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UNCERTAINTIES PAGE

Should women with HIV, or at high risk of contracting HIV, use progestogen-containing contraception?

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Cite this as: *BMJ* 2013;347:f6695
doi: 10.1136/bmj.f6695

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic, please email us at practice@bmj.com.

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Previous articles in this series

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- Does gluten sensitivity in the absence of coeliac disease exist? (*BMJ* 2012;345:e7907)
- Does mindfulness based cognitive therapy prevent relapse of depression? (*BMJ* 2012;345:e7194)

Nearly 150 million women worldwide use hormonal methods of contraception, predominantly oral contraceptives taken daily (both combined hormonal pills and progestogen-only pills for the purpose of this article) and long acting injectables such as depot medroxyprogesterone acetate and norethisterone enantate.[1] When used correctly, these are highly effective in preventing pregnancy and are reversible. Side effects of medroxyprogesterone are similar in those who are seropositive for HIV and those who are HIV negative,[2] and antiretroviral therapy does not reduce its effectiveness.[3] However, antiretroviral therapy can make oral contraceptives less effective at preventing pregnancy, and oral contraceptives can increase antiretroviral drugs' toxicity.[3]

Concerns have been raised about possible harmful effects of hormonal contraception in patients infected with HIV and those at high risk of contracting HIV. These effects can be considered in three main categories: HIV acquisition, HIV infectivity, and rate of progression of HIV. Several biologically plausible mechanisms have been proposed for these effects, including effects on genital HIV viral shedding, vaginal epithelial thickness, degree of cervical ectopy, or local and systemic immune responses.[4] However, there is little consistent evidence.

Any potential for harm is important given that in sub-Saharan Africa, women of childbearing age are disproportionately affected by HIV. It is essential to offer women the opportunity to prevent HIV acquisition, not only for their own health but to prevent mother to child transmission. The most upstream means of primary prevention for HIV is preventing unintended pregnancy in the first place. Disease progression puts the woman at risk of opportunistic infections and increases the risk of transmitting the disease to an uninfected partner.

However, it is equally important to avoid denying access to contraceptives without adequate evidence, since those areas where unintended pregnancy poses the greatest threat to women's lives are often the same areas where the risks of HIV acquisition are the highest.

There are no firm recommendations to guide the contraceptive choices for HIV positive patients, and even recent advisory publications by the World Health Organization[5] and Centers for Disease Control and Prevention[6] have seemed reluctant to take a definitive stand.

What is the evidence of uncertainty?

We searched PubMed and the Cochrane Library for randomised controlled trials and systematic reviews published up to and including July 2013, using the search terms "contraception" AND "hormonal" AND "HIV" to answer the following questions.

Does use of progestogen-containing contraceptives increase acquisition of HIV by women?

Oral contraceptives

Most observational studies found no statistically significant association between oral contraceptive use and HIV acquisition (with most studies analysing oral contraceptives as a group). A recent systematic review[7] identified eight prospective observational studies meeting minimum quality criteria. Seven of the studies assessed the impact of oral contraceptives on HIV acquisition, only one of which found a borderline significant effect (adjusted hazard ratio 1.46 (95% confidence interval 1.00 to 2.13)).[8] A secondary data analysis of 4913 women, too recent to be included in the systematic review, showed no significant association between HIV acquisition and use of progestogen-only pills or combined hormonal pills.[9]

Injectable contraceptives

In the systematic review,[7] there was inconsistent evidence of a relation between use of injectable contraceptives and HIV acquisition: three studies noted an increased rate of HIV acquisition, whereas five showed no association. This heterogeneity could reflect differences in study design. The three studies showing positive associations had methodological strengths including short inter-survey intervals, adjustments for time-dependent confounding, and validation of reported contraception use with clinical records. However, the degree of effect seen was variable, with adjusted hazard ratios ranging from 1.48 (1.02 to 2.15)[10] to 2.05 (1.04 to 4.04).[11] Some of the effect, if present, could be mediated by differences in sexual behaviour in hormonal contraception users.

