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

Genetic predisposition + immune TH1 response + risk factors

Brown M. May 2011
Pathogenesis of Pre-eclampsia

Genetic predisposition + immune TH1 response + risk factors

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

Brown M. May 2011
The putative role of COMT/2-methoxyestradiol (2-ME) in pregnancy.

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
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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

Pathogenesis of Pre-eclampsia

- Genetic predisposition + immune TH1 response + risk factors

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

- Utero-placental ischemia and/or hypoxia

- Fetal growth restriction / hypoxia

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

*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*
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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, PIGF, 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
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 endothelioses,
  - placental abnormalities, intrauterine growth restriction,
  - elevated sFlt

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
DOI: 10.1161/HYPERTENSIONAHA.109.141465
Relationship between AT1R-AA and TNFα in pre-eclampsia

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

Pathogenesis of Pre-eclampsia

Genetic predisposition + immune TH1 response + risk factors

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

Utero-placental ischemia and/or hypoxia

Fetal growth restriction / hypoxia

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

Risk factors:
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sFlt-1, endoglin, PIGF, AT-1AA & TNFα, uric acid, SNS stimulation

Brown M. May 2011
Putative mechanisms of impaired uric acid handling in pre-eclampsia

<table>
<thead>
<tr>
<th>Putative mechanism</th>
<th>Factors that reduce plasma urate levels in normal pregnancy</th>
<th>Factors that increase plasma urate levels in pre-eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilution</td>
<td>Plasma volume expansion</td>
<td>Plasma volume contraction</td>
</tr>
<tr>
<td>Impaired filtration</td>
<td>Increased GFR</td>
<td>Reduced GFR</td>
</tr>
<tr>
<td>Altered tubular response</td>
<td>Uricosuric action of estrogen; plasma volume expansion</td>
<td>Relative hypovolemia, which stimulates urate reabsorption; insulin or angiotensin II stimulation of urate reabsorption; impaired excretion owing to competition by lactate for tubular transporter</td>
</tr>
<tr>
<td>Tissue ischemia mechanisms</td>
<td>Not applicable</td>
<td>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 cytотrophoblast tissue45</td>
</tr>
</tbody>
</table>

Abbreviation: GFR, glomerular filtration rate.

Mechanism(s) for Uric acid endothelial dysfunction

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

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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
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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
At which phases can we intervene?

Genetic predisposition + immune TH1 response + risk factors

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

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

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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\textsuperscript{a}, Mark A. Brown\textsuperscript{b,c,d}, George Mangos\textsuperscript{b,c,d} and Gregory K. Davis\textsuperscript{b}

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

<table>
<thead>
<tr>
<th>Non-proteinuric PE compared to proteinuric PE</th>
<th>More common in Non-proteinuric PE</th>
<th>Less common in Non-proteinuric PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>● Thrombocytopenia</td>
<td>● Severe hypertension</td>
</tr>
<tr>
<td></td>
<td>● Liver Disease</td>
<td>● Pre-term (&lt;37 weeks) birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Perinatal mortality</td>
</tr>
</tbody>
</table>

Non-proteinuric PE compared to gestational hypertension

<table>
<thead>
<tr>
<th>More common in Non-proteinuric PE</th>
<th>Pre-term delivery</th>
<th>Severe hypertension</th>
<th>Small for gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-term delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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


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

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.

‘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

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

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

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist. aIncludes one twin pregnancy.

Mrs PE : 31 weeks 4 days

- Progress ultrasound
  - Fetal growth fallen 50\textsuperscript{th} to 10\textsuperscript{th} 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?

Trials evaluating magnesium sulfate for prevention of eclampsia

<table>
<thead>
<tr>
<th></th>
<th>magnesium sulphate n/N</th>
<th>control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>No. of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 outcomes for the woman</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>maternal death</td>
<td>11/5400</td>
<td>21/5395</td>
<td>0.54 [0.26, 1.10]</td>
<td>2</td>
</tr>
<tr>
<td>eclampsia</td>
<td>43/5722</td>
<td>107/5722</td>
<td>0.41 [0.29, 0.58]</td>
<td>6</td>
</tr>
<tr>
<td>serious morbidity</td>
<td>196/5164</td>
<td>183/5168</td>
<td>1.08 [0.89, 1.32]</td>
<td>2</td>
</tr>
<tr>
<td>renal failure</td>
<td>49/5055</td>
<td>61/5055</td>
<td>0.80 [0.55, 1.17]</td>
<td>2</td>
</tr>
<tr>
<td>coagulopathy</td>
<td>73/5055</td>
<td>86/5055</td>
<td>0.85 [0.62, 1.16]</td>
<td>1</td>
</tr>
<tr>
<td>stroke</td>
<td>3/5055</td>
<td>6/5055</td>
<td>0.50 [0.13, 2.00]</td>
<td>1</td>
</tr>
<tr>
<td>antihypertensive</td>
<td>3964/5400</td>
<td>4080/5395</td>
<td>0.97 [0.95, 0.99]</td>
<td>2</td>
</tr>
<tr>
<td>resp depression</td>
<td>52/5344</td>
<td>26/5333</td>
<td>1.98 [1.24, 3.15]</td>
<td>1</td>
</tr>
<tr>
<td>any side effects</td>
<td>1201/4999</td>
<td>228/4993</td>
<td>5.26 [4.59, 6.03]</td>
<td>1</td>
</tr>
<tr>
<td>flushing</td>
<td>1032/5066</td>
<td>110/5061</td>
<td>9.38 [7.74, 11.37]</td>
<td>2</td>
</tr>
<tr>
<td>caesarean section</td>
<td>2528/5082</td>
<td>2370/5026</td>
<td>1.05 [1.01, 1.10]</td>
<td>6</td>
</tr>
<tr>
<td>blood loss &gt;500ml</td>
<td>754/4482</td>
<td>775/4427</td>
<td>0.96 [0.88, 1.05]</td>
<td>2</td>
</tr>
</tbody>
</table>

| 02 outcomes for the baby |                        |             |                   |               |
| fetal/neonatal death    | 634/5003               | 611/4958    | 1.04 [0.93, 1.15] | 3             |
| death or SCBU >7days    | 1330/4538              | 1302/4486   | 1.02 [0.95, 1.08] | 1             |
| intubated at birth      | 175/4162               | 171/4098    | 1.01 [0.82, 1.24] | 1             |
| admission to SCBU       | 1629/4162              | 1591/4098   | 1.01 [0.96, 1.06] | 1             |

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
- Ivı 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
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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

Risk factors for recurrent pre-eclampsia

Risk factors for recurrent pre-eclampsia

B

D

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

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.

Yoge 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 unmask GN ???
- Possibly common vascular risks ??

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