Pre-eclampsia and HIV

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Background

- HIV + hypertensive diseases - important conditions
- Both related to maternal and perinatal morbidity and mortality

*Saving mothers 2012; Hall et al., 2008; Taliep et al., 2010*

- Pre-eclampsia (PE) & HIV exact a heavy toll on mothers and their babies in SA
Etiology of pre-eclampsia is multifactorial:

- **Immune system** plays a key role (Robertson et al., 2003)
- Immune tolerance to pregnancy induced:
  - paternal antigens (semen) & female genital tract sexual intercourse
- But - if new partner (primipaternity), with insufficient duration of exposure to sperm antigens, risk of pre-eclampsia increases (cond; AssRep) (Verwoerd et al., 2002)
Background

• Pregnancy: up-regulation of the immune response

  Redman 1999

• Pre-eclampsia - excessive generalized maternal inflammatory response

• Thus when conditions of acquired/induced immune deficiency are present (HIV), immune hyper reactivity may be inhibited - ?
  lower incidence of pre-eclampsia?
Studies

• Context NB
  Rapid developments in HIV field:
  screening (selective – universal)
  diagnosis (+ clinical - CD$_4$ – viral load)
  Mx (intra-partum – T$_3$ AZT – HAART)

• Chronological approach
• HIV+ pregnant women

HIV+ women on no ARVs, significantly lower rate of pre-eclampsia than HIV+ women on ARV Rx \( (p < 0.01) \)

Wimalasundera et al., 2002

• Letter to editor: “HAART causes pre-eclampsia - direct toxic effect on the liver”

Mawson 2003

• Message:

Untreated HIV+ women may have less pre-eclampsia
Mattar et al., 2004

• Retrospective study – Brazil

• 123 HIV+ women on monotherapy or HAART compared to 1708 healthy controls

• Median CD4 study group was 531 (200-1378)

• Significantly lower rate of pre-eclampsia amongst HIV positive (Rx) women compared to controls 0.8% vs. 10.6%, p < 0.01

• Data differ from those of Wimalasundera – message

Even HIV+ women on Rx may have less pre-eclampsia

Perhaps ARV therapy promotes differential restoration of immune function?
Frank et al., 2004

- Adequately powered study - investigated whether untreated HIV+ pregnant women have lower rate PE/eclampsia than HIV-
- In contrast to Wimalasundera, Frank et al., found no reduction in rate PE in untreated HIV+ women
- However no indication of immune competence (only 13x CD₄ counts)
Frank et al., 2004

- Lack of significant difference amongst the two groups: explained by women having higher CD$_4$ counts or lower viral loads
- General: Rx must be taken into account - combination Rx - greater suppression of viral replication & allows greater/longer recovery of immune function than monotherapy
- Message: Does HIV status make any difference?
• Studied general population & an HIV infected population before/after introduction of HAART

• Multivariate analysis: HIV+ Rx with HAART prior to pregnancy associated with significantly higher risk for pre-eclampsia and fetal death

• Known that the toxic effects of antiretrovirals may mimic pre-eclampsia (RCOG Guideline, 2004)

• Message: Here the risk of PE had not just returned to baseline with Rx but had actually increased
• Case-control study - incidence PE did not differ significantly in HIV+ and HIV- women Boer et al., 2007

• Review: results conflicting - studies small/retrospective
  - proposed powered prospective study Hall, 2007
Moving from association to cause

- **Temporality**: predictor HIV occurs before PE ✔
- **Biologic plausibility**: makes biologic sense ✔
- **Consistency**: uncertain due to study quality ?
• Syst. Rev. & meta-analysis Conde-Agudelo et al., 2008

• **Title:** “Maternal infection and risk of pre-eclampsia”

  x7 studies: no association HIV infection & PE

• Although more IUDs in HIV+ preg., evidence - HAART has sig. increased live birth rate Sharma et al., 2007

• **Report:** preg. outcomes 10 women - perinatally acquired HIV. PE: 2nd most common complication (21%) in their pregnancies Williams et al., 2009
Studies 2012

• Small, case-control study where HIV infected women received HAART, found no association with pre-eclampsia ~ Boer et al., 2007 Boyajian et al., 2012

• A retrospective study (SA): significantly fewer HIV+ women developed pre-eclampsia (p = 0.001, OR 0.62 95% CI 0.47-0.82) but provided no data on the immune status Kalumba et al., 2012
• Immune status (deficiency) argument:
direct/surrogate markers of immune competence e.g. CD$_4$ lymphocyte count, viral load - explain differences in incidence of immune mediated disease
• This information has been lacking in most studies
• Botswana: pre-HAART viral load (> 100 000 copies) - predicted PE in women starting HAART in preg.
  (p = 0.004; OR 5.8 95% CI 1.8-19.4)
Hall et al., 2014

- Determine whether PE & gestational hypertension are less common in HIV infected women
- Powered, prospective cohort study - Paarl Hospital
- HIV negative & positive women without chronic renal or chronic HT - continuously recruited
- During study period HIV+ cases received either mono- or triple (HAART) antiretroviral therapy
Hall et al., 2014

- Routine clinical mx performed
  - files evaluated again after delivery
  - development of hypertensive disease - pregnancy
- Large: 2266 women

- Significantly fewer cases of pre-eclampsia in HIV+
  Same for gestational HT

Results were confirmed - multiple logistic regression

\[(p < 0.01, \text{OR} 0.46; 95\% \text{ CI} 0.28 – 0.76)\]
• Interesting: incidence of PE in HIV+ women did not differ using CD4 count threshold = 350 cells/mm$^3$.
• Could be due to: threshold itself, multifactorial etiology of PE, stage of disease and/or…
• Therapeutic approaches
  HAART - greater suppression of viral replication &
            - longer recovery of immune function
            than monotherapy
Discussion

- Final word?
- Consistency
- No - ? systematic review
Evidence from our large study supports the finding that pre-eclampsia and gestational hypertension are less common in HIV infected women being managed with mono- or triple anti-retroviral therapy.
Future?

- More women onto HAART before/during pregnancy
- Different HAART regimens continuously being refined
- Future studies should provide comprehensive details on immune status and viral loads
Thank you