Only three studies in the systematic review[7] and a more recent (unpublished) secondary analysis of a large multicountry microbicide trial specifically evaluated use of injectable norethisterone enantate,[12] showing no significant association with HIV acquisition. If norethisterone is truly safer than medroxyprogesterone acetate regarding HIV acquisition, this might reflect differences in the degree of ovulation suppression (as evidenced by increased likelihood of amenorrhoea with medroxyprogesterone[13]), resulting in different degrees of vaginal atrophy. Additionally, molecular studies suggest that these progestogens may modulate local immune capacity in the vaginal epithelium in different ways.[14]

Does use of progestogen-containing contraceptives increase HIV infectivity (that is, HIV transmission to seronegative male partners)?

Only one, well conducted, observational study directly measured incident HIV infection rate in male sexual partners.[11] Although it suggests that use of injectable contraception (but not oral contraception) significantly increased female-to-male HIV transmission, it was underpowered to do so.

Two systematic reviews were identified,[15 16] and the 2013 review identified only observational studies.[16] Apart from the one study directly measuring incident HIV infection in male partners,[11] the other 11 studies considered genital viral shedding or plasma viral load as an imperfect proxy for infectivity.

The direct study included 2476 serodiscordant couples in which the seronegative partner was male. It showed a doubling of HIV transmission to male partners of HIV positive women using medroxyprogesterone with an adjusted hazard ratio of 1.95 (1.06 to 3.58). There was also an increased risk with use of oral contraception (mostly combined oral contraceptives), but this was not statistically significant.[11] This study had many methodological strengths, including frequent follow-up, low loss to follow-up, and statistical adjustment for multiple confounders, as well as genetic linkage of HIV transmission, but the total number of transmissions was small, and statistical power and precision limited.

Most of the indirect studies were cross-sectional, with associated difficulty in assigning temporal association, and most showed no effect of hormonal methods on genital RNA or DNA shedding. There was also no convincing association between use of hormonal contraception and viral load.

Does use of progestogen-containing contraceptives affect disease progression in HIV positive women?

In a 2013 systematic review of 11 studies,[17] only one flawed randomised trial showed increased disease progression in HIV positive women using hormonal contraception,[18 19] while the other 10 cohort studies (only two of which were considered methodologically strong[20 21]) did not suggest any increase in disease progression.

The randomised trial was carried out in 599 HIV infected postpartum women who were not receiving antiretroviral therapy at the time of randomisation.[18 19] However, it was not designed or powered to detect an impact on HIV progression by method of contraception, lacked a control group receiving no contraception, and had a high loss to follow-up and disproportionate discontinuation of contraceptive method in the group using an intrauterine device. Thus actual use analysis was performed in addition to intention to treat, although this negates the advantages of randomisation. This showed a significant increase in composite disease progression in users of hormonal contraception compared with users of a copper intrauterine device (the T380A): with intention to treat analysis, medroxyprogesterone had a hazard ratio of 1.81 (1.30 to 2.53) and oral contraceptive had a hazard ratio of 1.52 (1.00-2.32); with time varying analysis, adjusted hazard ratios for medroxyprogesterone and oral contraceptive were 1.62 (1.16 to 2.28) and 1.67 (1.10 to 2.51) respectively (results for the two types of hormonal contraception were not significantly different).[19] Importantly, the rate of pregnancy was also higher in users of hormonal contraception (hazard ratio 2.4 (1.3 to 4.7)).

The systematic review included seven prospective cohort studies (including a large multicountry analysis[22]), none of which reported an increase in HIV disease progression with hormonal contraception. Some studies had few contraceptive users, and the relatively long follow-up periods (usually at least 2 years) may still be insufficient.

Is ongoing research likely to provide relevant evidence?

We searched the Clinical Trials database, using the search terms "hormonal" AND "HIV" AND "contraception" and were unable to find any upcoming trials relevant to this article. However, a meta-analysis pooling the individual patient data for about 37 000 women from 18 studies is reportedly being undertaken by Morrison and colleagues at Family Health International, and this may shed more light on the impact of hormonal contraception on HIV acquisition.

What should we do in light of the uncertainty?

In 2012 the WHO recommended that there should be no restriction on the use of any hormonal contraceptive method for women living with HIV or at high risk of acquiring it.[5] However, it also recommended that women using progestogen-only injectable contraception be strongly advised to use condoms (male or female) and other preventive measures against HIV transmission (such as encouraging voluntary counselling and testing and avoiding high risk sexual behaviours). Subsequent recommendations by the Centers for Disease Control and Prevention concurred with this guidance.[6]

Current evidence suggests that medroxyprogesterone (but not oral contraceptives) may increase HIV acquisition, albeit to an uncertain degree and without high quality evidence. Norethisterone may be a safer injectable option, but further work is needed to clarify this. Oral contraceptive use does not seem to increase HIV acquisition (and limited observational evidence for progestogen-only pills is reassuring[9]).

