Angiogenesis and Adverse Pregnancy Outcomes in Women with HIV: The AAPH study

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and the AAPH team

Women and HIV Workshop
Jan 15, 2013

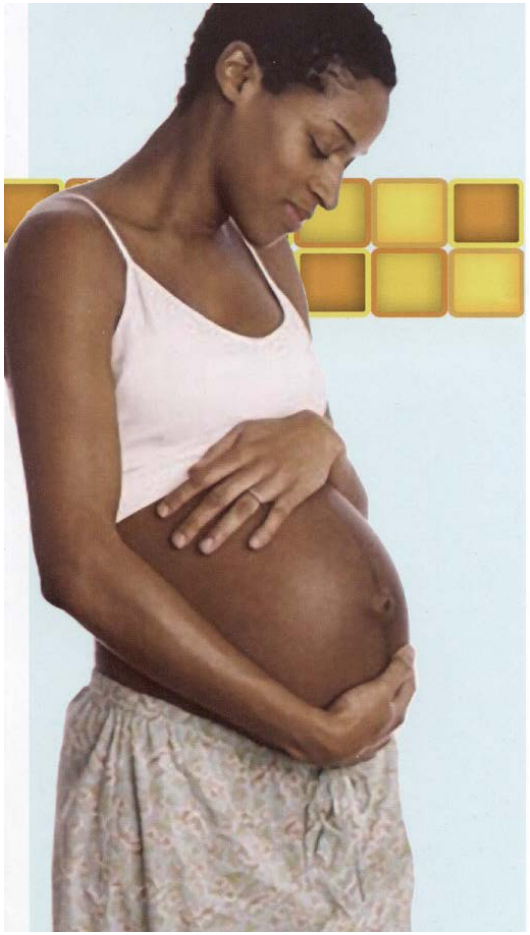
HIV and pregnancy

- Women account for 30% of all HIV infections in Ontario, 20% in Canada, 40% worldwide, 50% in the US
- Many of these women are of childbearing age and are considering pregnancy
- MTCT has been reduced dramatically with cART

HIV-positive women have more adverse pregnancy outcomes than uninfected women

- Spontaneous abortion
- Fetal growth restriction
- Pre-term delivery
- Pre-eclampsia

cART may contribute to the development of adverse pregnancy outcomes



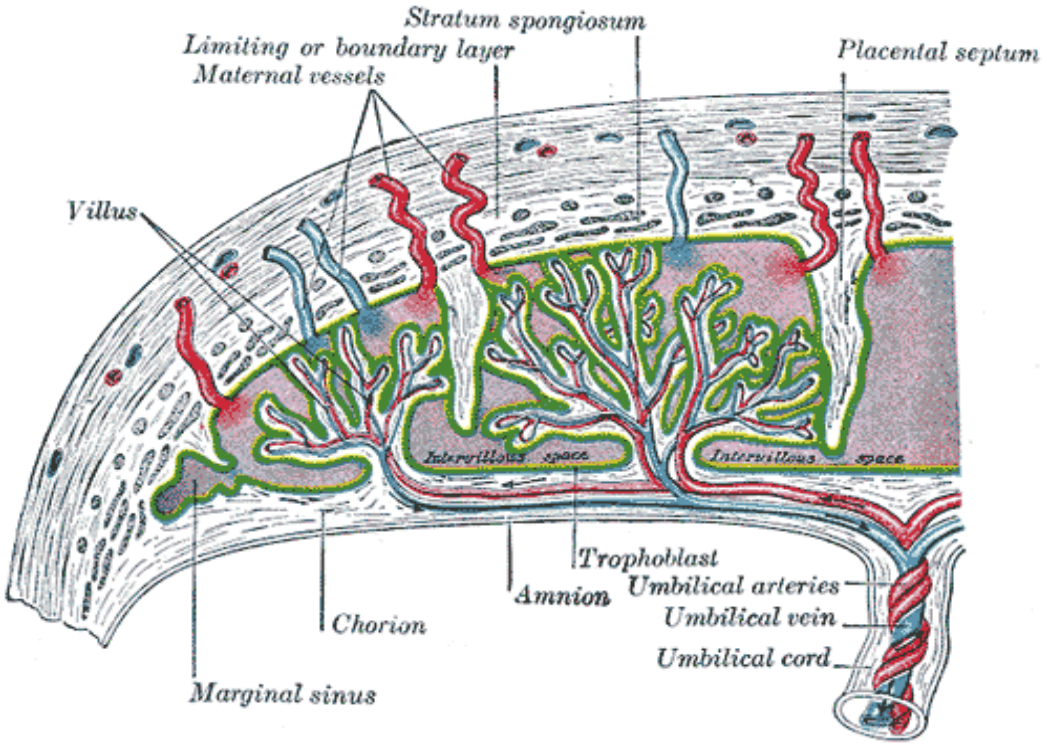
- cART associated with greater incidence of adverse outcome
- Protease inhibitors in particular associated with increased risk
  - Randomised trial, combivir plus either lopinavir/rit (PI) or abacavir (NRTI)
    - 2 fold increase in pre-term delivery in the PI group

Why do HIV+ women experience more adverse events in pregnancy?

