PRE-EMPT
improving pre-eclampsia/eclampsia care across the continuum

Peter von Dadelszen
BMedSc, MBChB, DipObst, DPhil, FRANZCOG, FRCSC, FRCOG
Professor and Academic Head of Obstetrics & Gynaecology, SGUL
Pre-eclampsia defined

- Definition (classical)
  - Hypertension
    - sBP ≥140mmHg and/or dBP ≥90mmHg
  - Significant proteinuria
    - ≥300mg protein/24 hours
    - ≥30mg protein/mmol creatinine on spot urinary protein:creatinine ratio
    - ≥++ dipstick proteinuria

- This paradigm does not fully recognise the systemic nature of pre-eclampsia
Pre-eclampsia redefined
pre-eclampsia is more than hypertension & proteinuria

- hypertension
- proteinuria
- acute renal failure
- eclampsia
- stroke
- pulmonary oedema
- DIC/abruption
PRE-EMPT overview

• Five objectives
  – Prevention
  – Monitoring
  – Treatment
  – Global Pregnancy CoLaboratory
  – Knowledge translation
Prevention
the Calcium And Pre-eclampsia trial
PI: Justus Hofmeyr
Calcium And Pregnancy (CAP) Trial

• Rationale
  – In diet-deficient (calcium <600mg/d) women, calcium supplementation (≥1000mg/d) in 2nd half of pregnancy decreases the incidence of pre-eclampsia
    • i.e., proteinuric GH (RR 0.68 [95% CI 0.49, 0.94])
  – Is the reduction in pre-eclampsia an epiphenomenon of decreasing BP by 3-5mmHg?
  – Might calcium mask risks (e.g., HELLP)?
  – Might earlier (preconceptual & early pregnancy) calcium have greater effect?
A new review
low-dose calcium and pre-eclampsia prevention

• Data collection and analysis
  – Randomised and quasi-randomised trials of low-dose calcium (<1g /day), with/without other supplements.

• Main results
  – Pre-eclampsia reduced consistently (9 trials, n=2234, RR 0.38 [0.28-0.52])

• Conclusions
  – Limited data consistent with reducing the risk of pre-eclampsia & have implications for current WHO guidelines and their global implementation

Hofmeyr et al. BJOG 2014
Calcium And Pregnancy (CAP) Trial

- **Trial design**
  - Placebo-controlled RCT

- **Population**
  - South Africa, Zimbabwe, & Argentina
  - Women who have previously experienced severe pre-eclampsia or eclampsia (± perinatal loss), who are planning another pregnancy

- **Enrolment (before pregnancy) until 20wk GA**
  - Intervention: Calcium supplementation (500mg/d)
  - Control: Placebo

- **Both arms to receive Ca2+ from 20+0wk**

- **Outcomes**
  - Primary: pre-eclampsia (proteinuric GH)
  - Secondary
Calcium And Pregnancy (CAP) Trial

ARTICLE IN PRESS


Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women’s Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Original Article

The effect of calcium supplementation on blood pressure in non-pregnant women with previous pre-eclampsia: An exploratory, randomized placebo controlled study

G.J. Hofmeyr a,b, A.H. Seuc c, A.P. Betrán c, T.D. Purnat d, A. Ciganda e, S.P. Munjanja f, S. Manyame f, M. Singata g, S. Fawcus h,i, K. Frank j, D.R. Hall k, G. Cormick e,a, J.M. Roberts l, E.F. Bergel c, S.K. Dreibit m, P. Von Dadelszen m, J.M. Belizan e, on behalf of the Calcium and Pre-eclampsia Study Group

<table>
<thead>
<tr>
<th>Calcium</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>Week after randomization</td>
<td>105</td>
<td>12.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>105</td>
<td>-6</td>
<td>14.7</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>105</td>
<td>-2.6</td>
<td>10.9</td>
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<table>
<thead>
<tr>
<th>Placebo</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>Week after randomization</td>
<td>112</td>
<td>12.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>112</td>
<td>-2.8</td>
<td>15.6</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>112</td>
<td>0.8</td>
<td>11.3</td>
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<thead>
<tr>
<th>Difference</th>
<th>MD</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>With severe preeclampsia in previous pregnancy</td>
<td>3.2</td>
<td>-0.9–7.3</td>
</tr>
<tr>
<td>Without severe preeclampsia in previous pregnancy</td>
<td>3.4*</td>
<td>0.4–6.4</td>
</tr>
</tbody>
</table>