Medroxyprogesterone may be associated with an increased female-to-male transmission of HIV, but the evidence is weak. The data regarding HIV progression are conflicting. There is a lack of good quality work considering newer hormonal methods. Options to discuss in counselling women should include:

- *Simultaneous use of condoms*, particularly (but not exclusively) if medroxyprogesterone is the chosen method of contraception. This would offer additional protection against other sexually transmitted infections, which would be beneficial since Herpes simplex virus 2, in particular, increases heterosexual transmission of HIV. However, dual use is not commonly practised by couples, even in research settings, and its promotion may stigmatise barrier methods. In addition, many women choose injectable contraception because they are unable to use condoms.
- *Alternative methods of contraception*—Oral contraceptives (though with potential interactions with antiretroviral therapy[3]), the copper intrauterine device (with careful exclusion of sexually transmitted infections and monitoring for pelvic infection), and possibly injectable norethisterone (if superior safety is confirmed) seem safer than injectable medroxyprogesterone. We await further information on other methods of female contraception such as the cap (which may offer cervical protection against HIV) and intrauterine devices containing levonorgestrel and implants containing progestogen (as these contain far lower levels of progestogen than medroxyprogesterone and so may carry less risk).

- *Importance of accessing antiretroviral therapy*—A recent (unpublished) small cohort study showed no change in HIV infectivity (assessed indirectly by viral load) in HIV positive women taking antiretroviral therapy who started medroxyprogesterone, leading the authors to recommend priority initiation of antiretroviral therapy in women intending to use hormonal contraception.[23]

We should not deny medroxyprogesterone to women who want to use it, as there is insufficient evidence against its use; preventing unintended pregnancy must continue to be at the forefront. Some healthcare providers might be reluctant to discuss the possible risks, for fear that patients will abandon medroxyprogesterone without seeking an alternative method of contraception. It is important help providers understand the evidence in context and equip them to counsel women effectively, as well as to train them to provide alternative methods such as intrauterine devices. Involving male partners in contraception counselling may make simultaneous use of condoms or use of less familiar methods more acceptable.

Contextualising any potential risk with hormonal contraception is of the utmost importance; it must be balanced against the risks of maternal morbidity and mortality, infant morbidity and mortality, and unsafe abortion[24]—risks that are substantial in sub-Saharan Africa.[25]

Contributors: SLG conceived of and designed the article, undertook the initial literature search, and wrote the initial draft. Both authors interpreted and revised the data, and approved the final article.
Competing interests: None declared.
Provenance and peer review: Commissioned; externally peer reviewed.

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10-MINUTE CONSULTATION

Abnormal vaginal discharge

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Cite this as: *BMJ* 2013;347:f4975
doi: 10.1136/bmj.f4975

This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.

A 29 year old woman complains of a one week history of thick, white, odourless vaginal discharge and vulval pruritus. There was no dyspareunia or abnormal vaginal bleeding. On examination, the abdomen is not tender, the vulva seems normal, and speculum examination reveals thick white discharge.

What you should cover

Characteristics of the discharge—Onset, duration, colour, odour, consistency (a discharge that is heavier, thicker, or more offensive than usual is abnormal), cyclical changes, exacerbating factors (such as after intercourse) (see table for details).

Any associated symptoms—Itch, dyspareunia, abdominal pain; abnormal vaginal bleeding or pyrexia is more likely to indicate sexually transmitted infection (see table).

FURTHER READING

- Patient UK. Vaginal discharge (www.patient.co.uk/doctor/Vaginal-Discharge.htm) —Comprehensive patient information leaflet
- Faculty of Sexual & Reproductive Healthcare. *Management of vaginal discharge in non-genitourinary medicine settings*. 2012. www.fsrh.org/pdfs/CEUGuidanceVaginalDischarge.pdf.
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- Dental pain (*BMJ* 2013;347:f6539)
- Flashes, floaters, and a field defect (*BMJ* 2013;347:f6496)
- An adult with a neck lump (*BMJ* 2013;347:f5473)
- Umbilical hernia (*BMJ* 2013;347:f4252)
- A pain in the bottom (*BMJ* 2013;347:f4192)

Sexual history—Is patient at increased risk of sexually transmitted infection (age <25 years, new sexual partner or more than one sexual partner in past year, previous sexually transmitted infection)?

