, Joris A M van der Post, Frans J M E Roumen, Hubertina C J Scheepers, Christine Willekes, Ben W J Mol, Maria G van Pampus, for the HYPITAT study group*

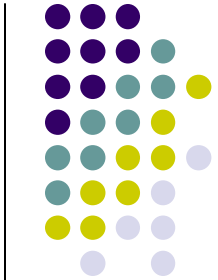
Summary

Background Robust evidence to direct management of pregnant women with mild hypertensive disease at term is

Lancet 2009; 374: 979–88

- 756 women GH or mild PE 36-41 weeks
- Excluded
  - Prior LSCS; severe ht; SGA; proteinuria >5g/d
- difference 1 vs. 6 days to labour
- Primary Outcome - Maternal – severe ht; PPH; eclampsia; HELLP
- 48% of expectant group ended up IOL – mostly severe ht
- IOL group - Less primary outcome 29 vs. 42%; Less LSCS 14 vs. 19%
  - **Recommend IOL for GH or PE at 36+ weeks**

Expectant care before 34 weeks: what the evidence tells us



- 40% need delivery in 48hrs
- Pregnancy prolonged 7-14 days (only 1/3 beyond 7 days)
- 2/3 women developed severe hypertension
- <5% developed severe maternal complications e.g.. Eclampsia, dialysis
- 20 % reached ≥ 34 weeks

Conclusions :

- Similar maternal risks with either approach
- some fetal benefit (less prematurity complications)with expectant approach
- RCT needed

Magee LA. *Hypertension in Pregnancy, 28:312–347, 2009*
72 publications, primarily developed world; most had expectant care
Almost 5000 women from 41 cohorts; only 2 RCTs

“Late onset pre-eclampsia is not an innocuous condition”

- 264 pre-eclamptic women presenting after 34 weeks (South Africa)
- 29% SGA; 2% IUFD
- 31% developed a maternal complication other than severe hypertension
  - (13% eclampsia)

- Probable differences with developed countries
- but ……late onset pre-eclampsia should not be treated lightly.

L. Kenneth, et al. Hypertension in Pregnancy 2010, Vol. 29, No. 3 : Pages 262–270

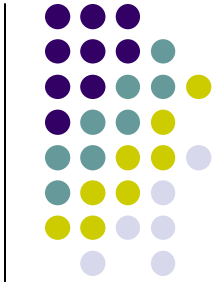
‘Google’-directed treatment of Hypertension in Pregnancy

Antihypertensive drug therapy for mild to moderate hypertension (140-169/90-109 mmHg) during pregnancy

- **Benefits:**
  - Fewer severe hypertension episodes
  - Less IOL
  - Less RDS
- **Adverse effects**
  - More neonatal bradycardia
  - maternal side effects
- **No effect** on:
  - Preterm birth
  - SGA
    - Possible adverse effect on SGA <5th percentile

Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews* 2007

Drugs often used for ‘chronic’ lowering of BP in pregnancy



- ***1st line***
  - oxprenolol, labetalol
  - pindolol, (atenolol)
  - Methyldopa
- ***2nd line*** (add)
  - hydralazine or prazosin or nifedipine
- ***3rd line***
  - add another choice from 2nd line

Antihypertensive drugs to avoid in pregnancy

- ***Diuretics***
  - lower plasma volume ; increase uric acid
- ***ACEI***
  - IUGR; oligohydramnios; neonatal ARF
  - 'fetal hypotensive syndrome'
- ***All receptor blockers*** probably as for ACEI
- care with long term ***atenolol***
  - ? IUGR

Are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers safe in pregnancy: a report of ninety-one pregnancies

Outcomes [*n* (%)]	ACE-Is in early pregnancy	ARBs in early pregnancy
Miscarriage before 20 weeks gestation	8 (11.3)	2 (10.0)
Termination of pregnancy	1 (1.4)	0 (0)
Intrauterine or early neonatal death (no anomaly detected except trisomy 13)	3 (4.2)	1 (5.0)
Live births	59 (83.1)	19 (95.0)[a]
Developmental malformations		
None	53 (74.6)	17 (85.0)[a]
Small ventricular septal defect	1 (1.4)	0 (0)
Mild sensorineural deafness	1 (1.4)	0 (0)
Mild microcephaly	1 (1.4)	0 (0)
Mild hypospadias	1 (1.4)	0 (0)
Small umbilical hernia	1 (1.4)	0 (0)
Small inguinal hernia	0 (0)	1 (5.0)
Neonatal hypotonia	1 (1.4)	0 (0)
Craniosynostosis with tower skull	0 (0)	1 (5.0)
Total	71 (100)	20 (100)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist. [a]Includes one twin pregnancy. Journal of Hypertension

Outcome data in 91 pregnancies in women who received ACEI or ARB in early pregnancy

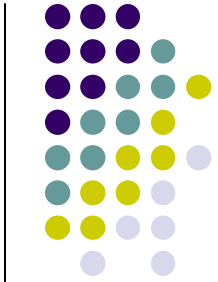
UK retrospective analysis

Argues that congenital effects are mostly minor but still avoid till more data

Wolters Kluwer Health | Lippincott Williams & Wilkins

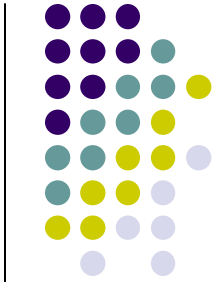
Karthikeyan, et al. J Hypertension. 29(2):396-399, February 2011.