* Statistically significant.
Monitoring
the miniPIERS model: development & validation
PI: Peter von Dadelszen
Maternal death from pre-eclampsia by diagnosis – UK; 1952 – 2008

Number of maternal deaths/triennium

Surveillance, Timed delivery & Reproductive choice
Antihypertensives
Magnesium

Data from CEMD, UK
PIERS combined adverse maternal outcome

One or more of maternal morbidity or mortality:

- Maternal death
- Eclampsia (≥1)
- Glasgow coma score <13
- CVA/RIND/TIA
- Cortical blindness/retinal detachment/PRES
- Positive inotropic support
- Infusion of a 3rd parenteral antihypertensive
- Myocardial ischaemia/infarction
- $\text{SpO}_2 < 90\%$; $\geq 50\% \text{FiO}_2$ for $>1\text{hr}$; pulmonary oedema
- Intubation (other than for C/S)
- Transfusion of any blood product
- Platelets $<50 \times 10^9$/L with no transfusion
- Hepatic dysfunction
- Hepatic haematoma/rupture
- Acute renal insufficiency (no prior renal disease)
- Acute renal failure (prior renal disease)
- Placental abruption
- Other (ascites/Bell’s palsy)
miniPIERS study design

- Study design
  - miniPIERS recruited 2081 women with HDP-complicated pregnancies admitted to facilities in less-developed countries

miniPIERS model
development & validation with bootstrapping

- AUC ROC = 0.77 [95% CI 0.73, 0.81]

- Includes
  - Parity (0, ≥1), gestational age, maternal chest pain/dyspnoea, maternal headache/visual disturbances, maternal abdominal pain with bleeding, sBP, and dipstick proteinuria

- Dipstick proteinuria not a necessary component - included for face validity
  - Highly predictive of perinatal mortality
    - 4+: OR = 7.1 [95% CI 3.3, 15.5]

miniPIERS model + SpO2
miniPIERS model + SpO₂

[AUC ROC 0.77 (95% CI 0.74, 0.80)]

• High-risk group defined using a predicted probability ≥25%
• Identify 65% of women with adverse outcomes

[AUC ROC 0.80 (95% CI 0.76, 0.85)]

• High-risk group defined using a predicted probability ≥25%
• Identify 85% of women with adverse outcomes

miniPIERS model + SpO₂

[AUC ROC 0.77 (95% CI 0.74, 0.80)]

- High-risk group defined using a predicted probability ≥25%
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- Identify 85% of women with adverse outcomes
PIERS on the Move

Dunsmuir et al. IEEE J Biomed Health Inform 2014
Treatment
the Community-Level Interventions in Pregnancy (CLIP) trials
PI: Peter von Dadelszen
CLIP FEASIBILITY STUDIES

PIs: Rahat Qureshi & Peter von Dadelszen
Multiple methods of data collection employed to explore feasibility of the CLIP Trial

- Focus Group Discussions
- In Depth Interviews
- Document Review
- Participatory Observation
- Facility Assessment
- Self-Administered Questionnaires
- Community Surveillance
CLIP Feasibility Studies

publications

• **Three supplements to *BMC Reproductive Health***
  - December 2015
    • Mixed-methodology for assessing the feasibility of Community Level Interventions for Pre-eclampsia in South Asian and African contexts
    • Community perceptions of pre-eclampsia (all four countries)
    • Health care seeking behaviours for obstetric care (all four countries)