Contraceptive use can affect vaginal discharge.

Pregnancy can affect vaginal discharge and is an important factor in patient management.

Concurrent medications and previous treatments used such as antibiotics, corticosteroids, over the counter drugs such as clotrimazole.

Medical conditions such as diabetes, immunocompromised state.

Non-infective causes of discharge such as allergic reaction, known cervical ectopy or polyps, genital tract malignancy, foreign body (such as tampons).

Elicit any patient concerns and expectations

The most common causes of vaginal discharge are physiological, bacterial vaginosis, and candidiasis.

What you should do

Examination

Always offer examination, but, if the patient declines, treatment for candidiasis or bacterial vaginosis may be given without examination if the risk of sexually transmitted infection is low and there are no symptoms indicative of upper genital tract infection.

Abdominal palpation for tenderness or mass (may indicate malignancy).

Inspect the vulva for discharge, erythema, ulcers, other lesions or skin changes (see table).

Bimanual pelvic examination for adnexal or uterine tenderness or mass, and for cervical motion tenderness (this can indicate pelvic inflammatory disease).

Speculum examination to inspect vaginal walls, cervix, and characteristics of discharge. Although not mandatory, vaginal pH can be checked by using a swab to collect discharge from the lateral vaginal wall and rubbing on to narrow range pH paper. This can help discriminate between bacterial vaginosis, trichomoniasis, and candidiasis. Take endocervical swabs if there is risk of sexually transmitted infection and send off for nucleic acid amplification testing. High vaginal swabs are of limited diagnostic value except in pregnancy, post-instrumentation, failed treatment, recurrent symptoms, or to confirm candidiasis. This can also be an opportunity to carry out cervical screening.

Alternatively, you can advise the patient to attend the local genitourinary medicine clinic for the above examinations if she is at risk of sexually transmitted infection.

Characteristics of different causes of abnormal vaginal discharge

	Infection		
Signs and symptoms	Bacterial vaginosis	Candidiasis	Trichomoniasis
Discharge	Thin	Thick white	Scanty to profuse
Odour	Fishy	Non-offensive	Offensive
Itch	None	Vulval itch	Vulval itch
Other possible symptoms	Dyspareunia Dysuria	Soreness Superficial dyspareunia	Lower abdominal pain
Visible signs	Discharge coating vagina and vestibule No vulval inflammation	Normal findings *or* Vulval erythema Oedema Fissuring Satellite lesions	Frothy yellow discharge Vulvitis Vaginitis Cervicitis
Vaginal pH	>4.5	≤4.5	>4.5

Management

When to consider referral to genitourinary medicine

- Gonorrhoea, trichomoniasis, or pelvic inflammatory disease is suspected, although treatment should be started
- Partner notification is required
- Diagnostic uncertainty
- Recurrent or persistent symptoms.

Infective (non-sexually transmitted infection)

Bacterial vaginosis—Treat even in the absence of a positive HVS. It is important to treat in pregnancy as it can cause complications. Metronidazole 400 mg twice daily for 5-7 days or intravaginal therapies may be used. In recurrence, use oral metronidazole for 3 days at start and end of menstruation. Always counsel about alcohol with metronidazole.

Candidiasis—Vaginal and oral azole antifungals are equally effective but avoid oral treatment in pregnancy. In recurrence, an induction and maintenance regimen may be used for six months.

Infective (sexually transmitted infection)

- Always offer an annual chlamydia screen to sexually active women aged <25 years.
- Offer blood tests for HIV infection and syphilis.
- *Chlamydia*—Treat with either a single dose of azithromycin 1 g or twice daily dose of doxycycline 100 mg for seven days.
- *Gonorrhoea*—Uncomplicated infections should be treated with an intramuscular injection of ceftriaxone 500 mg and oral azithromycin 1 g, both as single doses. Everyone should have a test of cure.

Personal hygiene and advice

- Advise patient to avoid douches, perfumed products, and tight synthetic clothing.
- Educate patient about normal vaginal discharge.

Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

Accepted: 2 July 2013