What are the mechanisms underlying these adverse events?

A healthy placenta is important to the developing fetus.

Photo taken without permission from the Montreal museum of contemporary art.



Provides nutrients, oxygen, waste removal

Angiogenesis

- Proper angiogenesis is needed for
  - optimal formation of the maternal and fetal vasculature
  - optimal function of the placenta
  - for pregnancy success
- A balance between pro and anti-angiogenic factors is required

Anti-angiogenic state = bad pregnancy outcome

- An “anti-angiogenic state” implicated as a mechanism of disease in pre-eclampsia, pre-term labour, fetal growth restriction, and spontaneous abortion

- altered patterns of the angiogenic factors PlGF and VEGF and the anti-angiogenic factors sEng and sFlt-1 could predict an adverse outcome
  - Roche just released a sFlt-1/PlGF test for early detection of pre-eclampsia

Could alterations in the angiogenic balance caused by either HIV or cART contribute to increased pregnancy complications?

Angiogenesis and Adverse Pregnancy Outcomes in Women with HIV - study

- Dr. Mona Loutfy
  - HIV specialist (Maple Leaf Medical)
- Dr. Mark Yudin
  - obstetrician (St. Michael's Hospital)
- Dr. Kellie Murphy
  - MFM (Mount Sinai Hospital)
- Dr. Sharon Walmsley
  - HIV specialist (Toronto General Hospital)
- Dr. Anita Rachlis
  - HIV specialist (Sunnybrook)
- Logan Kennedy and the IHPREG Team

Overall Hypothesis

- HIV infection and/or cART disrupt the angiogenic balance required for a successful pregnancy and thus contribute to adverse pregnancy outcome in HIV-positive women

Angiogenesis and adverse pregnancy outcomes in women with HIV

- Do levels of angiogenic and anti-angiogenic factors differ between HIV-positive and uninfected women throughout pregnancy?
- Do levels of these factors predict who will develop adverse pregnancy outcomes?
- Is this feasible to do?

Study design

- Longitudinal cohort study
- Pilot sample size 15 HIV+, 15 HIV-
  - Full study: 100 HIV+, 100 HIV-
- Singleton pregnancies
- Recruit in first trimester (as early as possible)
- Blood samples at each prenatal visit – 20mls (serum, EDTA plasma, heparin plasma)
- At delivery: peripheral blood, cord blood, placental blood, placenta sections frozen, placental sections fixed
- Record adverse pregnancy outcomes: Pre-term delivery (less than 37 weeks), SGA (below 10^{th} percentile by gestation age), other adverse events
- Two ultrasounds with Doppler (second and third trimester)
- Medical chart review and questionnaire (relevant demographic and medical history data)

Inclusion/Exclusion Criteria

Inclusion criteria:

- at least 18 years old
- documented HIV infection / HIV uninfected (partner also HIV-negative)
- pregnant
- able to provide consent

Exclusion criteria:

- multiple pregnancy
- chronic hypertension, diabetes, renal disease, autoimmune diseases, collagen vascular disease
- illicit drug use, tobacco use
- morbid obesity
- documented opportunistic infection

Serum/Plasma sample analysis

- Angiogenic factors:
  - VEGF, PlGF, TGFβ, Ang1, Ang2, sFlt-1, sEng, sTie-2
- Complement:
  - C5a, C3a
- Inflammatory factors:
  - TNFα, IFNγ, IL-6, IL-1β, IL-10
- Sex steroids (with Dr. Michael Silverman)
  - progesterone, estrogen, free testosterone, corticotropin-releasing hormone, Sex hormone binding globulin, and hCG
- Drug levels (with Dr. Bill Cameron)

Placenta

- Gross pathology
- Histology

  Vascular morphology:

  - non-branching - mixed - branching
  - Indicator of placenta oxygenation

- Immunohistochemistry

Recruitment so far

- Recruited **50** HIV+ women

St. Michael's Hospital	26
Maple Leaf Clinic	11
Toronto General Hospital	6
Mount Sinai Hospital	6
Sunnybrook HIV Clinic	now recruiting
Biobank (Mount Sinai)	1

- 36 have completed the study

Recruitment so far

- Recruited **11** HIV- women

St. Michael's Hospital	7
Mount Sinai Hospital	3
Biobank	1

Matching on race, age, parity, and BMI

- 3 have completed the study

Our participants

- Race:
  - Black **68.4%**
  - White **15.8%**
  - Asian **10.5%**
  - Hispanic **5.3%**

Our participants

- Income (in thousands):
  - < 20 **20%**
  - 20-40 **40%**
  - 40-60 **6.7%**
  - 60-80 **6.7%**
  - did not answer **26.7%**