  - **Women Deliver 2016**
    • Human resource constraints and the prospect of task-shifting (all four countries)
    • Community health worker knowledge and management of pre-eclampsia (all four countries)
    • The influence of relationships on maternal well-being in Mozambique
    • The spatial epidemiology of maternal deaths in Gaza and Maputo provinces, Mozambique
    • Personal relationships, social capital and resilience in Southern Mozambique

  - **RCOG World Congress 2016**
    • Estimates of pre-eclampsia, maternal and perinatal mortality: results from the Community Level Interventions for Pre-eclampsia (CLIP) baseline surveys (all four countries)
CLIP sites
≈87,000 pregnant women

CLIP sites include:
- Maputo & Gaza Provinces, Mozambique
- Ogun State, Nigeria
- Sindh Province, Pakistan
- Karnataka State, India
**App-guided CLIP package of care (≥1 trigger)**

- 750mg methyldopa po (only if sBP ≥160; not repeated in PHC)
- 10g MgSO₄ im (if sBP ≥160, eclampsia, miniPIERS p ≥25%, pv bleeding + sBP ≥140; not repeated in PHC)
- urgent transport (if sBP ≥160, eclampsia, coma, stroke, miniPIERS p ≥25%, pv bleeding, ++++ protein, no FM ≥12h)

**App-guided CLIP triggers to initiate community interventions**

- miniPIERS p ≥25%
- sBP ≥160
- eclampsia
- pv bleeding (presumed abruption)
- ++++ proteinuria
- absent fetal movements ≥12h

**OVERCOMING THE 3 DELAYS**

- Triage/Transport/Treatment

**facility capacity enhancement**

- CME/CPD
- M&M reviews

**CEmOC facility for definitive care**

- ongoing BP control
- ongoing MgSO₄ delivery – IOL vs C/S newborn care

**community engagement & cHCP education**

**home-based**

- (± transfer to PHC)

**non-urgent transport (<24h)**

- (if: miniPIERS p <25%, sBP 140-159mmHg, <+ +++ protein)

**urgent transport (<4h)**

- (if: miniPIERS p ≥25%, sBP ≥160, stroke, coma, eclampsia, pv bleeding, ++++ protein, absent FM ≥12h)
App-guided CLIP triggers to initiate community interventions

OVERCOMING THE 3 DELAYS

- miniPIERS p ≥ 25%
- Triage/Transport/Treatment

urgent transport
(if: sBP ≥ 160, eclampsia, coma, stroke, miniPIERS p ≥ 25%, pv bleeding, +++ protein, no FM ≥ 12h)

non-urgent transport
(if: miniPIERS p < 25%, sBP 140-159 mmHg, < +++++ protein)

community engagement & cHCP education

CEmOC facility for definitive care
ongoing BP control
ongoing MgSO4 delivery – IOL vs C/S
newborn care

facility capacity enhancement
CME/CPD
M&M reviews
home-based (± transfer to PHC) or PHC-based assessment & initial management

- 750mg methyldopa po (only if sBP ≥160; not repeated in PHC)
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- App-guided CLIP triggers to initiate community interventions
- The 3 DELAYS: miniPIERS p ≥25%

  - Triage/Transport/Treatment sBP ≥160
  - Triage/Transport/Treatment eclampsia
  - Triage/Transport/Treatment pv bleeding (presumed abruptio)
  - Triage/Transport/Treatment ++++ proteinuria
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- urgent transport (<4h) (if: miniPIERS p ≥25%, sBP ≥160, stroke, coma, eclampsia, pv bleeding, ++++ protein, absent FM ≥12h)
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- community engagement & CHP education
- ongoing BP control
- ongoing MgSO$_4$ delivery – IOL vs C/S
- newborn care

- facility capacity enhancement
  - CME/CPD
  - M&M reviews
  - CEmOC facility for definitive care
  - ongoing BP control
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App-guided CLIP triggers to initiate community interventions

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**App-guided CLIP triggers to initiate community interventions**

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**OVERCOMING THE 3 DELAYS**

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**home-based (± transfer to PHC) or PHC-based assessment & initial management**

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ongoing BP control

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newborn care
App-guided CLIP triggers to initiate community interventions

