HIV and Hormonal Contraception

Southern African Clinicians Society 2012

Professor Helen Rees
Executive Director, Wits Reproductive Health & HIV Institute
Personal Professor, Department of Obstetrics & Gynaecology, University of Witwatersrand
Honorary Professor, London School of Hygiene & Tropical Medicine
“Love is the answer, but while you are waiting for the answer, sex raises some pretty good questions.” Woody Allen
What do we know about contraception?

Women have a right to decide whether they want to become pregnant and bear children irrespective of their HIV status. Women must be enabled to make informed, voluntary decisions about contraception and then receive a safe, effective method of her choice.
Contraception and Maternal Mortality

Avoidance of unintended pregnancy is most effective way of reducing number of deaths: 40% of global deaths averted in 2008 by contraception. (Darroch & Singh 2011: Ahmed et al 2011)

WHO 2010
Many women use hormonal methods

Over 150 million women use hormonal contraception worldwide, primarily oral contraceptives (OCs) and injectable depot-medroxyprogesterone acetate (DMPA).
The overall demand for contraception is increasing.

% of married women aged 15–49

Latin America & Caribbean
North Africa & West Asia
South & Southeast Asia
Sub-Saharan Africa

Unmet need
Met need

Legend:

- Unmet need
- Met need
The importance of some reasons for non-use has changed over time.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominican Republic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Health/side effects</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Opposition</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Colombia</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Peru</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>Health/side effects</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Opposition</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Kenya</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Health/side effects</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Opposition</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Uganda</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Health/side effects</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Opposition</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mali</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>Health/side effects</td>
<td>44</td>
<td>24</td>
</tr>
<tr>
<td>Opposition</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Bolivia</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

Legend:
- Lack of knowledge
- Health/side effects
- Opposition
Women’s choice of method is influenced by age, relationship status and health services

Currently married (CM) & sexually active not married (NM) women, % using specific method

Source: DHS 2006-2010
Contraception is the neglected second element of PMTCT

- Prevention of HIV in women, especially young women
- Prevention of unintended pregnancies in HIV-infected women
- Prevention of transmission from an HIV-infected woman to her infant
- Support for mother and family
We are not very good at offering HIV positive women modern contraceptive methods

851 non-pregnant women on different ARV regimens recruited from 4 WRHI-supported sites between August 2009 – January 2010

*Schwartz, Black, Rees et al 2011*

<table>
<thead>
<tr>
<th>Contraceptive Use</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent condom use</td>
<td>540 (63.5%)</td>
</tr>
<tr>
<td>Injectables</td>
<td>175 (20.6%)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>45 (5.3%)</td>
</tr>
<tr>
<td>Implants</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>IUDs</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Dual (Condoms+HC)</td>
<td>131 (15.4%)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>631 (74.1%)</td>
</tr>
</tbody>
</table>
How far can we push Dual Method use?
Condom use at last sexual intercourse, amongst injectable contraception users

Glass ceiling?

Source: Demographic and Health Surveys 2004-1010
Hormonal Contraception and HIV: Considerations
Hormonal Contraception and HIV: Considerations

- Women at risk for HIV
  - Prevention
  - Acquisition
  - Infectiousness

- Women infected with HIV
  - Disease progression
  - Drug interactions
WHO’s Medical Eligibility Criteria for Contraceptive Use
Research

WHO consultants & committee:
Systematic review, Grading of scientific evidence

The evidence is used to develop international recommendations and includes expert opinion where evidence is not available

International recommendations are adapted for national guidelines

Job aids (tools) are developed
Eligibility Criteria for Contraceptive use: WHO Classifications

<table>
<thead>
<tr>
<th>Classification of Conditions</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No restriction on use</td>
</tr>
<tr>
<td>2</td>
<td>Benefits generally outweigh risks</td>
</tr>
<tr>
<td>3</td>
<td>Risks generally outweigh benefits</td>
</tr>
<tr>
<td>4</td>
<td>Unacceptable health risk</td>
</tr>
</tbody>
</table>
What triggered the concerns about hormonal contraception and HIV?
Progesterone implants enhance SIV vaginal transmission and early virus load

Preston A. Marx1,2, Alexander I. Spira1,2, Agegnehu Gettie1, Peter J. Dailey3, Ronald S. Veazey4, Andrew A. Lackner5, C. James Mahoney6, Christopher J. Miller6, Lee E. Claypool1, David D. Ho7 & Nancy J. Alexander8