Our participants

- Education:
  - high school **42.9%**
  - college **42.9%**
  - undergrad **14.3%**

Our participants

- Maternal age [median (range)]:
  - **31.5 years (21-42)**
- Parity
  - Parity 0 **36.8%**
  - Parity 1 **36.8%**
  - Parity 2 or more **26.3%**
- Previous miscarriage **36.8%**

Delivery data

- Mode of delivery
  - vaginal birth **50.0%**
  - c-section with no labour **29.2%**
  - emergency c-section **20.8%**
- Sex of the baby
  - **51.6%** girls and **48.4%** boys

Delivery data

- Gestational age at delivery
  - Median with range:
    - 39.1 weeks [28 - 41]
  - Geometric mean with 95% CI:
    - 38.03 weeks [36.95 - 39.14]

Drug regimens – backbone

- NRTI backbone regimens used
  - Truvada (tenofovir+emtricitabine) **31.0%**
  - Combivir (AZT+3TC) **27.6%**
  - Kivexa (3TC+Abacavir) **27.6%**
  - Trizivir (AZT+3TC+Abacavir) **6.9%**

Drug regimens – most on a PI containing regimen

- **PI vs. non-PI**
  - PI-containing **72.4%**
  - Non-PI **24.1%**
- **PIs (all ritonavir boosted):**
  - Lopinavir **51.7%**
  - Atazanavir **20.7%**
  - Darunavir **3.4%**
- **Non-PIs**
  - Nevirapine **13.8%**
  - Efavirenz **3.4%**
  - Etravirine **3.4%**
  - Raltegravir **3.4%**