- miniPIERS p ≥25%
- sBP ≥160
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- pv bleeding (presumed abruptio placenta)
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OVERCOMING THE 3 DELAYS

- urgent transport (<4h)
  (if: miniPIERS p ≥25%, sBP ≥160, stroke, coma, eclampsia, pv bleeding, ++++ protein, absent FM ≥12h)

- non-urgent transport (<24h)
  (if: miniPIERS p <25%, sBP 140-159 mmHg, <++++ protein)

facility capacity enhancement
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CEmOC facility for definitive care
ongoing BP control
ongoing MgSO₄ delivery – IOL vs C/S
newborn care

community engagement & CHCP education

home-based (± transfer to PHC) or PHC-based assessment & initial management
CLIP sites – pilot trials
≈17,000 pregnant women

- Sindh Province, Pakistan
- Karnataka State, India
- Ogun State, Nigeria
- Maputo & Gaza Provinces, Mozambique
CLIP pilot trial
interim data

• **Nigeria**
  – 10,320 women enrolled
  – 3248 women visited
  – 5% incidence HDP
  – 121/163 (74%) referrals immediately accepted

• **Pakistan**
  – 4356 women enrolled
  – 1653 women visited
  – 7.7% incidence HDP
  – 82/127 (65%) referrals immediately accepted

• **India**
  – 2209 women enrolled
  – 964 women visited
  – 4.9% incidence HDP
  – 33/47 (70%) referrals immediately accepted
CLIP site – CRADLE device
≈87,000 pregnant women
Additional diagnostic performance

Nigeria

- **Microlife**
  - CRADLE BP device

App-guided CLIP triggers to initiate community interventions

- miniPIERS p ≥25%
- sBP ≥160
- dBP ≥110
- SI ≥1.7
- eclampsia
- pv bleeding (presumed abruption)
- ++++ proteinuria
- absent fetal movements ≥12h

OVERCOMING THE 3 DELAYS

miniPIERS p ≥25%, sBP ≥160, dBP ≥110, SI ≥1.7, eclampsia, pv bleeding, ++++ protein, absent FM ≥12h

App-guided CLIP package of care (≥1 trigger)

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Community engagement & CHP education

home-based (± transfer to PHC) or PHC-based assessment & initial management

Urgent transport (<4h)
(if: miniPIERS p ≥25%, sBP ≥160, dBP ≥110, SI ≥1.7, stroke, coma, eclampsia, pv bleeding, ++++ protein, absent FM ≥12h)

Non-urgent transport (<24h)
(if: miniPIERS p <25%, sBP 140-159mmHg, <+ +++ protein)

CEmOC facility for definitive care
ongoing BP control
ongoing MgSO₄ delivery – IOL vs C/S newborn care

Facility capacity enhancement
CME/CPD
M&M reviews
Additional diagnostic performance
Mozambique & Pakistan

- LionsGate Technologies
  - Phone oximeter® through AudioOx® port
    - Adds SpO₂ to miniPIERS
    - Crowd-funded through the Sensor Project (http://www.thesensorproject.org/)
CLIP sites - oximetry
≈87,000 pregnant women

- Maputo & Gaza Provinces, Mozambique
- Ogun State, Nigeria
- Sindh Province, Pakistan
- Karnataka State, India
App-guided CLIP triggers to initiate community interventions

- miniPIERS p ≥25%
- sBP ≥160
- SpO₂ <93%
- eclampsia
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OVERCOMING THE 3 DELAYS

- Triage/Transport/Treatment

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community engagement & chCP education

community engagement & chCP education
• **Maternal death ("maternal death rate")**
  - deaths during pregnancy or ≤42d of pregnancy (or last contact day if contact not maintained to 42d) /1,000 identified pregnancies

• **Maternal morbidity**
  - one/more life-threatening complications of pregnancy during pregnancy or ≤42d of pregnancy (or last contact day if contact not maintained to 42d) /1,000 identified pregnancies

• **Perinatal & late neonatal death ("perinatal death rate")**
  - IUFD [≥20⁺0 and/or ≥500g], early neonatal mortality [d0-6 of postnatal life] and late neonatal mortality [d7-28 of postnatal life]/1,000 identified pregnancies

