

LOWER PROGESTERONE LEVELS AFTER PROTEASE INHIBITOR EXPOSURE *IN VITRO AND IN VIVO*

A POTENTIAL MECHANISM FOR LOW BIRTH WEIGHT AND
PRETERM DELIVERIES IN HIV-POSITIVE cART
EXPOSED WOMEN



IHPREG
INTERDISCIPLINARY
HIV PREGNANCY
RESEARCH GROUP

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Antiretroviral therapy in pregnancy



Combination therapy (cART) to prevent MTCT

- NRTIs: AZT+3TC
- Protease inhibitors (LPV/r, DRV/r, ATV/r)

Safe for women, no birth defects in babies

BUT

low conception rate, miscarriage,
small babies, pre-term delivery

Mechanism unknown

HIV drugs influence sex steroids

PIs reduce sex steroid hormone levels (contraceptive drugs!)

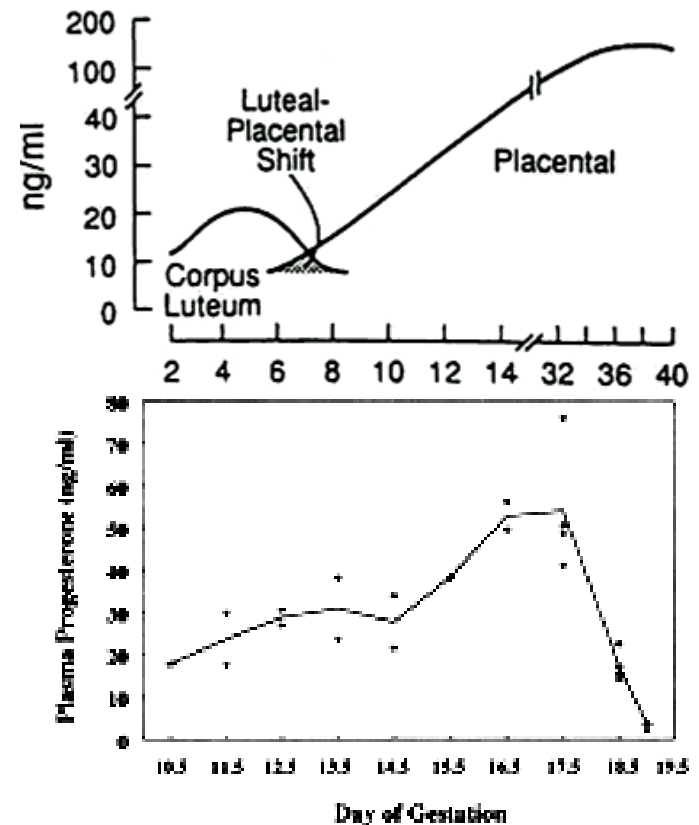
- Aromatase inhibition
- Cholesterol metabolism

Progesterone:

Needed to maintain pregnancy

Synthesis:

- Ovaries (corpus luteum)
- Humans: placenta after week 8



Very low levels: pregnancy loss

Decreased (20%) levels: low birth weight, preterm

Questions

- Does PI-containing cART affect
 - Progesterone levels?
 - Birth outcomes?
 - Is progesterone level change responsible for birth outcomes?