Mrs PE : 31 weeks 4 days



- Progress ultrasound
  - Fetal growth fallen 50th to 10th centile
  - AFI normal; dopplers normal
  - CTG normal
- Maternal status
  - BP 140 / 90 mmHg
    - Oxprenolol + hydralazine
  - Platelets 110,000
  - Creatinine 100 umol/L
  - AST 190
  - Reflexes normal
- Decision for IOL next morning
  - Neonatalogists & team aware

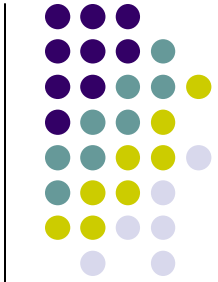
But……..that night



- Sudden onset severe epigastric pain
- Reflexes brisk, clonus, severe headache
- BP 190 / 120 mmHg
- CTG reactive
- AST 700, platelets 70,000; Hct 0.50, creatinine 120umol/L

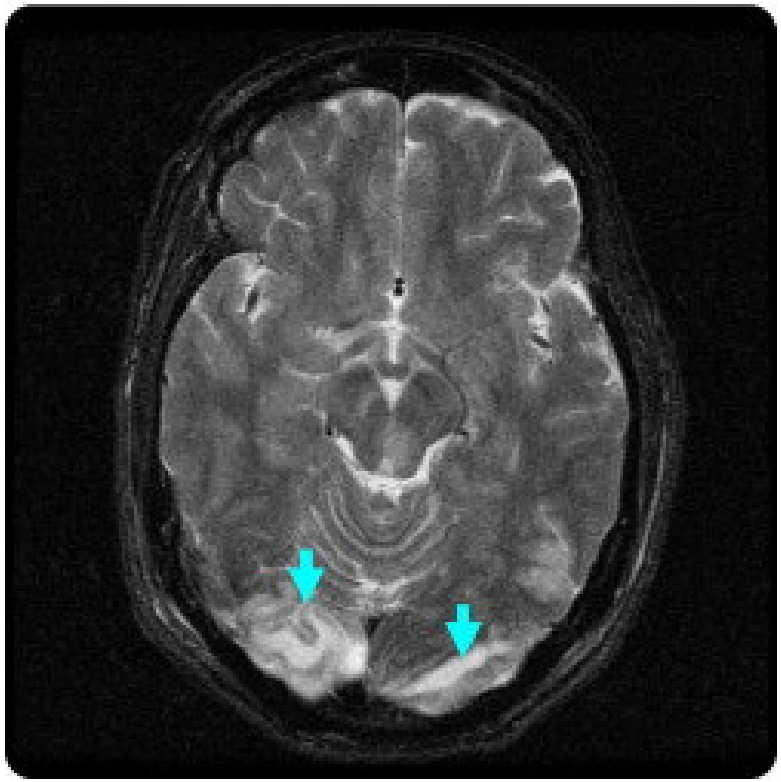
- ***Urgent LSCS planned***
  - ***How to stabilise first ?***

Drugs often used to lower BP acutely in pregnancy



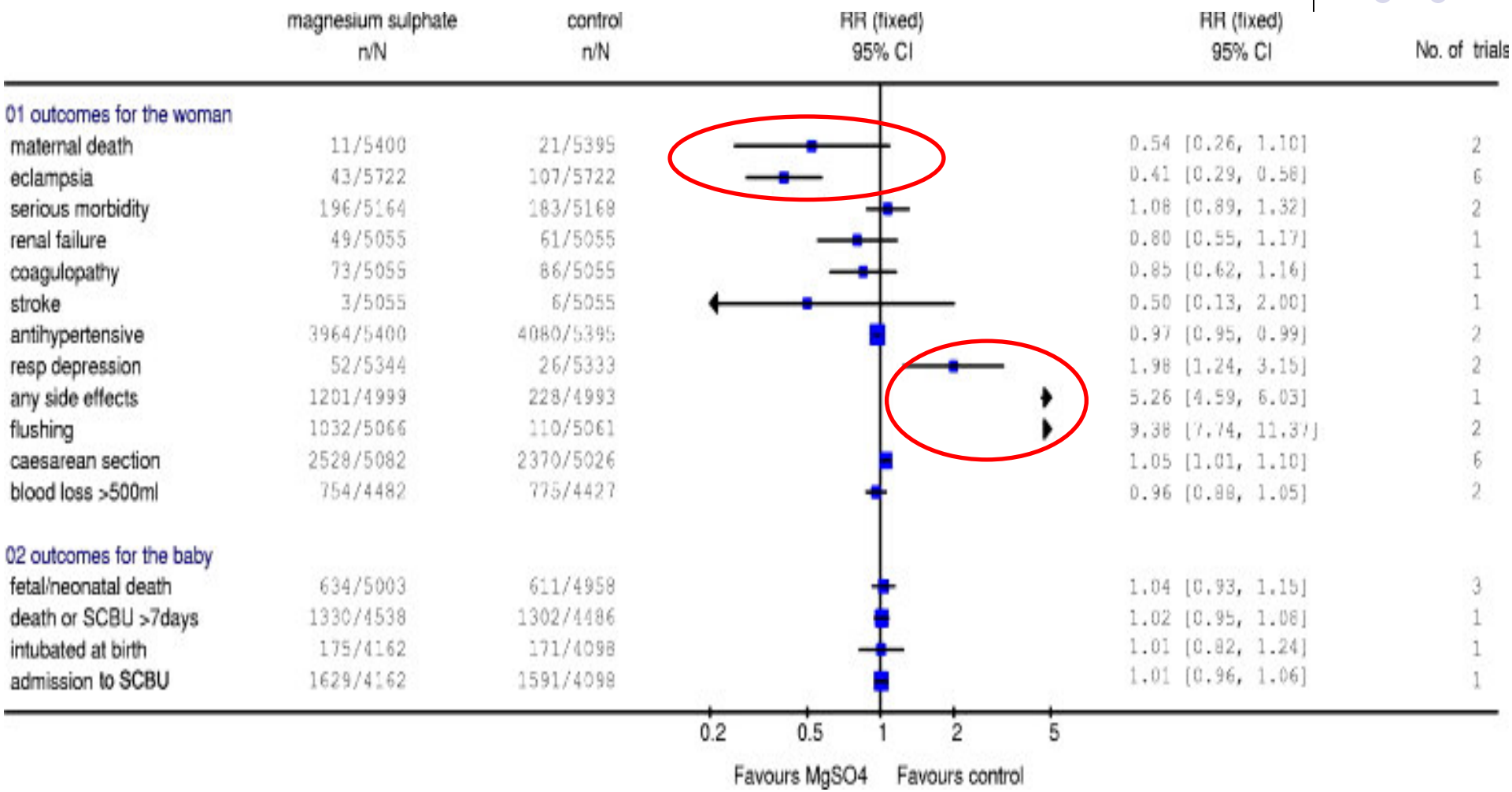
- Nifedipine (oral)
- Labetalol (ivi)
- Hydralazine (ivi or imi)
- Mg sulphate – suboptimal
- GTN

