Hormonal Contraceptive Use is Associated with Elevated Innate Immune Effector Molecules in Cervicovaginal Secretions of HIV-1-uninfected Women

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Abstract

BACKGROUND. The injectable hormonal contraceptive depot medroxyprogesterone acetate (DMPA) may increase risk of HIV-1 acquisition. Sex hormones may affect the cationic polypeptides that constitute an important arm of the innate immune response in the cervicovaginal mucosa. We assessed cationic polypeptide levels in relation to DMPA use.

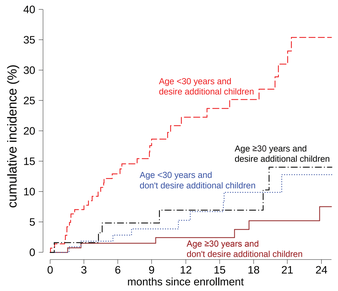
METHODS. HIV-1-uninfected women were recruited from among couples testing for HIV in Nairobi, Kenya. Cervicovaginal secretion (CVS) samples were collected and cationic polypeptide concentrations were measured by enzyme-linked immunosorbent assays (ELISA). Levels of cationic polypeptides in CVS were compared between women who were not using hormonal contraception and those using DMPA, oral, or implantable contraception.

RESULTS. Among 228 women, 165 (72%) reported not using hormonal contraception at enrollment, 41 (18%) used DMPA, 16 (7%) used an oral contraceptive, and 6 (3%) used a contraceptive implant. Compared to non-users of hormonal contraception, DMPA users had significantly higher mean levels of HNP1-3 (2.38 vs. 2.05 log10 ng/ml; p=0.024), LL-37 (0.84 vs. 0.48 log10 ng/ml; p=0.026), and lactoferrin (3.03 vs. 2.68 log10 ng/ml; p=0.001), whereas SLPI and HBD-2 were similar.

CONCLUSIONS. Three out of five cationic polypeptides investigated were elevated in the CVS of HIV-1 seronegative women using DMPA. While some of these cationic polypeptides have intrinsic antiviral capacity, they are also potent recruiters of target cells for HIV infection and are associated with increased HIV infection risk. This indicates that one potential mechanism for increased HIV risk associated with DMPA is the recruitment or activation of cells susceptible to HIV infection.

Background

- **Pregnancy rates are high, with a large proportion unplanned.** [1]



  - **39 (44%) of 70 pregnancies were 'unplanned'**
  - **Proportion of unplanned pregnancies did not differ by HIV status (51% among HIV+ vs. 65% among HIV-)**
  - **Only 44% of women with an unplanned pregnancy reported any non-condom modern contraception**

- **DMPA may increase risk of HIV acquisition.** [2]
  - **DMPA is the most popular form of long acting reversible contraception in sub-Saharan Africa**
  - **Biological risk (as opposed to behavioral risk) of DMPA remains controversial**
  - **WHO guidance continues to include DMPA in HIV endemic regions, emphasizes risk reduction** [3]

Methods

Study Populations:

- **HIV-1-uninfected women in stable heterosexual couples recruited from VCTs**
- **Questionnaires to assess sociodemographics, sexual behavior, and medical history**

Laboratory:

- **Cervicovaginal secretions (CVS) were collected by rotating a cotton swab 360° in the cervical os and rotating another swab across the vaginal wall**
- **Cationic polypeptides were quantified by enzyme-linked immunosorbent assay (ELISA)**
- **Prostate-specific antigen (PSA) in CVS measured using ARCHITECT Total PSA assay (Abbott)**

Statistics:

