Progesterone Increases are Associated With HIV Susceptibility Factors in Women

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HIV susceptibility due to progesterone

• Association between HIV risk and exogenous progesterone usage
  • Polis CB and Curtis KM. 2013. *Lancet Infect Dis*
  • Ralph LJ *et al.* 2015. *Lancet Infect Dis*

• Association between SHIV infection and endogenous progesterone levels in macaques
  • Vishwanathan SA *et al.* 2011. *J Acquir Immune Defic Syndr*
  • Kersh EN *et al.* 2014. *J Med Primatol*

• Do increased progesterone levels during the luteal phase increase markers of susceptibility in HIV target cells?
Study Design

• 7 participants scheduled for 5 study visits in a single menstrual cycle
  • Approximately days 0, 7, 10, 14, 21 following menses

• Whole blood collected at each visit

• Plasma:
  • Luminex multiplex assay for Progesterone and Estradiol

• PBMC:
  • Stained with antibodies to CD4, CCR5, CD38
  • Stimulated *ex vivo* for 5 hours in presence of golgi inhibitors
  • Stained for intracellular production of TNFα, IL-2 and IFN-γ
Progesterone rises during the luteal phase

- Women completed 28 total visits
  - 1 woman – 5 visits
  - 5 women – 4 visits
  - 1 woman – 3 visits

- No detectable sustained rise in progesterone in 2 of 7 women (red)
Expression of HIV coreceptor CCR5 increases during the luteal phase

- **CCR5 Expression:**
  - %CD4+ cells expressing CCR5

- Proportion of CD4+ T cells expressing CCR5 increased during the luteal phase of the menstrual cycle

\[ \text{Proportion of CD4+ cells expressing CCR5} \]

\[ \text{Progesterone (ng/mL)} \]

\[ \text{CCR5 (% positive)} \]

\[ p = 0.012 \]
Expression of cell activation markers on HIV target cells increases during the luteal phase

- **CD38 Expression:**
  - %CD4+ cells expressing CD38

- Proportion of CD4+ T cells expressing CD38 increased in 6 of 7 women during the luteal phase of the menstrual cycle

\[ p = \text{n.s.} \]
Responsiveness of HIV target cells to stimulation increases during the luteal phase

- TNFα Expression: %CD4+ cells expressing TNFα following 5 hour ex vivo stimulation

- Proportion of CD4+ T cells able to respond to stimulation increased during the luteal phase of the menstrual cycle
Expression of HIV coreceptor CCR5 increases with increased progesterone

- Proportion of CD4+ T cells expressing CCR5 increased in association with increased progesterone concentrations
Responsiveness of HIV target cells increases with increased progesterone

- Proportion of CD4+ T cells able to respond to ex vivo stimulation increased in association with increased progesterone concentrations
Conclusions

• The proportion of CD4+ T cells expressing the HIV coreceptor CCR5 and responding to ex vivo stimulation increased during the luteal phase of the menstrual cycle in association with increased plasma progesterone

• HIV target cells in the blood are primed to support viral replication when progesterone concentrations rise during the luteal phase of the menstrual cycle

• Future studies will need to examine changes at the surface of the genital mucosa in the presence of progesterone to help identify risks for progestin-based contraceptives
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