1. Do ARV drugs effect on placental progesterone production?

BeWo (human Chorioblastoma) cells

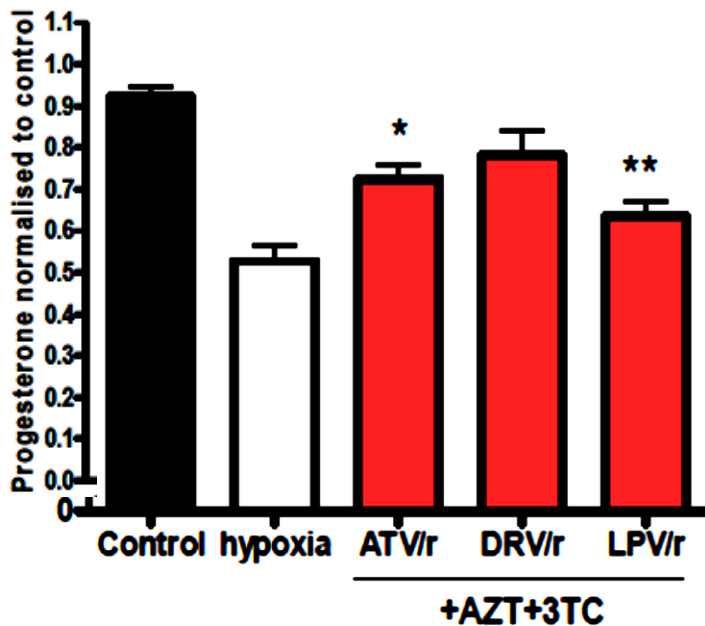
- Model for third trimester placenta
- Produces progesterone

- Exposed to human plasma equivalent levels
 - AZT+3TC (Combivir)
 - LPV+RTV(Kaletra)
 - DRV+RTV (Prezista +Norvir)
 - ATV+RTV (Reyataz+Norvir)
 - Individually and in combination

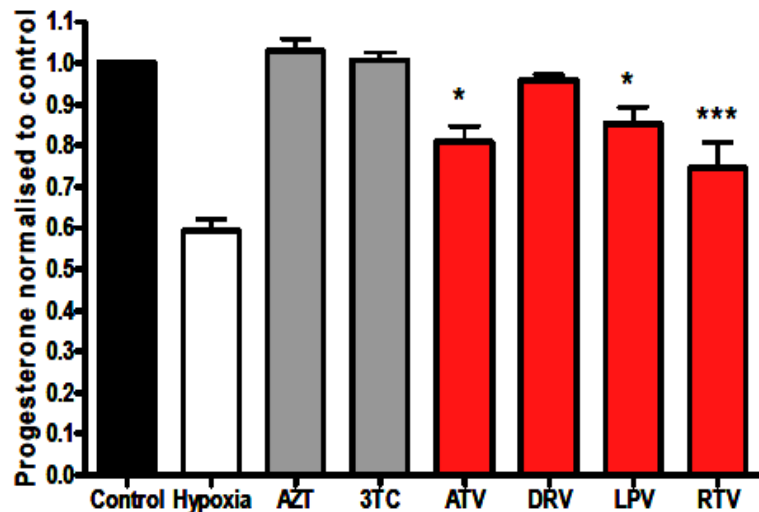
- Positive control: hypoxia (1% oxigen)

PIs inhibit progesterone production in BeWo cells

Combination



Individual drugs



~20% decrease in progesterone production
is clinically significant!

Objective:

- To investigate if cART exposure is associated with progesterone level changes and adverse birth outcomes in a mouse model.

Hypothesis:

- Pregnant mice exposed to cART will have
 - Decrease in progesterone levels
 - More adverse pregnancy outcomes

Do PI-containing cART effect progesterone levels and birth outcomes *in vivo*?

Mouse model:

- C57Bl6 mice
- Pregnant, not infected
- Exposed to human-equivalent doses of cART:
 - Combivir+Kaletra (cART)
 - water control
- Followed throughout gestation
From Day 0: conception - Day 18: term

Outcome measurements

Adverse events in pregnancy

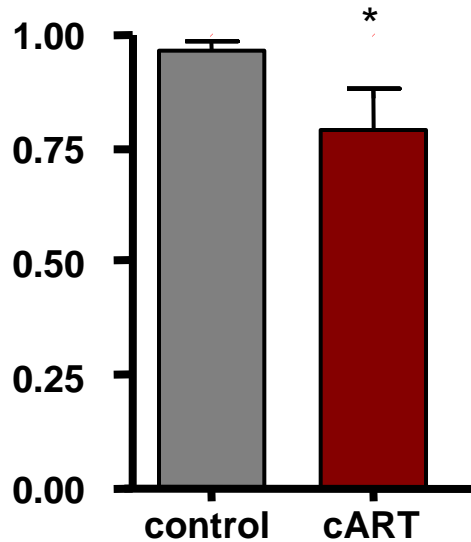
- pregnancy loss
- fetal outcomes: viability, weight
- placental weight: marker of placental development