‘Standard management’:
Is it safe to withhold convulsion prophylaxis?



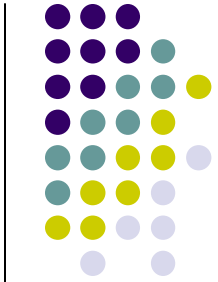
Sibai. Diagnosis and management of atypical preeclampsia-eclampsia. Am J Obstet Gynecol 2009

Trials evaluating magnesium sulfate for prevention of eclampsia



Duley L. Seminars in Perinatology Volume 33, Issue 3, June 2009, Pages 130-137

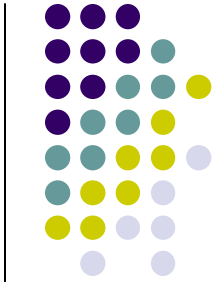
Should we use Mg for all pre-eclamptics ?



In Australia & NZ limit to :

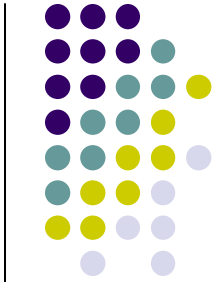
1. Severe pre-eclampsia, and/or
2. Those with neurological signs

Urgent treatment of pre-eclampsia



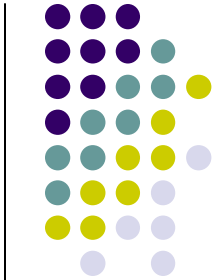
- BP
  - Oral nifedipine then ivi hydralazine infusion
- Narcotics for pain relief
- Magnesium loading then infusion
- Ivi colloid 125 ml/hr for 4 hrs
  - Clinical assessment for pulmonary edema
  - SaO2 measures
  - Hourly urine measure

Mrs PE : day 1 post-partum



- Healthy girl, 1500gm
  - Progressing well
- Magnesium infusion (for 48hrs)
- Good urine output
- Maternal status
  - Creatinine 110 umol/L
  - AST 1000
  - Platelets 50,000
  - BP 150 /90 mmHg on hydralazine infusion
    - Oxprenolol & hydralazine restarted

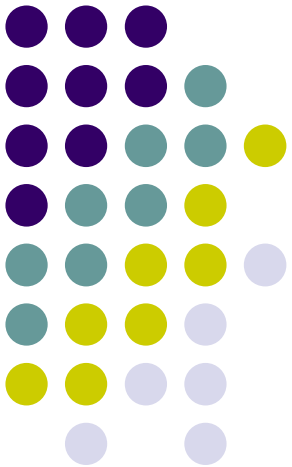
Mrs PE



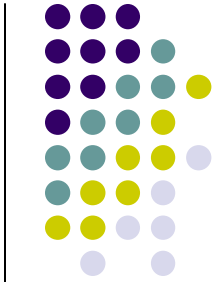
- Recovers well
- Leave hospital day 7
  - No antihypertensives; BP 140 / 90 mmHg
  - Laboratory tests normal
  - Urinalysis – 2+ proteinuria
- Baby in nursery for several weeks

- 3 month review
  - **Will this happen again in another pregnancy?**
  - **Will I have high BP when I'm not pregnant?**

Long term outcomes



Q. Following pre-eclampsia, which of the following is correct?



A. Recurrence in the next pregnancy is on average 40%

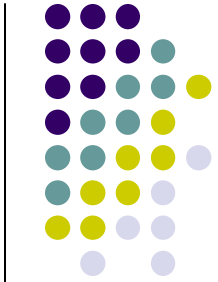
B. Recurrence risk in the next pregnancy is not affected by pre- next pregnancy body weight