Progestin-based contraceptive suppresses cellular immune responses in SHIV-infected rhesus macaques

Nataliya Trunova9, Lily Tsaia, Stephanie Tunga, Eric Schneidera, Janet Harousea, Agegnehu Gettiea, Viviana Simona, James Blanchardb, Cecilia Cheng-Mayera,8

Abrogation of Attenuated Lentivirus-Induced Protection in Rhesus Macaques by Administration of Depo-Provera before Intravaginal Challenge with Simian Immunodeficiency Virus mac239

Kristina Abel1, Tracy Rourke1, Ding L, Kristen Bost, Michael B. McChesney, and Christopher J. Miller

- Pal et al., Virology 2009
- Turville et al., PLoS One 2008
## Reported effects of progesterone and its derivatives on immune system & HIV-1 infection.

<table>
<thead>
<tr>
<th>Reported effect of progesterone or its derivatives</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of IgG and IgA production and trans-epithelial transport</td>
<td>(78;87-96;129-134)</td>
</tr>
<tr>
<td>Decreased frequency of antibody-secreting cells in women and female macaques</td>
<td>(90;96)</td>
</tr>
<tr>
<td>Decreased specific IgG and IgA responses following mucosal immunization with attenuated HSV-2; induction of permissive conditions for intravaginal infection of mice with HSV-2 and <em>Chlamydia trachomatis</em></td>
<td>(132-134)</td>
</tr>
<tr>
<td>Inhibition of T cell responses and cytotoxic activity</td>
<td>(139-143;147)</td>
</tr>
<tr>
<td>Inhibition of perforin expression in T cells</td>
<td>(140-142;144-146)</td>
</tr>
<tr>
<td>Decreased proliferation and Th1-type cytokine production by VZV-specific CD4&lt;sup&gt;+&lt;/sup&gt; T cells in HIV-1 patients</td>
<td>(148)</td>
</tr>
<tr>
<td>Altered migration and decreased activity of NK cells</td>
<td>(105;106;106;135;159;251;252)</td>
</tr>
<tr>
<td>PIBF-mediated shift towards Th2 cytokine expression profile</td>
<td>(133;149-154)</td>
</tr>
<tr>
<td>Altered migration and infiltration of lymphocytes, macrophages, and NK cells into the female genital tract tissues</td>
<td>(117;118;157;158;183;191;253)</td>
</tr>
<tr>
<td>Increased expression of CCR5 on cervical CD4&lt;sup&gt;+&lt;/sup&gt; lymphocytes</td>
<td>(81;82)</td>
</tr>
<tr>
<td>Thinning of cervico-vaginal epithelium in rhesus macaques</td>
<td>(42;66)</td>
</tr>
<tr>
<td>Increased frequency of Langerhans cells in vaginal epithelium</td>
<td>(76;77)</td>
</tr>
<tr>
<td>Regulation of HIV replication and LTR activity</td>
<td>(254)</td>
</tr>
<tr>
<td>Suppression of IL-1, IL-2, and IL-6 release by human lymphocytes</td>
<td>(148;177)</td>
</tr>
<tr>
<td>Inhibition of TLR-9-induced IFN-α production by human and mouse pDCs</td>
<td>(162)</td>
</tr>
<tr>
<td>Increased shedding of HIV-1 in the genital tract</td>
<td>(35-37)</td>
</tr>
<tr>
<td>Decreased FcγR expression on monocytes</td>
<td>(159;160)</td>
</tr>
<tr>
<td>Decreased vaginal colonization with H&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;-producing <em>Lactobacillus</em></td>
<td>(70)</td>
</tr>
</tbody>
</table>

*Hel Z. et al., Endocrine Rev., 2010, 79-97*
Serum progestin levels in different hormonal contraceptives

Graph showing serum concentration of progestin (ng/mL) over a nine-month period.

Source: Goldzieher & Fotherby (1994), Pharmacology of Contraceptive Steroids, Pages 1118, 166; Fang et al. 2004; Jadelle; Siivin et al. 2001; Implanon; Organon 2006; Funk et al. 2005; Norplant; Nash 1996; IUD; Ewies 2009; POP; Ewies 2009; Organon 2009
Biology?