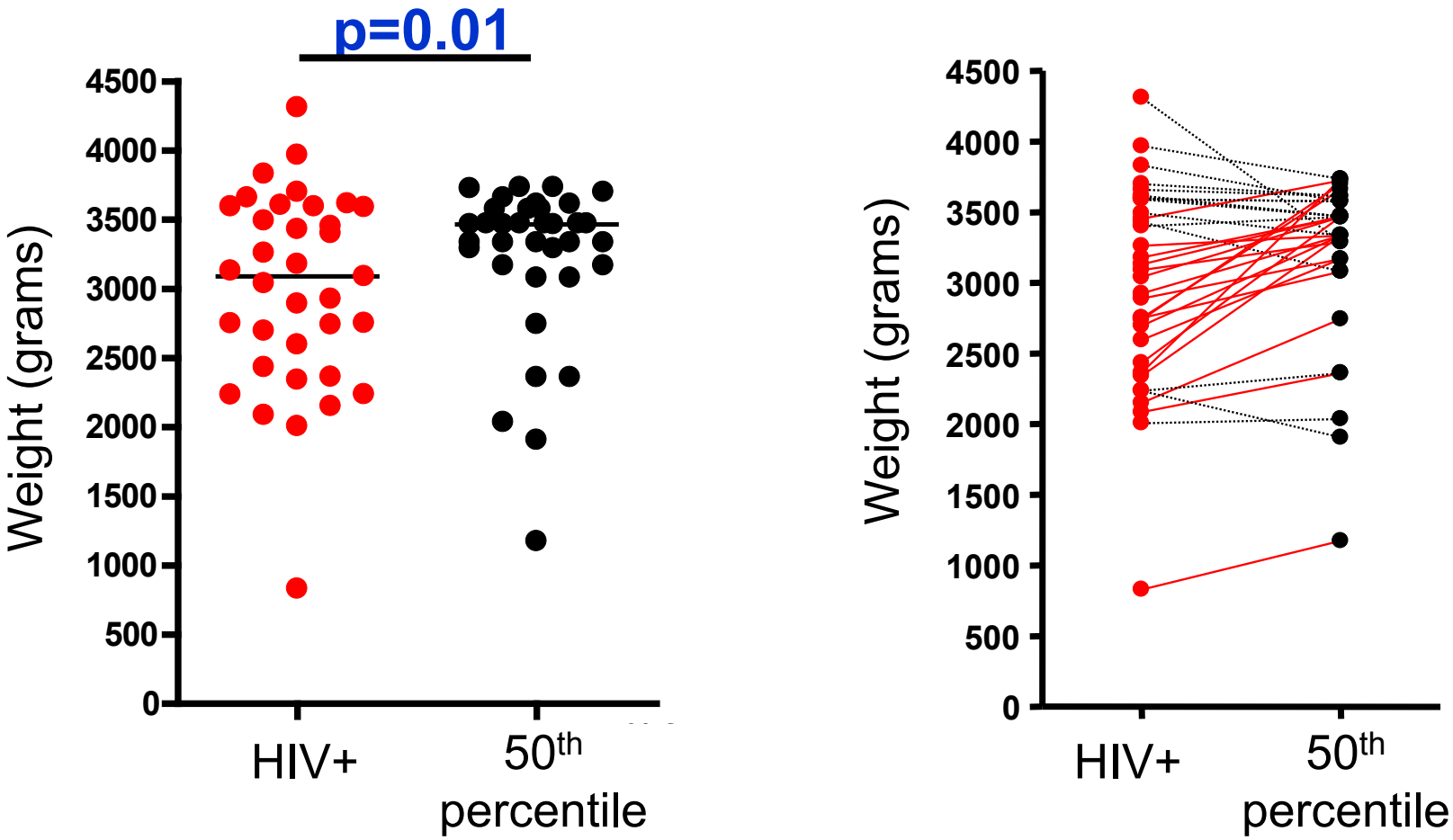
Birth outcomes

- Of 36 HIV+ women that completed the study:
  - 6 pre-term deliveries (28, 32, 33, 34 (2), 36 weeks)
    - **16.7%** – normal 8.1% in Ontario
  - 7 small for gestational age (<10th percentile)
    - **19.4%** – normal 9.3% in Ontario
  - 1 fetal demise at 12 weeks
    - **2.8%**

- **30.5%** rate of either pre-term or SGA

Source Canadian Institute for Health Information for 2010-2011

Birth weight compared to match or the 50th percentile



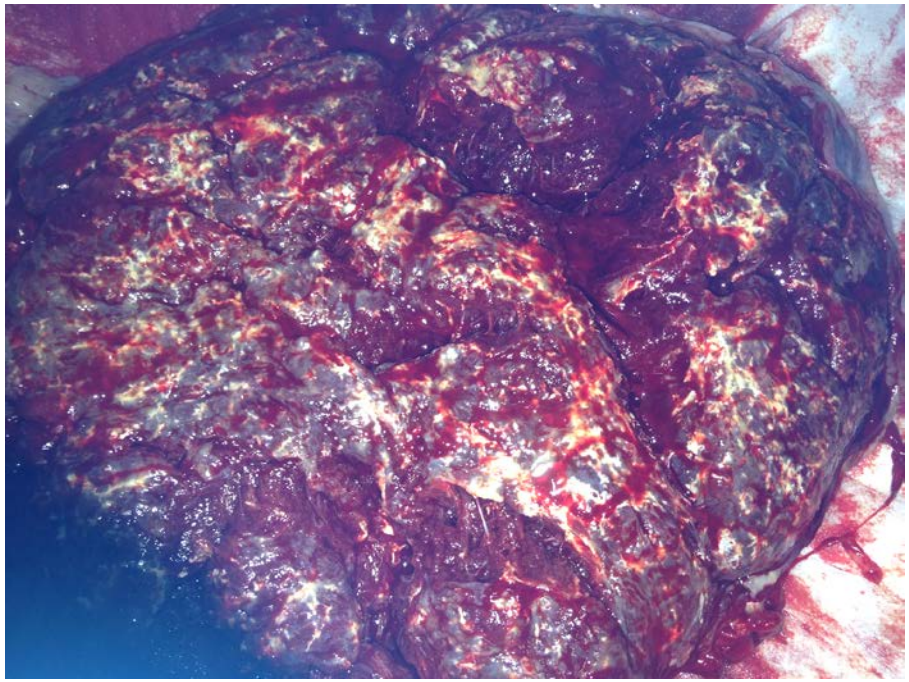
Median wt: **3090** g [2433-3594] vs. **3465** g [3169-3576]

Geometric mean wt: **2893** g [2612-3205] vs. **3144** g [2898-3412]