Progesterone levels in maternal blood (EIA)

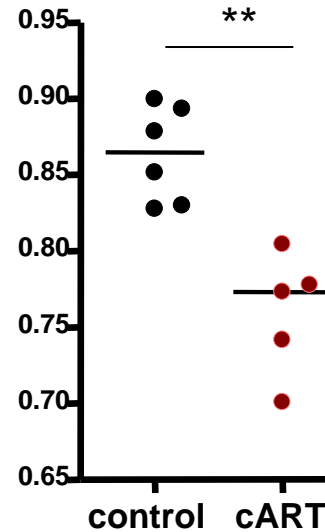
Statistics: ANOVA, Pearson correlation

Adverse pregnancy outcomes; fetal loss, lower fetal and placental weight

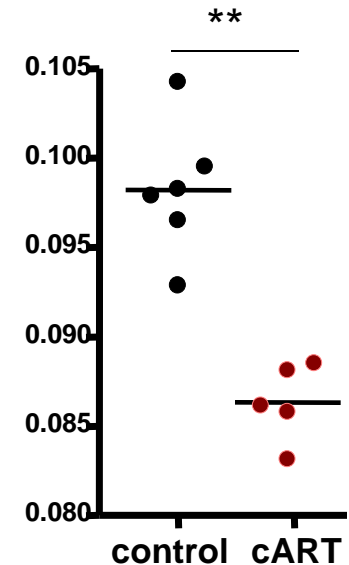
~30% increase in pregnancy loss



Ratio of viable pups

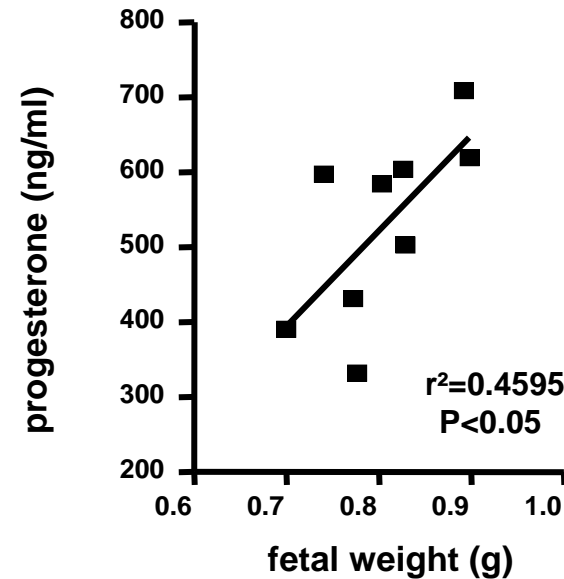
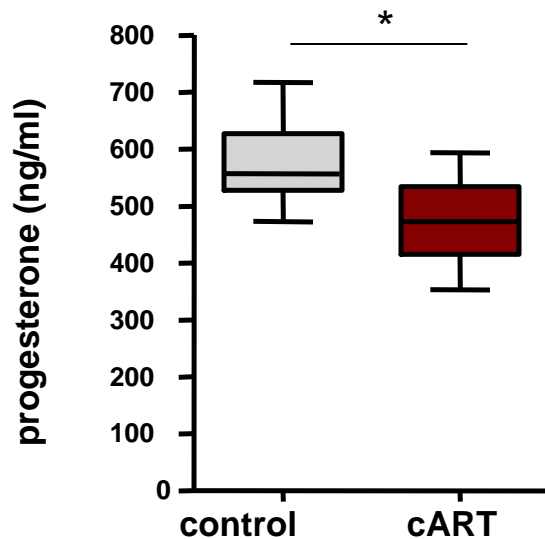