C. Vitamin E and C are safe to use in pregnancy and prevent pre-eclampsia to a small extent

D. SGA rate is increased in the next pregnancy even if pre-eclampsia does not recur

E. There is no greater likelihood of later life cardiovascular disease than in women who had normal pregnancies

A. Following pre-eclampsia, which of the following is correct?



A. Recurrence in the next pregnancy is on average 40%

B. Recurrence risk in the next pregnancy is not affected by pre- next pregnancy body weight

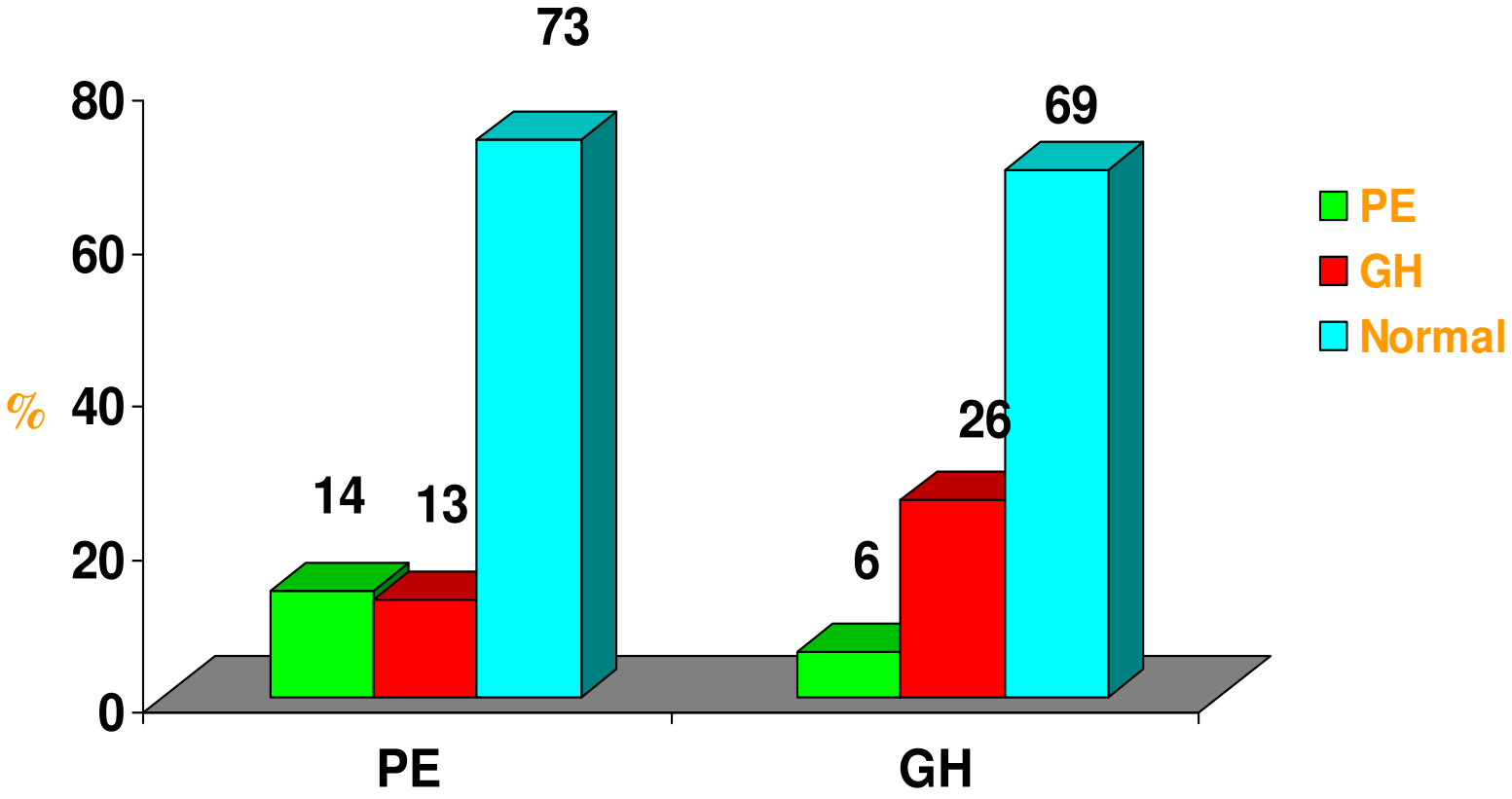
C. Vitamin E and C are safe to use in pregnancy and prevent pre-eclampsia to a small extent

D. SGA rate is increased in the next pregnancy even if pre-eclampsia does not recur

E. There is no greater likelihood of later life cardiovascular disease than in women who had normal pregnancies

Can we predict recurrence of pre-eclampsia or gestational hypertension?