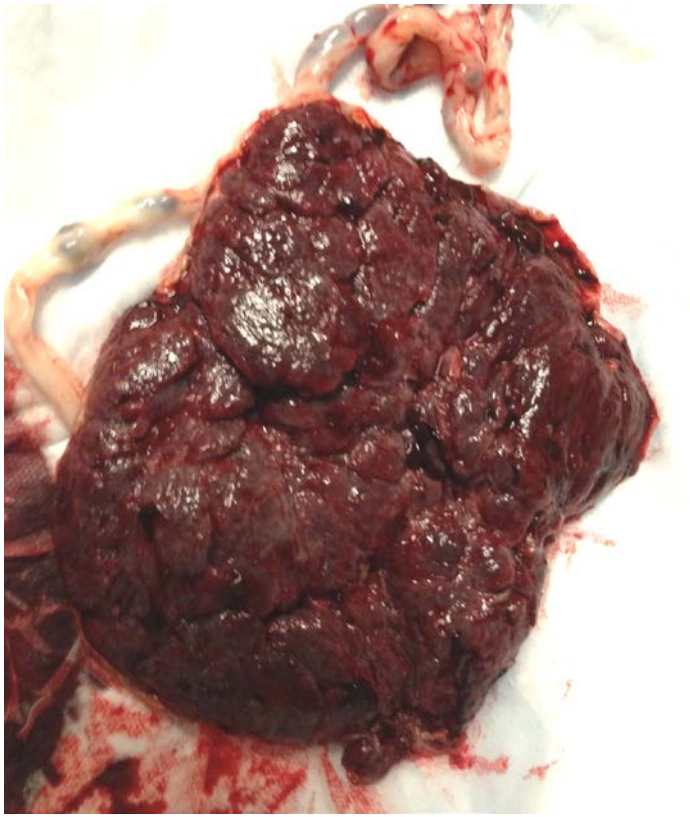
Placenta characteristics

- Pathological findings:
  - Intervillous thrombi
  - Villous immaturity
  - Fibrotic lesions
  - Inflammation
  - Succenturiate lobe (12% – normal rate is 1-5%)
  - Velamentous insertions (20% - normal rate is 1-2%)

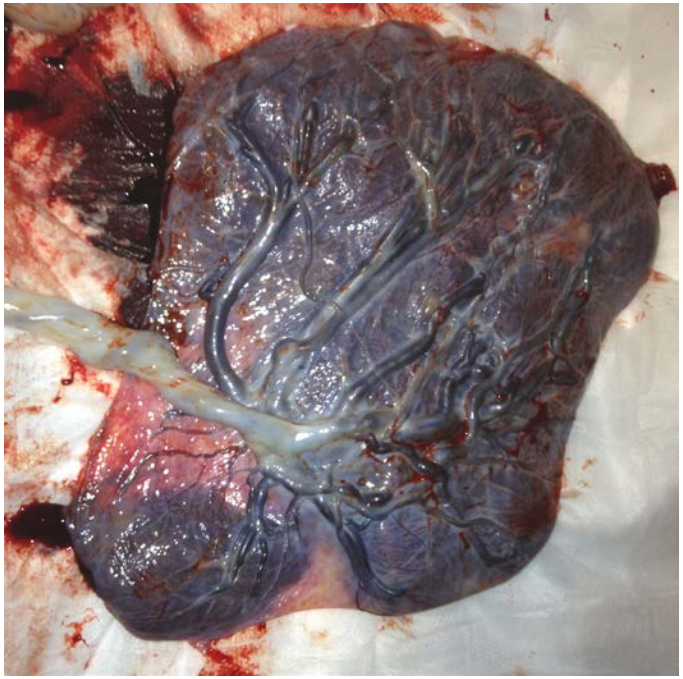
Thick placenta with numerous fibrotic lesions