- Vaginal and cervical epithelium (mucosal thickness, cervical ectopy, etc.)
- Changes in cervical mucus
- Menstrual patterns
- Vaginal and cervical immunology
- Viral (HIV) replication
- Acquisition of other STI that may serve as mediators

However, data are often sparse or potentially could point in different directions, and, most importantly, no laboratory study would be sufficient for this question....
WHO Medical Eligibility Criteria 2009

- Combined hormonal contraception use for women at high risk of HIV, HIV infected or AIDS
- “Intermediate” level of evidence
- Category 1 - “No Restriction” apart from women taking ARVs
## WHO Medical Eligibility Criteria 2009

<table>
<thead>
<tr>
<th>ARV</th>
<th>COC/P/R</th>
<th>CIC</th>
<th>POP</th>
<th>DMPA/NET-EN</th>
<th>LNG/ETG Implants</th>
<th>CU IUD</th>
<th>LNG IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1/1</td>
<td>I 2/3</td>
<td>C</td>
<td>C 2</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1/2</td>
<td>I 2/3</td>
<td>C</td>
<td>C 2</td>
</tr>
<tr>
<td>Ritonavir boosted protease inhibitors</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1/2</td>
<td>I 2/3</td>
<td>C</td>
<td>C 2</td>
</tr>
</tbody>
</table>
WHO Medical Eligibility Criteria 2009

• Injectable progestins for women at high risk of HIV, HIV infected or AIDS

• “Intermediate” level of evidence

• Category 1 - “No Restriction” apart from women taking ARVs

“Balance of evidence suggests no association between progestin contraceptives, although studies of DMPA use conducted among higher risk populations have repeated inconsistent findings”
Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Nelly Muga, Edwin Were, Guy de Bruyn, Edith Nakku-Joloba, Kenneth Nguere, James Kiarie, Robert W Coombs, Jared M Baeten, for the Partners in Prevention HSV/HIV Transmission Study Team*

Summary

Background Hormonal contraceptives are used widely but their effects on HIV-1 risk are unclear. We aimed to assess the association between hormonal contraceptive use and risk of HIV-1 acquisition by women and HIV-1 transmission from HIV-1-infected women to their male partners.

Methods In this prospective study, we followed up 3790 heterosexual HIV-1-serodiscordant couples participating in two longitudinal studies of HIV-1 incidence in seven African countries. Among injectable and oral hormonal contraceptive users and non-users, we compared rates of HIV-1 acquisition by women and HIV-1 transmission from women to men. The primary outcome measure was HIV-1 seroconversion. We used Cox proportional hazards regression and marginal structural modelling to assess the effect of contraceptive use on HIV-1 risk.

Published Online October 4, 2011
DOI:10.1016/S1473-3099(11)70454-7
See Online/Comment
DOI:10.1016/S1473-3099(11)70473-3

* Members listed at end of paper
Department of Epidemiology
[Department name]

WRHI
UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER
PARTNERS IN PREVENTION

Global Health
## Contraception and HIV acquisition from men to women

<table>
<thead>
<tr>
<th></th>
<th>HIV incidence per 100 person years</th>
<th>Adjusted Cox PH Regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>3.78</td>
<td>1.00</td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>6.61</td>
<td><strong>1.98 (1.06 – 3.68)</strong></td>
</tr>
<tr>
<td>Injectables</td>
<td>6.85</td>
<td><strong>2.05 (1.04 – 4.04)</strong></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>5.94</td>
<td><strong>1.80 (0.55 – 5.82)</strong></td>
</tr>
</tbody>
</table>

21.2% of women used HC at least once during study
Contraception and HIV acquisition from women to men

<table>
<thead>
<tr>
<th></th>
<th>HIV incidence per 100 person years</th>
<th>Adjusted Cox PH Regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>1.51</td>
<td>1.00</td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>2.61</td>
<td>1.97 (1.12 – 3.45)</td>
</tr>
<tr>
<td>Injectables</td>
<td>2.64</td>
<td>1.95 (1.06 – 3.55)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>2.50</td>
<td>2.09 (0.75 – 5.84)</td>
</tr>
</tbody>
</table>
Strengths and limitations

**Strengths**
- Large cohort
- Frequent measurement of HIV, contraceptive use and sexual behavior
- Very high rates of follow up (>90% retention)
- HIV negative partners knew they were being exposed to HIV & all were exposed
- Attention to confounding factors using multiple statistical techniques (multiple additional analyses demonstrate consistent findings)
- First report of female to male transmission and partial biological explanation from increased genital viral loads

**Limitations**
- Observational data
- Inability to distinguish between types of injectables used
- Limited data on oral contraceptive risk
- Limited number of infections among those using contraception
Studies of Progestin Injectables & HIV Acquisition, 2011

Source: Adapted from Polis (2011)
If the data is real then the choice for an HIV Uninfected Woman ..... 