MA Brown,[a] C Mackenzie,[b] W Dunsmuir,[c] L Roberts,[d] K Ikin,[b] J Matthews,[b] G Mangos,[a] G Davis[d]

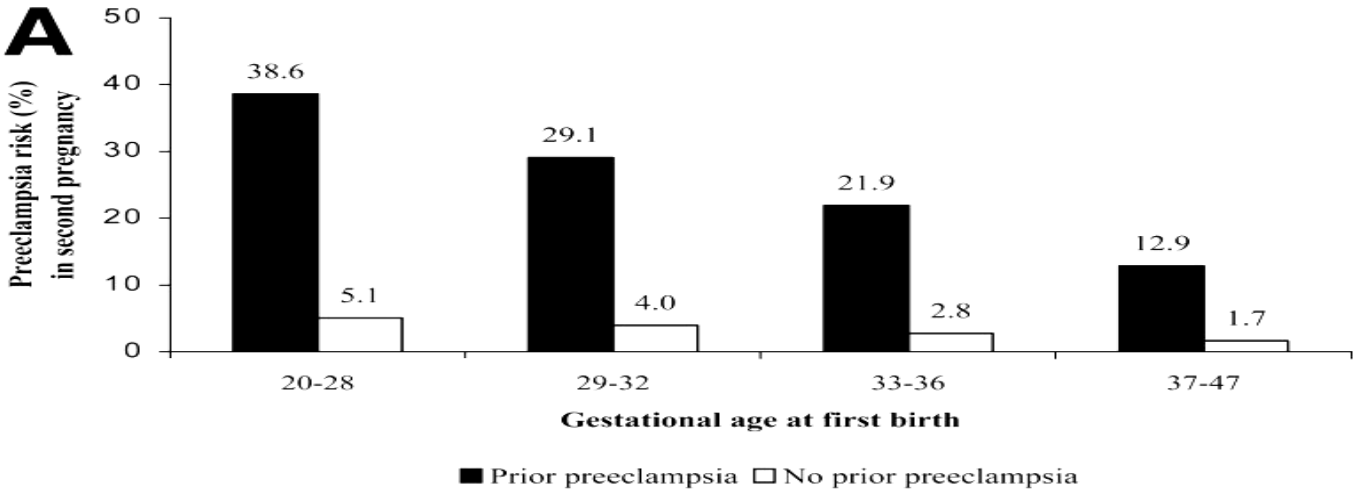


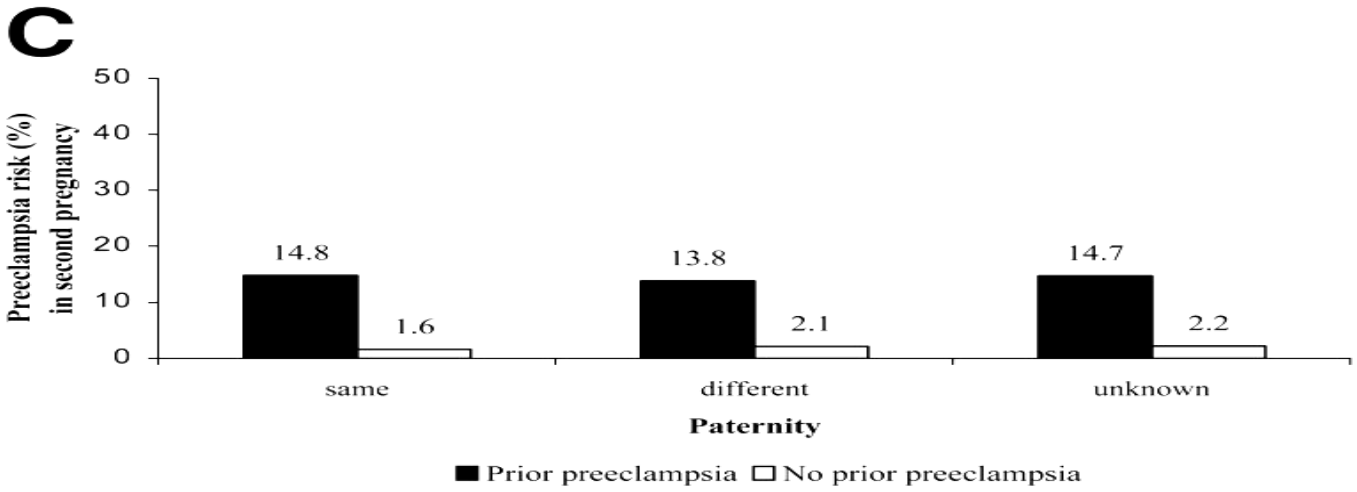
1515 women with PE or GH; 759 next pregnancies

St George Hospital. Sydney.

BJOG 2007;114:984–993.

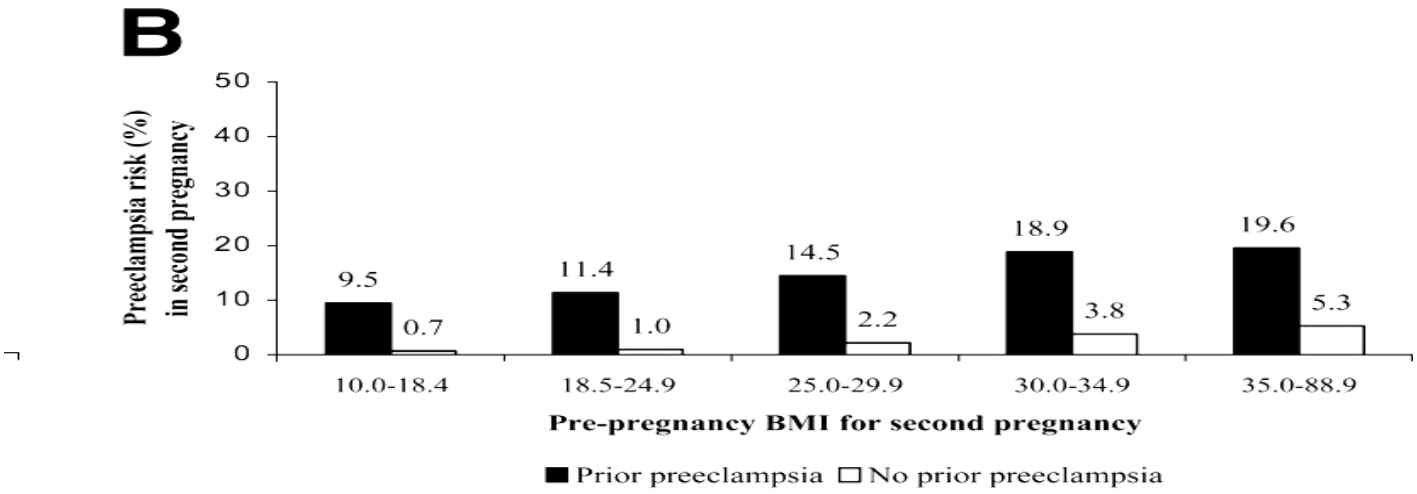
Risk factors for recurrent pre-eclampsia