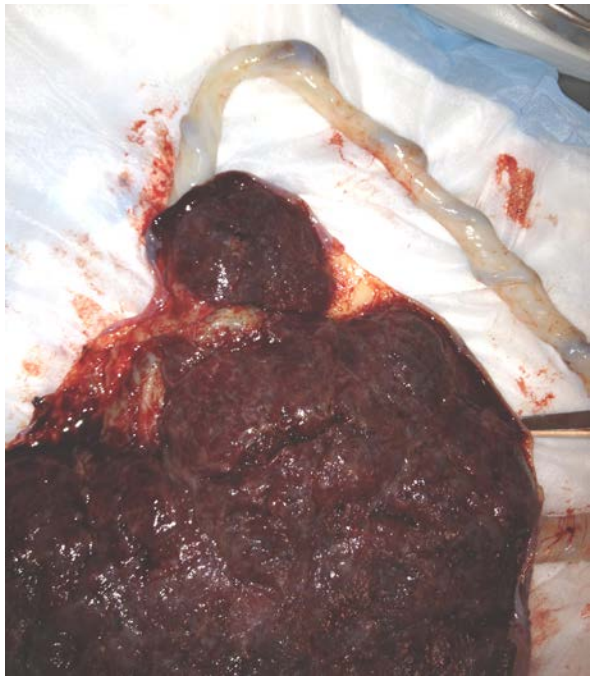


baby <3rd percentile



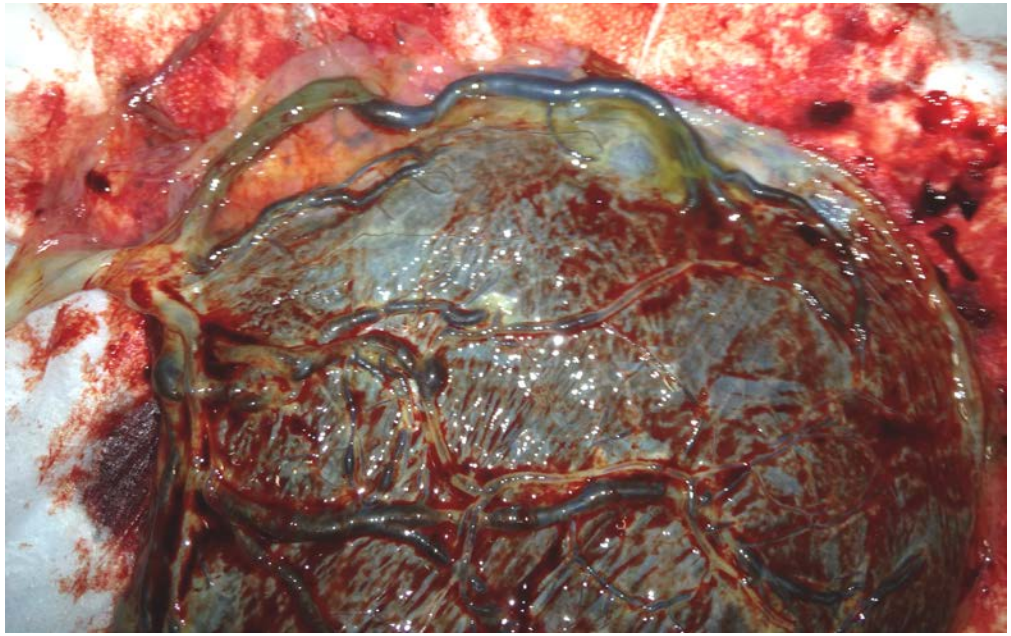
Partial velamentous insertion of the cord with succenturiate lobe with communication fetal vessels





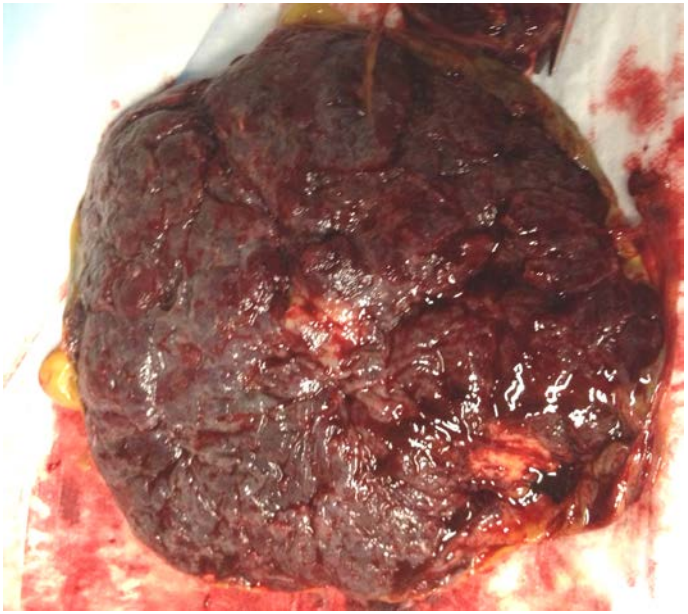
Very small placenta (<10th percentile)
Cord blood hematocrit 72% - may indicate low oxygen
Baby normal weight

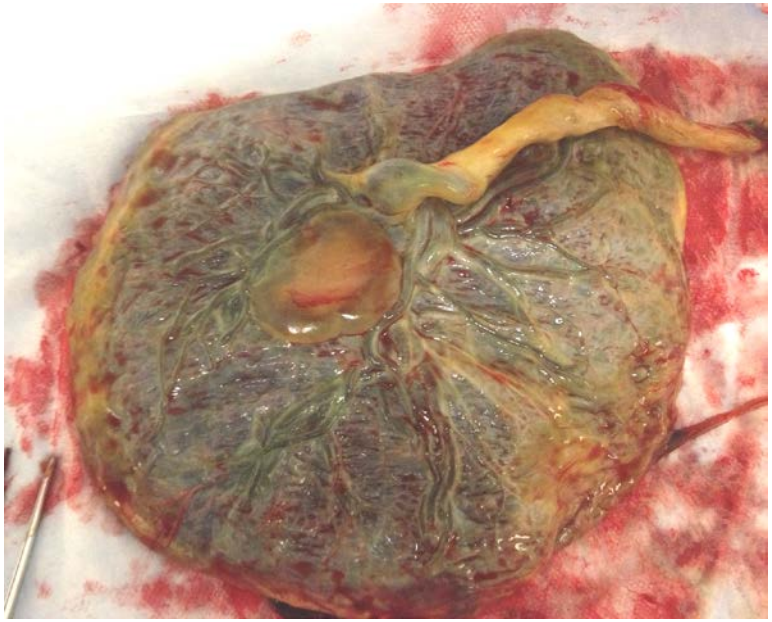
Partial velamentous insertion of the cord