Fetal weight (g)



Placental weight (g)

Lower progesterone levels after cART exposure - correlation with fetal weight



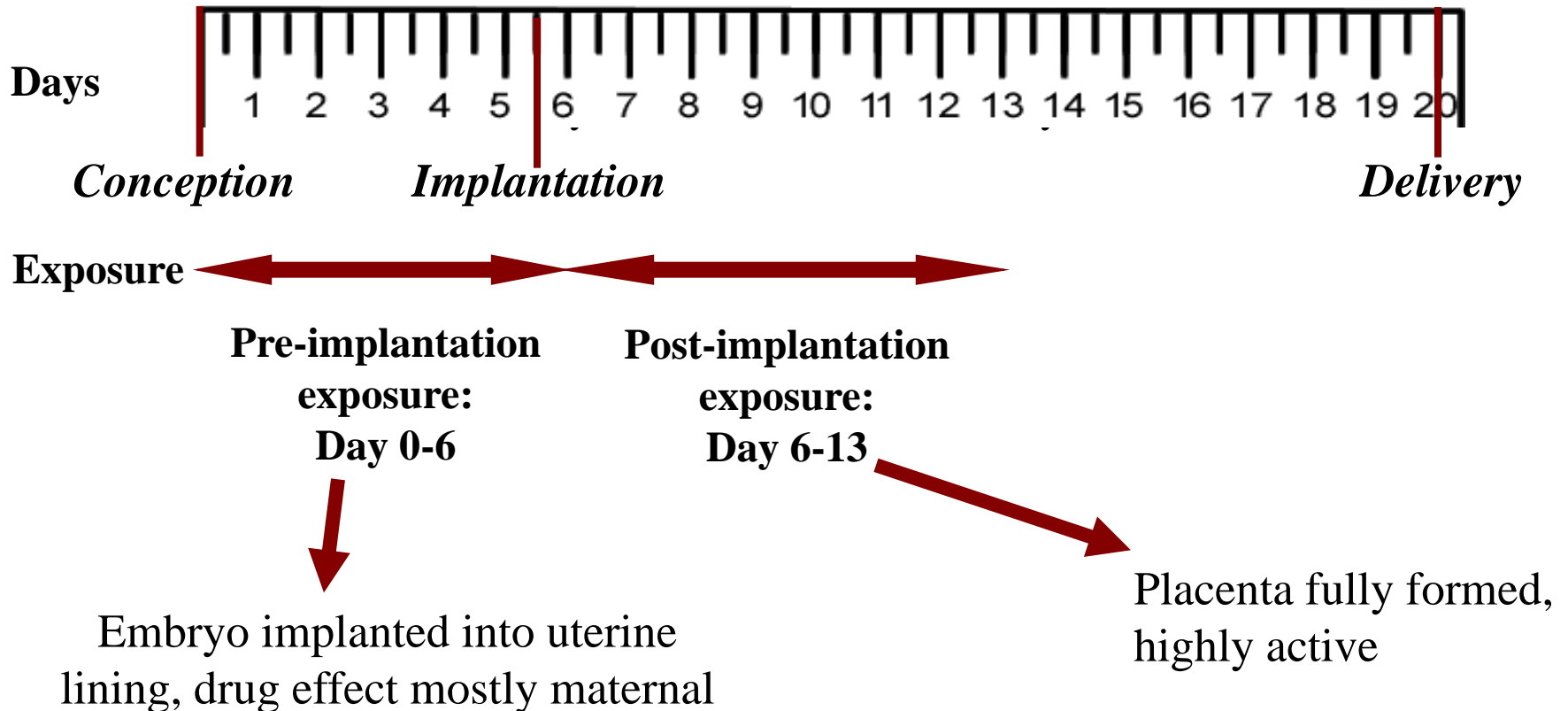
Placental weight decrease –PG independent