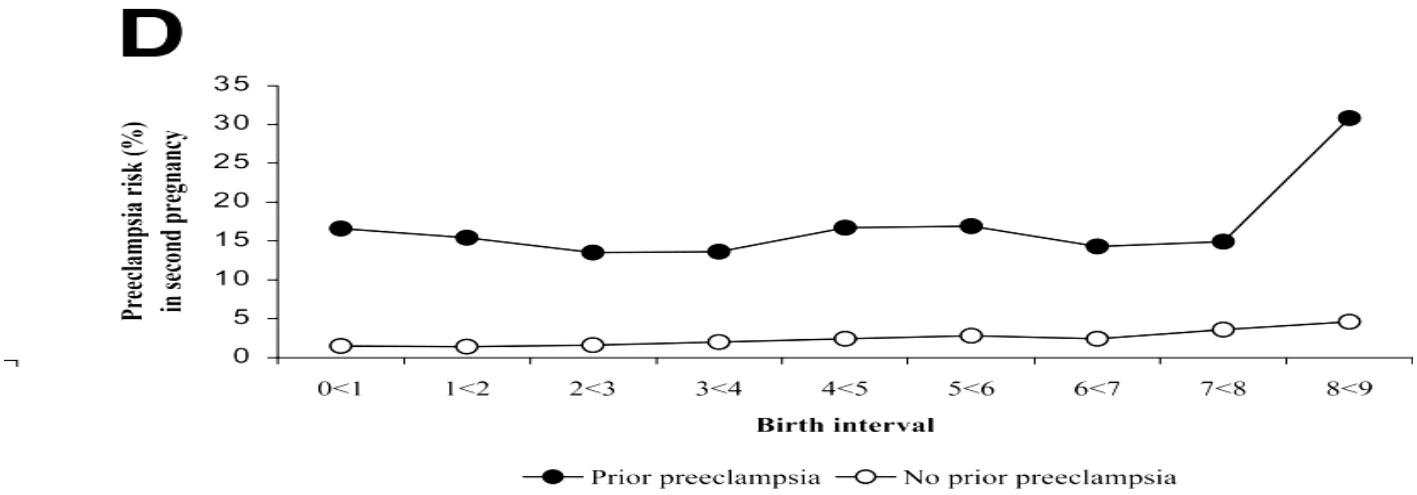




Mostello D, Kallogjeri D, Tungsiripat R, et al. Am J Obstet Gynecol 2008;199:55.e1-55.e7

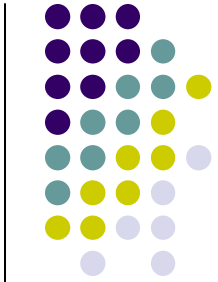
Risk factors for recurrent pre-eclampsia





Mostello D, Kallogjeri D, Tungsiripat R, et al. Am J Obstet Gynecol 2008;199:55.e1-55.e7

Previous preeclampsia : risks of adverse outcomes in subsequent non-preeclamptic pregnancies



- Swedish cohort (n = 354,676); 1992 - 2006
- risks of adverse outcomes in the second pregnancy compared with women without pre-eclampsia in the first pregnancy
- prior **preterm** preeclampsia in second pregnancy > doubled risks of:
  - stillbirth, (0.45 vs 0.22%)
  - placental abruption, (0.94 vs 0.32%)
  - preterm births, (5.6 vs 2.5%)
  - SGA <2.5th percentile (4.7 vs 1.2%)
- **Term** pre-eclampsia increased risk for SGA only

Wikstrom et al. **AJOG.** Volume 204, Issue 2, February 2011, Pages 148.e1-148.e6

Aspirin

- 30,000 women
- OR (all significant) :

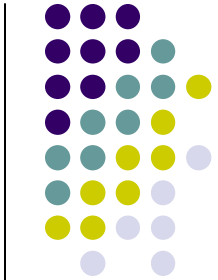
  0.85 for PE

  0.92 for preterm delivery

  0.86 for fetal death

- treat 90 women to prevent 1 case PE
- > 75mg/d appears to have better effects
- treating before 20 weeks appears to have better effects