Placenta <10th percentile
SGA infant

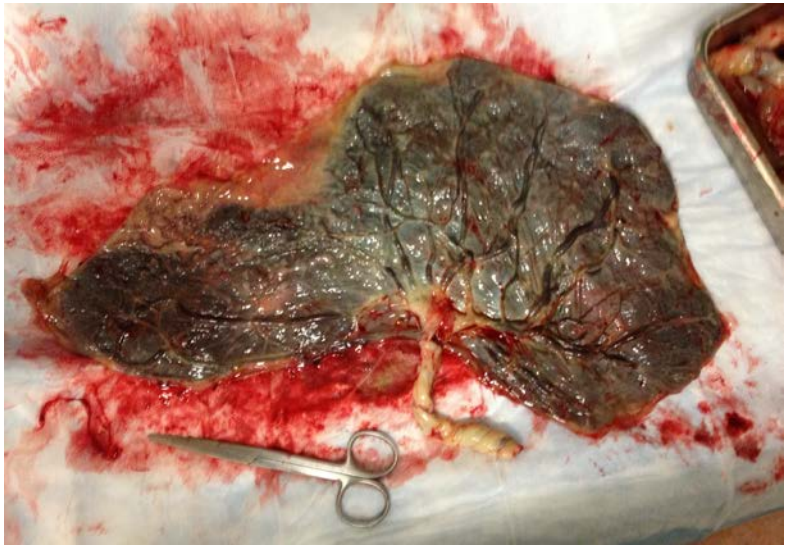
Two infarcts

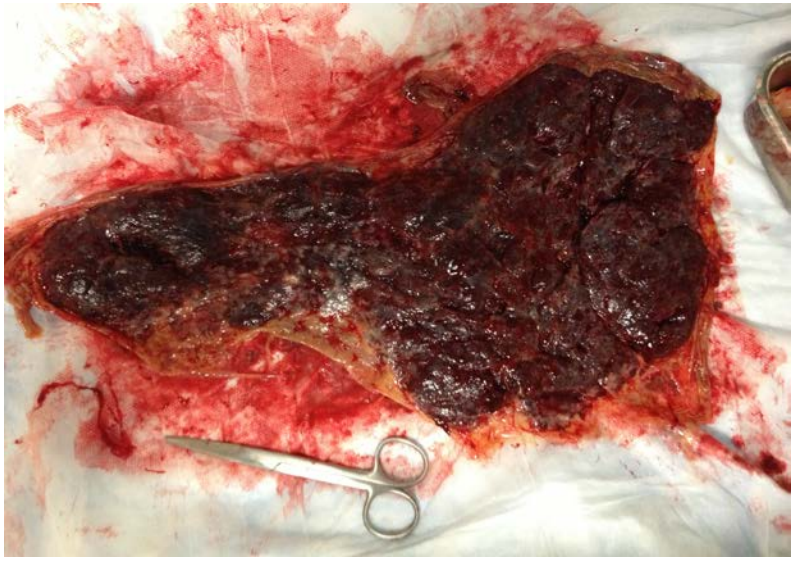




Placenta below 10th percentile
Infant at 10th percentile
Emergency c-section – placenta dysfunction noted