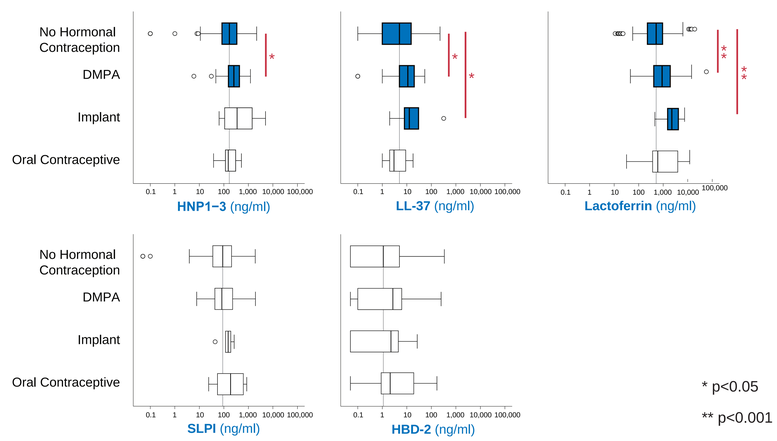
- **Concentrations of cationic polypeptides were $\log_{10}$ transformed for normality**
- **Linear regression was used to compare polypeptide levels by hormonal contraceptive use**

Results

Cohort Characteristics

	Hormonal Contraception			
	None N=165	DMPA N=41	Oral N=16	Implantable N=6
Characteristic	n (%) or median (IQR)			
Age	28 (24, 34)	26 (24, 30)	27.5 (23, 32.5)	29 (24, 38)
Lifetime STI	38 (24.1)	6 (15.0)	2 (12.5)	0 (0)
HSV-2 seropositive	94 (57.3)	21 (52.5)	8 (53.3)	5 (83.3)
Sex acts in past month	5 (2.5, 8.5)	5 (2.5, 8)	11 (6, 12.25)	5 (2, 11.5)
Any unprotected sex	64 (38.8)	16 (39.0)	12 (75.0)	0 (0)
Vaginal washing	40 (24.2)	16 (39.0)	3 (18.8)	2 (33.3)
Vaginal drying	77 (46.7)	25 (61.0)	11 (68.8)	3 (50.0)
Bacterial vaginosis	27 (17.1)	7 (20.0)	0 (0)	1 (16.7)
Desire additional children	87 (52.7)	23 (56.1)	12 (75.0)	1 (16.7)
PSA present	22 (14.3)	9 (23.7)	4 (28.6)	0 (0)

Levels of Cationic Polypeptides by Hormonal Contraceptive Use



Correlation Between Polypeptides

	HNP1−3	LL37	Lactoferrin	SLPI	HBD2
HNP1−3	1				
LL37	**0.49****	1			
Lactoferrin	**0.44****	**0.39****	1		
SLPI	0.04	-0.08	0.11	1	
HBD2	**0.17****	**0.15****	**0.41****	0.07	1

HIV Seroconversion Rates

(among 158 women in HIV-discordant relationships)

Characteristic	Seroconversions	Rate per 100 woman-years	HR (95% CI)
Not using hormonal contraception	4	1.9	1 (ref)
DMPA	0	0	NA
Implant	2	22.8	10.0 (1.8–54.9)
Oral contraceptive	0	0	NA

Key Findings

- **DMPA users had higher levels of some innate immune effector molecules:**
  - **HNP1-3,**
  - **LL-37**
  - **Lactoferrin**
- **There were no differences in levels of innate immune effector molecules between oral contraceptive users and women not using hormonal contraception**

Discussion

- **Higher levels of some innate immune factors (HNP1-3, LL-37) have been associated with increased HIV acquisition.**[4] **This provides a potential biological link between DMPA use and HIV risk.**
- **A mechanism for increased HIV risk with DMPA may be through immune modulation via recruitment of target cells or alteration of surface receptors**
- **Other studies found DMPA decreases IFNα and prevents down-regulation of CXCR4 and CCR5 on the surface of T cells** [5,6]
- **DMPA appears to have a complex affect on the innate immune response in the vagina, with some factors up-regulated and others down-regulated**
- **Research is needed that looks collectively at the overall innate immune response rather than focusing on a small number of immune factors.**
- **Large numbers of unplanned pregnancies demonstrates the need for long acting reversible contraception that is safe and acceptable**
- **Improving the method mix would provide more options to women with fewer affects on immune responses**

References

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