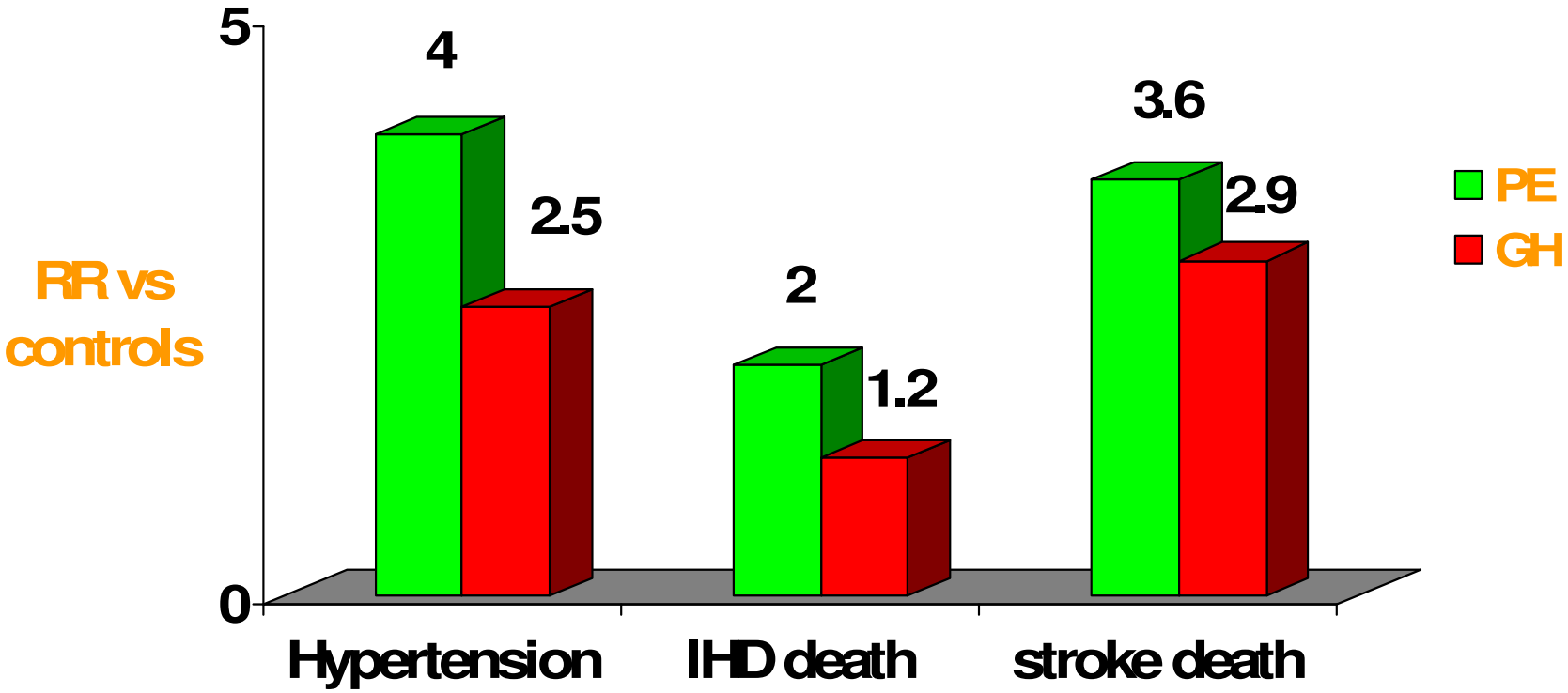
Advanced maternal age



- 177 women over ≥ 45 cf 1770 in younger age groups
- Israel study, 2000 - 2008
- Higher risks for :
  - GDM 17% vs 6%
  - preeclampsia 11% vs 2%
  - Preterm delivery
  - cesarean delivery (OR 32)
  - placenta praevia,
  - postpartum hemorrhage,
  - adverse neonatal outcome
- Risks begin for some factors at age 40, worse if > 50.

Yogev et al. AJOG. Volume 203, Issue 6, December 2010, Pages 558.e1-558.e7

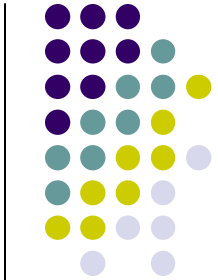
Long term follow up Pre-eclampsia



3,500 women
Median age 60 at follow up
Glasgow,Scotland

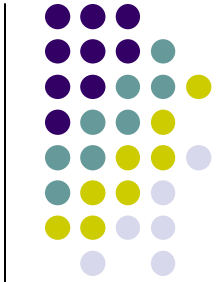
Wilson et al.BMJ.2003;326:845-52

Long term risks of Pre-eclampsia



1. Fatal & non-fatal IHD
2. Stroke
3. Hypertension
4. Thromboembolism by 5 years
5. Need for a renal biopsy
6. ESKD
7. Diabetes
8. Death from any cause

