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The Impact of Maternal HIV Infection on Placental and Neonatal Immunology among Children HIV-Exposed and Uninfected (CHEU)

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No conflicts to declare
Outline

• The problems in infants associated with HIV/ARV drug exposure
  – Impact of ARV timing on placenta pathology
• A focus on immunity in the placenta, cord blood and birth
  – Macrophages
  – T regulatory cells and responses to BCG
Evidence for ARV Treatment & adverse birth outcomes in Africa


• ARV-treated maternal HIV infection: ↑ Pre-term deliveries Malaba et al 2017

• ARV before conception: ↑ preterm or very preterm, low-birthweight. Uthman et al 2017
Is there a breakdown of maternal-fetal tolerance?

- Uterine overdistension
- Decidual senescence
- Vascular disorders
- Infection
- Decline in progesterone action
- Cervical disease
- Stress
- Unknown
- Breakdown of maternal-fetal tolerance

Vause, and Johnston 2000
Tolerance is an immune balancing act
Is the timing of ARV exposure sparing on the placenta?

tenofovir, emtricitabine and efavirenz
Cohort of HIV infected pregnant women in Gugulethu, Cape Town, South Africa.

Stable ART (n=47)

- Risk of preterm birth or small for gestational age delivery?

Placentas collected at delivery
- Fixed in 10% Formalin

Macroscopic Inspection
- Basal plate weight
- Cord length
- Cord insertion

Histopathology
- Chorioamnionitis (Maternal inflammation)
- Cord vessel vasculitis (Fetal inflammation)
- Focal infarction
- Meconium exposure

Initiating ART (n=64)
- 15 weeks gestation
- Risk of preterm birth or small for gestational age delivery?

Marie-Louise Newell, Soton, UK
Landon Myer, UCT
Thoko Malaba, UCT
Histology of the placenta
Our findings..1

Commencing ARV before pregnancy or during gestation had no significant effect on placenta pathology.
But......our findings..2

<table>
<thead>
<tr>
<th></th>
<th>pre-term</th>
<th>SGA</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Focal infarct</td>
<td>5-fold trend</td>
<td>0.06</td>
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<tr>
<td>Prolonged meconium exposure</td>
<td>5-fold trend</td>
<td>0.08</td>
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<tr>
<td>10g lower basal plate weight</td>
<td>5-fold</td>
<td>10% increase</td>
<td>0.0008</td>
</tr>
<tr>
<td>1 cm displaced cord insertion</td>
<td>4% increase</td>
<td></td>
<td>0.01</td>
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Placentas with a displaced cord: reduced transport efficiency and a smaller birth weight (Yampolsky et al 2009)
Adverse birth outcomes are driven primarily by abnormalities in the placenta which do not appear to be associated with when a tenofovir, emtricitabine and efavirenz regimen is provided.
Look at the immunology of the placenta in more depth
The complexities of immune tolerance between mother and fetus

Decidua membranes

Fetal placenta

Classically activated inflammatory

IRF-5

M1 → IL-12

IFN-γ/LPS

IL-4/IL-13

CD163, CD206, CD209

Alternatively-activated regulatory

tolerance

Maternal Side

Decidual macrophages

Hofbauer cells

Fetal Side

inflammation

Does the timing of ARV disrupt the balance of M1 (pro-inflammatory) and M2 (regulatory) macrophages at the maternal-fetal interface?
Taking apart the placenta: decidua and villous tissue

Xu et al. (2015). Isolation of leukocytes from the human maternal-fetal interface. J. Vis Exp
M2 (CD163) staining of the placenta

Villous Tissue  Decidua Basalis  Decidua Parietalis

CD163

Stable ARV (pre-conception)

Initiating ARV (15-18 wks gest)

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ARV timing has no impact on macrophage distribution

Michael Zulu, PhD
What about T cells in the placenta?

T regulatory cells

Inflammatory T cells

Inflammation

Tolerance
T cells

• Two broad types: CD4 and CD8 T cells
• CD4 – different populations: Th1, Th2 ........ etc  .... Treg cells
  – Inflammatory CD4 cells
  – Regulatory CD4 cells
• CD8 – killing cells and protect against viral infections
The placental membranes mirror HIV infected maternal immunity

CD4+

CD3+CD4+ % (DP)

parietalis

basalis

villous tissue

Decidua tissue

P<0.0001

P=0.62

CD8+

CD3+CD8+ % (DP)

parietalis

basalis

villous tissue

Decidua tissue

P=0.0001

P=0.001

P=0.004

Nadia Ikumi

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Maternal viral load at enrolment before ARV impacts on decidual-resident T cells at delivery (when virally suppressed)

A

\[ R^2=0.3; P=0.007 \]

B

\[ R^2=0.4; P=0.002 \]
Villous tissue has less Treg cells in HIV exposed placentas

Nadia Ikumi
Walk out the door messages

• Maternal VL prior to ARV treatment has durable impact on tissue-resident T cells in the decidua membranes of the PL

• Highly Immunosuppressive Treg cells in the villous tissue (fetal placenta) is lower in HIV exposed PL

• The Treg cell constituents in cord blood are different from the PL
CHEU have low Treg cells at birth and altered immune response to BCG at 1 week.
The evidence so far……

- Maternal ARV (non-PI containing) timing appears sparing on placental pathology.
- Macrophage populations appear NOT disrupted between ARV groups.
- T cell populations in the placental membranes are affected by HIV exposure, even when the mother is virally suppressed.
- Treg populations in the cord blood are distinct from those found in villous tissue, which differs in the HIV exposed PL.
- CHEU are born with lower suppressive Treg cells and different CD4 T cell response to BCG.

**CHEU are born with different immune profiles which likely reflect events in the placenta.**
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