**Progesterone decreased, fetal and placental weight decreased
Pregnancy loss and fetal death**

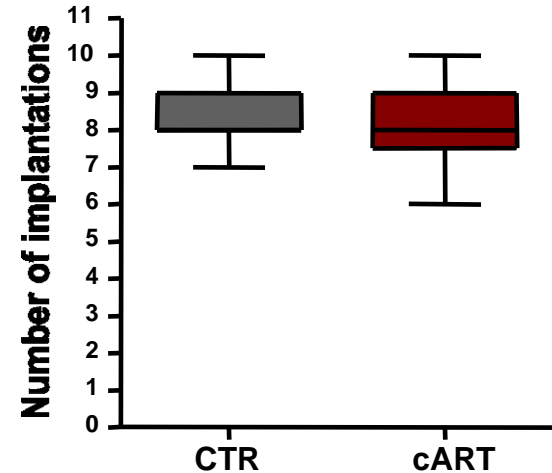
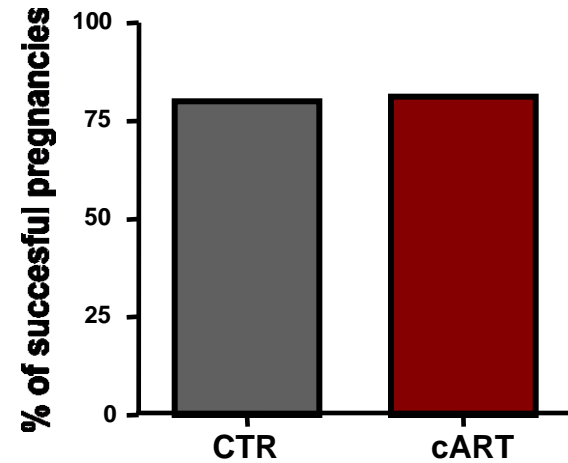
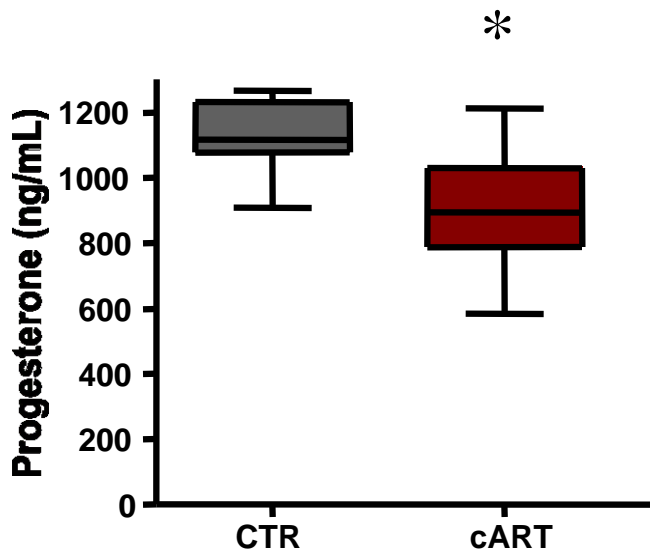
Which gestational stage is more affected?

Low progesterone:

Inhibits implantation and effect on fetal/placental development

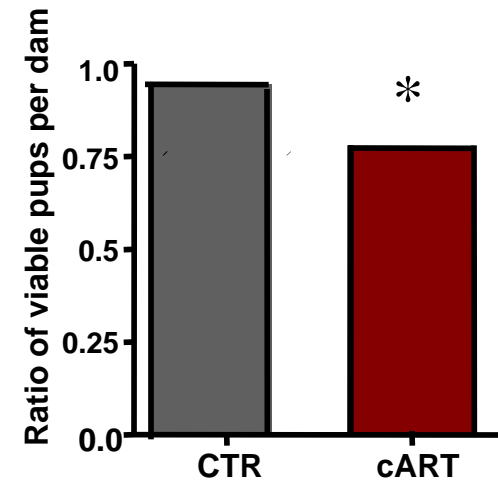
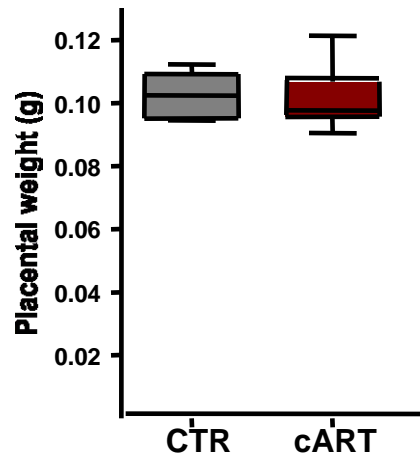
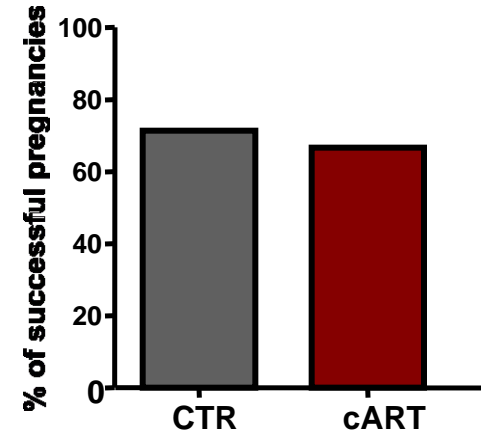
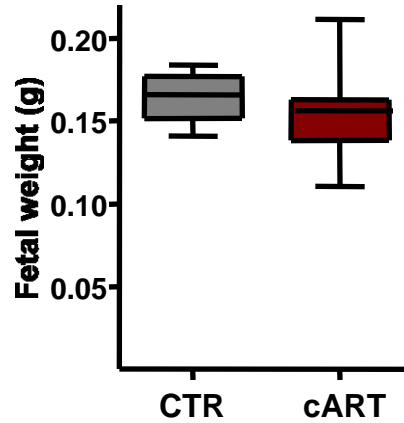
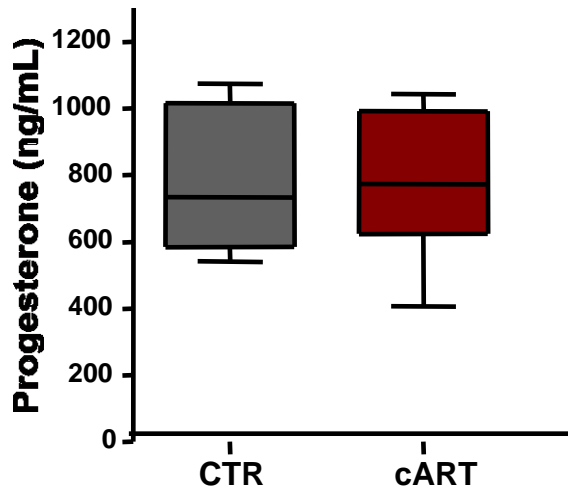


Pre-implantation exposure; Progesterone decreased, implantation unaffected



Quality of embryos?

Post-implantation exposure; Progesterone unaffected, less adverse events



Summary

	Exposure throughout	Pre-implantation exposure	Post implantation exposure
Progesterone decrease	+	+	-
Low fetal weight	+	N/A	-
Low placental weight	+	N/A	-
Fetal death	+	-	+
Pregnancy loss	+	-	-

Correlation of fetal weight with progesterone

PG might regulate fetal weight, placental weight

Fetal demise: progesterone independent?

Future plans

- Possible link of low PG level to small birth weight and pregnancy loss
 - *Progesterone supplementation: rescues low fetal weight, placental weight phenotype*
- Progesterone-independent fetal demise: Placental dysfunction?
 - *Placental development studies; vascular and cellular structure, angiogenic factors*
- Analyze progesterone, birth outcomes in human population
 - *Sample collection ongoing*

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