• If she uses injectable progestins  
  • Less risk of pregnancy  
  • More risk of HIV acquisition  
• If she stops injectable progestins  
  • Does she have other contraceptive options?  
  • If not, she may become pregnant  
  • More risk of HIV acquisition  
  • More risk of pregnancy morbidity & mortality  
  • Unwanted pregnancy may have worse infant outcomes
If the data is real then the choice for an HIV Infected Woman ..... 

• If she uses injectable progestins
  • Less risk of pregnancy
  • More risk of HIV transmission to partner

• If she stops injectable progestins
  • Does she have other contraceptive options?
  • If not she may become pregnant
  • More risk of HIV transmission to partner
  • More risk of pregnancy Morbidity & Mortality
  • Potential for transmission to infant
  • Unwanted HIV infected babies have higher morbidity and mortality than wanted infants
**CONTRACEPTIVES DOUBLE HIV RISK**

Women who use contraceptive pills and condoms are twice as likely to become infected with HIV compared to those who do not use these methods. The study, conducted in Kenya, involved 3,500 women who were monitored for five years. The researchers found that women who used both methods had a 200% higher risk of HIV infection compared to those who did not use any contraception. The study also highlighted the importance of promoting comprehensive sexual health education and access to quality contraceptives in prevention programs.
WHO Expert Consultation on HC and HIV

- Jan 2012, Geneva, 75 participants from 18 countries
  - HIV Acquisition
  - HIV Transmission
  - HIV Progression
- GRADE rating of the evidence
- Programmatic and research implications
Studies assessing COCs and progression to AIDS OR mortality (Adjusted hazard ratio)

Stringer RCT (2009)*
(OCs vs IUD)

Morrison (2011)
(OCs vs no HC)

Stringer Multi-Country (2009)
(OCs vs no HC)

Polis (2010)
(OCs vs no HC)

OCs decrease risk of progression

OCs increase risk of progression

*Actual use analysis
Studies assessing progestin injectables and progression to AIDS (Adjusted hazard ratio)

Stringer RCT (2009)*
(DMPA vs IUD)

Stringer Multi-Country (2009)
(Inj/imp vs no HC+)

Morrison (2011)
(DMPA vs no HC)

Kilmarx (2000)
(DMPA vs non-DMPA**)

*Actual use analysis  +DMPA, NET-EN or implant  **Mostly OCs
WHO Expert Consultation on HC and HIV

- HC/HIV transmission evidence
  - Rated “low overall quality”
  - Category 1
WHO Expert Consultation on HC and HIV

- Injectable progestins and HIV acquisition evidence
  - 8 cohort studies met minimum quality criteria
  - Rated “low overall quality” but better studies tended towards harm
  - Major focus of meeting
The Critique of the studies on Injectable progestins and HIV acquisition

- Observational data
- Possible selection bias
- Potential for Confounding
- Not always primary study endpoint
- HC use not always well documented
- Self reported condom use unreliable
- Condom use differed between non-HC arms and HC arms
Adjusted Cox PH

Apparent HR for IHC users

• Different levels of misreporting between reported IHC users and non-IHC users can generate a spurious association between HIV and HC use
• Large difference in misreporting required for observed HR to approach 2x risk
• Sensitive to reported level of condom use in the population

More misreporting by IHC users

More over-reporting by IHC users increases the observed HR.
• Observed HR <2 with 10x more or less misreporting by IHC users compared to HC non-users.

Less misreporting by IHC users

From: JA Smith, R Heffron, AR Butler, JM Baeten, TB Hallett (unpublished)
Progestin injectables and HIV acquisition: The Great Debate

1. If left an MEC 1 – no change implies that the data are not convincing enough to support even theoretical concerns about injectable progestins and HIV acquisition

2. If moved to MEC 2 – a change implies that there are theoretical concerns which still allows use but if misunderstood might scare women and jeopardize global use without many alternatives being available

3. The meeting was divided between 1 & 2
After detailed, prolonged deliberation...

...the group agreed that the data were not sufficiently conclusive to change current guidance.