• **Neonatal morbidity**
  - non-lethal events of seizure and coma during d0-28 of postanatal life /1,000 identified pregnancies
CLIP definitive trial
updates

• Nigeria
  – Start date: 15 March 2015

• Mozambique
  – Start date: 1 April 2015 (pending MgSO$_4$ sourcing)

• Pakistan
  – Start date: 18 January 2015

• India
  – Start date: 1 November 2014
IPD meta-analysis
≈87,000 pregnant women

- Sindh Province, Pakistan
- Karnataka State, India
- Ogun State, Nigeria
- Maputo & Gaza Provinces, Mozambique
Treatment
the Gynuity Health Projects Oral Antihypertensive trial
PI: Hillary Bracken
Gynuity HP oral antihypertensive trial

- **Site**
  - Nagpur, India

- **Individual patient open-label RCT for women with severe pregnancy hypertension**

- **Pilot phase (dose finding) & Definitive phase**
  - Comparing:
    - Oral nifedipine (10mg)
    - Oral labetalol (200mg)
    - Oral methyldopa (1000mg)

- **1st outcome**
  - BP within the target range at 6h without an adverse outcome
Nifedipine (sBP)

*Note: Case 2 received a second additional antihypertensive

Treatment goal (130-150 mmHg systolic)
Labetalol (sBP)

Treatment goal (130-150 mmHg systolic)
Methyldopa (sBP)

*Note: 5 cases (#12, 14, 15, 29, 26) received a second additional antihypertensive

Treatment goal (130-150 mmHg systolic)
Gynuity HP oral antihypertensive trial

• Definitive trial – approvals granted in January 2015
  – Drug Controller General of India
  – ICMR

• Recruitment to start this month

• Target recruitment: 671 women
  – nifedipine: 298 women
  – labetalol: 298 women
  – methyldopa: 75 women

• 1⁰ outcome
  – Successful outcome will be considered blood pressure that reaches the target (defined as sBP 130-150mmHg and dBP 80-100 mmHg) at 6h without an adverse outcome
  • Adverse outcomes include:
    – Hypotension (sBP <120mmHg and/or dBP <70mmHg and fetal compromise)
    – Caesarean section for fetal distress
    – Severe headache
    – Severe headache requiring discontinuation of drug
    – Eclampsia
Global Pregnancy Collaboration
PI: Jim Roberts

• A consortium of 35 academic groups to advance the understanding and to improve care of pre-eclampsia and other adverse pregnancy outcomes
  – Risk assessment
  – Prevention
  – Inform appropriate research strategies

• Approach used extensively in cancer and cardiovascular research
  – Bring together groups with data and biological samples
  – Pool resources
  – Allows questions to be answered that could be done in no other way

• More from Jim later ...
Knowledge translation

PI: Matthews Mathai

- WHO recommendations
  - Published 2011

- Preeclampsia Foundation
  - CEO, Eleni Tsigas
  - Support the Foundation’s mandate, particularly outreach to women, families and clinicians in LMICs
Use 2014 SOGC HDP guidelines as basis for GLOWM textbook

- Adapted from PPH textbook approach
- Broaden recommendations for LMICs
- Add content to increase LMIC relevance
- Use CLIP set of images
- CLIP wallchart will be produced by Sapiens/GLOWM – and modified for the textbook if found useful
- Include material from other recent evidence-based guidelines
  - WHO, NICE, ACOG, NVOG
- Free to purchasers in LMICs
Long-term goals

That the component studies of the PRE-EMPT initiative, and their follow-up activities, prove effective, and reduce the burden of

- Life-ending
- Life-altering (e.g., stroke)
- Life-threatening (e.g., sepsis)

complications that make the HDP, and the hypotensive disorders of pregnancy, so important
Acknowledgements
Thanks

Weebale Nnyo

Obrigado

Enkosi

Gracias

Mubrani

Kani Mambo

Vinaka vaka levu