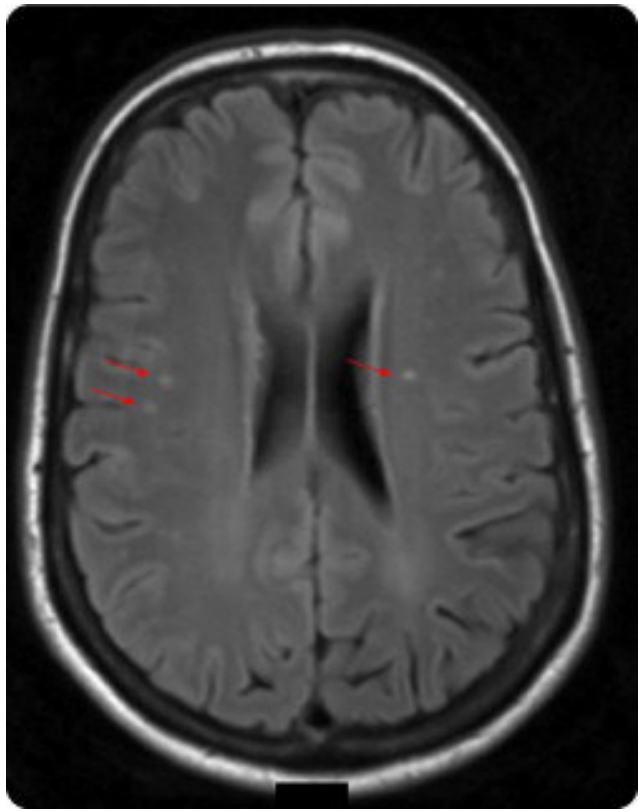
ESRD following pre-eclampsia



- Norwegian study; mean follow up 27 yrs after first pregnancy
- Adjusted for maternal age, yr of delivery, stillbirth
- ESRD increased x 4.3
- Rate ESRD 0.08% for pre-eclampsia
- Possible that reduced VEGF reduces nephrin production and unmasks GN ???
- Possibly common vascular risks ??

Vikse BE *et al*. (2008) Preeclampsia and the risk of end-stage renal disease. N Engl J Med 359: 800–809

Pre-eclampsia: a risk factor for dementia?



Women with eclampsia have more self- reported cognitive dysfunction; more WML

WML associated with cognitive dysfunction

Similar findings for Pre-eclampsia: ISSHP 2010

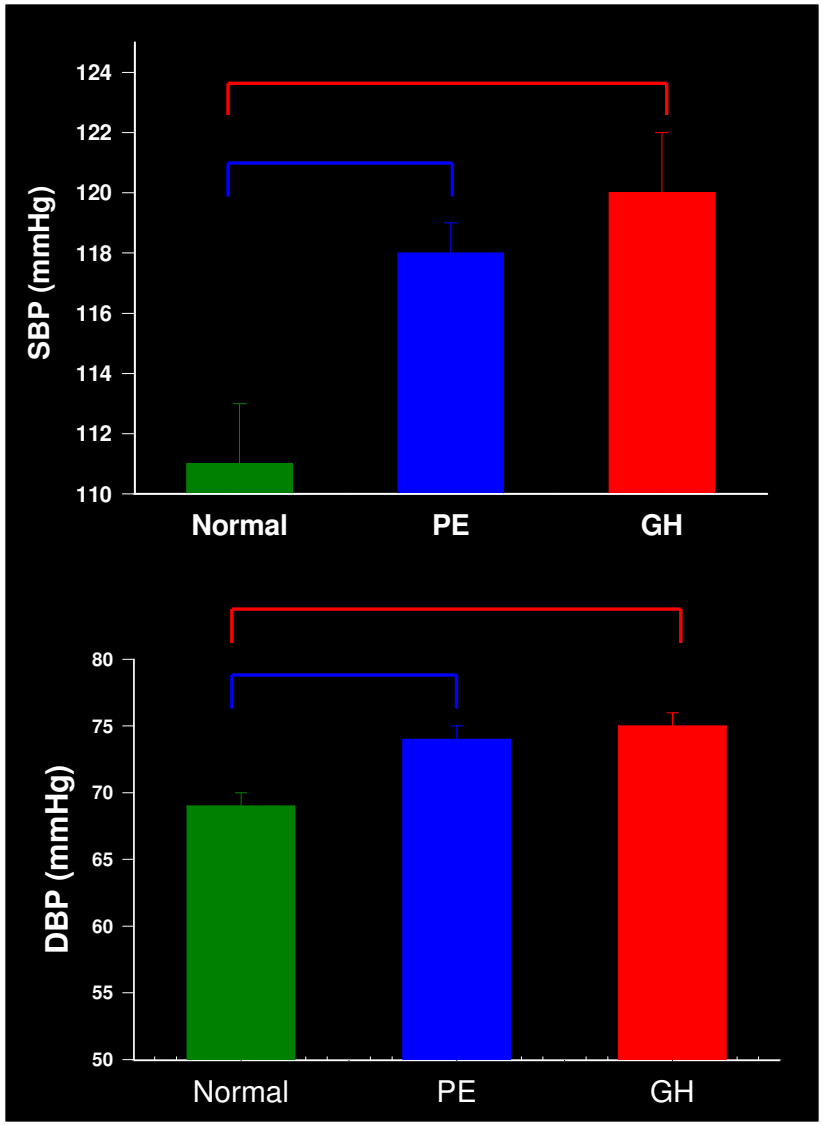
Aukes A. Am J Obstet Gynecol 2009

Post-partum studies : St George hospital average 4.5 yrs. later

Women with pre-eclampsia or GH had greater:

- BMI
- HOMA score
- Triglycerides
- Insulin

All results in ‘normal’ range



Summary : What we've considered

- The current knowledge regarding pathogenesis of pre-eclampsia
- **Decision to deliver** is based upon monitoring
  - Need to understand pathophysiology
- Management is all aimed at fetal growth & maturity
- There are **long term implications**
  - Recurrent pre-eclampsia
  - Essential hypertension
  - Cardiovascular risks