However, because of the inconclusive nature of the evidence, women using progestogen-only injectable contraception should be strongly advised to *also always use condoms*...

The group further wished to draw the attention of policymakers and programme managers to the potential seriousness of the issue and the complex balance of risks and benefits.

Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential.
What then happened? .......

The Guardian
HIV warning to women using injectable contraception
World Health Organisation advises use of contraception against infection

The New York Times
Switzerland: Agency Stands by

POZ
Health, Life & HIV

The Asian Age
‘Hormonal contraceptives safe for women’
TEENA THACKER
263 words
18 February 2012

Top News
News You Can Use

The Herald
Zimbabwe: World Health Organisation recommends use of hormonal contraceptives
By Paamoyo Chipurza, 22 February 2012

The Star
Kenya: Hormonal Contraception
By John Muchangi, 16 February 2012

Uganda Picks
World Health Organization clarifies guidance on hormonal contraception and HIV
Published: February 18, 2012
What then happened......

• Women’s health activists, women's organisations and journalists said they did not understand the Category ‘1’ and the clarification

• Requested clarity on the messaging that should be given to women users

• Widespread calls for increasing the method mix in developing countries and less dependency on injectables

• Researchers and donors considering an RCT of progestins versus IUD as a definitive study

• And the modellers are involved......
Where does high HIV prevalence coincide with high use of injectable hormonal contraceptives?

*Adult HIV prevalence given for China.

HIV: ‘high’ = > 1%; IHC: ‘high’ = upper quartile.

From: AR Butler, JA Smith, D Stanton, TB Hallett. The global impact of an interaction between injectable hormonal contraception and HIV risk
HIV infections attributable to hypothesised IHC-HIV interaction per year (% of total new infections) OR=1.2

Regions with high HIV incidence and high IHC use have the largest percentage of infections attributable to injectable hormonal contraceptive use

From: JA Smith, AR Butler, D Stanton, TB Hallett (unpublished)
Excess live births & maternal deaths per year on cessation of injectable HC use (% of current number per year)

Regions with a **high birth rate and high IHC use** have the largest % increase in live births on stopping IHC use.

Regions with **high maternal mortality and high IHC use** have the largest % increase in maternal deaths on stopping IHC use.

*From: JA Smith, AR Butler, D Stanton, TB Hallett (unpublished)*
Net effect: 80% women stopping IHC are reassigned to effective alternative contraceptive

% change in net maternal and AIDS deaths on cessation of injectable HC use

Alternative contraceptive: 99.2% effective per year, similar to IUD  OR=1.2

Reduction in AIDS deaths outweighs changes in maternal deaths with highly effective alternative contraceptive.

From: JA Smith, AR Butler, D Stanton, TB Hallett (unpublished)
Next Steps?

• More research
  – Randomized trial: other progestins including NET-EN, implants and DMPA
  – Observational analyses
  – Biologic studies
  – Combination prevention technologies

• More action
  – Change the method mix and reduce dependency on DMPA
  – Integrated family planning and HIV prevention and HCT
  – Messaging for women
If millions of men were on a high dose of a first generation statin when newer statins with the same efficacy and fewer side effects were available, and the higher dose made men......

- Put on weight
- Made their hair temporarily stop growing
- And it took 9 months to return to normal
- AND may possibly increase HIV risk

How long would the marketplace tolerate this?
Thanks to......

The many women who are willing to participate in research
Ward Cates & Charlie Morrison FHI 360
Jared Baeten, UW
The many donors and development partners
Women stop and start contraceptive methods

189 progestin injectable users followed up for 2 years in family planning clinic in Soweto

<table>
<thead>
<tr>
<th>Status</th>
<th>1 year (%)</th>
<th>1 year n</th>
<th>2 years (%)</th>
<th>2 years n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued</td>
<td>42</td>
<td>79</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>30</td>
<td>57</td>
<td>35</td>
<td>67</td>
</tr>
<tr>
<td>Discontinued</td>
<td>28</td>
<td>48</td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td>Withdrew</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Of those who discontinued:
- 40% ‘taking a break’
- >50% complained of side effects

Beksinska, Rees et al. Contraception 64(2001)