Placenta membranacea – extremely uncommon

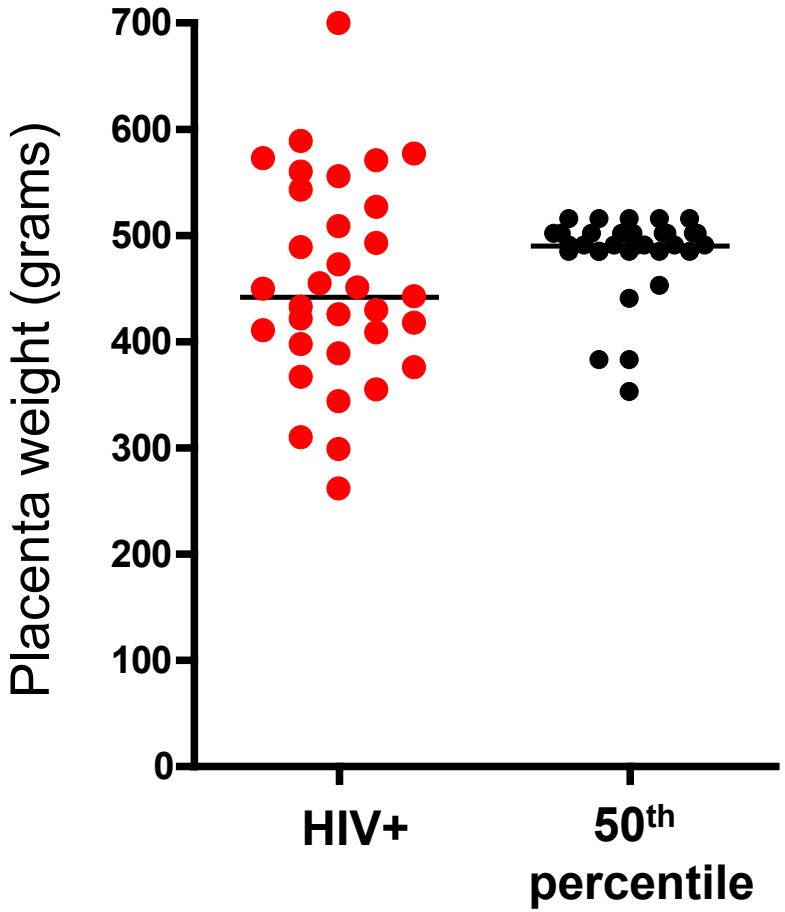




Diffuse placenta: large surface area but very thin

Risks: antepartum hemorrhage, IUGR, miscarriage, fetal demise, placenta previa

HIV+ placenta weight is below the 50th percentile

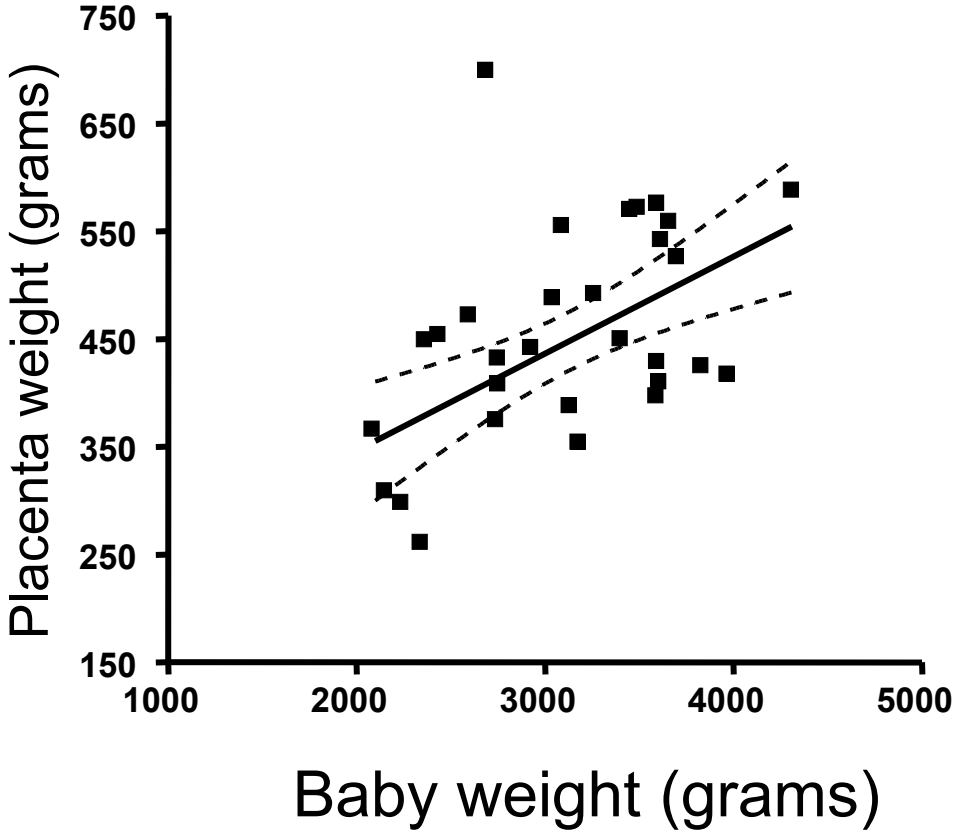


p=0.0356

Mean wt: 443.8g [410.9-479.3] vs. 480.9g [465.8-496.4]

Median wt: 442g [392.5-534.0] vs. 490g [484-501]

Smaller placenta size correlates with smaller infants



r^2=0.3697

p=0.0005

Summary – AAPH study

- Indication that adverse outcomes are high in our HIV+ women
  - High incidence of low birth weight
  - High incidence of placenta abnormalities
  - Must complete recruitment of HIV+ and control arms and analysis

Potential Impact

- Can we use angiogenic factors as biomarkers of pregnancy outcome?
  - Individual, combination, ratio
- Are they potential therapeutic targets?
  - Cancer field very interested in angiogenesis
  - Several inhibitors
- Potential to change treatment protocols for HIV-positive pregnant women – Which are the best ARV to use in pregnancy?

Many Thanks!

- **Eszter Papp** and Ashley DiMeo
- Central Coordinator:
  Logan Kennedy
- Maple Leaf Medical:
  Mona Loutfy
  Roberta Halpenny
- Mount Sinai Hospital:
  Kellie Murphy,
  MJ Martin,
  Sheryl Lynn Hewko,
  Kim Foshay,
  Carolyn Cesta
  Labour and Delivery Staff
- And most of all the women that participate in our study!
- Toronto General Hospital:
  Sharon Walmsley
  Adriana D'Aquila
  Rosemarie Clarke
  Gloria Crowl
- St. Michael's Hospital:
  Mark Yudin
  Leanne De Souza
  Jay McGillivray
  Labour and Delivery staff
- Sunnybrook:
  Anita Rachlis
  Linda Moran
- Michael Silverman
  Charles La Porte
  Stephen Lye
  John Sled

Thank you to our funders!
OHTN operating and JIDA grant
CIHR Catalyst Grant
CIHR Emerging Team Grant