



IPPF Medical Bulletin

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Mother-to-child transmission of HIV-1

James A McIntyre

The main source of HIV infection in children is the mother. The United Nations agencies estimate that over 1900 infected children are born daily worldwide, the overwhelming majority in the developing world, especially in sub-Saharan Africa.^{1,2} Knowledge of the timing and factors associated with mother-to-child transmission (MTCT) has enabled the development of effective prevention strategies. The more complex regimens, consisting of prolonged antenatal antiretroviral treatment combined with scheduled caesarean section at term and treatment of the child for six weeks, have decreased transmission rates from 25–30 % to less than 2%.³ Whilst antiretroviral interventions have become standard practice in developed countries, with large declines in transmission rates, implementation of preventive measures in resource-limited settings has been hindered by financial and political factors.

The prevention of MTCT encompasses three aspects – the primary prevention of HIV infection among parents-to-be; the prevention of unwanted pregnancies in HIV-positive women; and the prevention of viral transmission from mother to child. MTCT prevention should be integrated into a continuum of care that includes expanded access to care and support for HIV-positive mothers and their families, reproductive healthcare and family planning, treatment of opportunistic infections, and access to antiretroviral treatment.

HIV can be transmitted from mother to infant in three ways: infection may occur in utero; the virus can be transmitted to the infant at the time of delivery (by ascending infection, by ingestion of maternal blood or other fluids, or by breaks in the skin and subsequent direct exposure to infected blood or secretions); or it can be transmitted through breastmilk.⁴ The relative contribution of each of these routes will depend on the presence or duration of breastfeeding. In non-breastfed infants, around one-third of transmission occurs in the intrauterine period and two-thirds during or close to delivery. Where infants are breastfed, about half of the transmission occurs around the time of delivery, around one-third through breastfeeding, and a smaller proportion in utero.⁵ In the April 2002 issue of the *IPPF Medical Bulletin*, Nduati discussed the issues around infant feeding and HIV.⁶ The risk of MTCT is affected by numerous factors – maternal, fetal, viral and behavioural. These are summarised in panel 1.

Three strategies have been shown to have a major effect in preventing MTCT – antiretroviral prophylaxis; elective caesarean section; and modification of infant feeding.^{7,8} Alternative strategies such as vitamin A supplementation have not been successful.

Antiretroviral therapy

Where antiretrovirals are available, the decision about the need for treatment in pregnancy should be based on the woman's own immunological, virological, and clinical condition. Optimal antiretroviral therapy should not be withheld during pregnancy unless the risk of adverse effects to the mother, fetus, or infant outweighs the expected benefit to the woman, although the potential impact of such therapy on the fetus and infant must also be considered. Pregnancy may affect the choice of antiretroviral drugs.⁹ Antiretroviral therapy to reduce the risk of MTCT is recommended for pregnant women who do not yet need such treatment for their own disease.

Several antiretroviral regimens have been shown to be effective in reducing mother-to-child transmission of HIV, varying in length, complexity, and price. All these regimens include intrapartum treatment, with differing lengths of antepartum and postpartum treatment. The choice of regimen will depend upon the effectiveness of the intervention, the safety of the drugs, the risk of drug resistance, and the cost.¹⁰ If combination treatment or long-course monotherapy with zidovudine (ZDV) is not feasible, several short-course regimens with ZDV or ZDV plus lamivudine (3TC) have been shown to be effective, as has nevirapine given in labour to the mother and shortly after birth to the baby.

This regimen of one 200 mg dose of nevirapine orally to women at the onset of labour and one dose of 2 mg/kg to the baby within 72 hours has become the backbone of MTCT prevention programmes in developing countries because of its low cost, its feasibility, and its effectiveness in reducing the risk of transmission by close to 50%.¹¹ The development of resistance to the drug, following single-dose administration, may be the major disadvantage. A study in Uganda has demonstrated the development of nevirapine-resistant virus in 19% of women who received only one intrapartum dose of nevirapine.¹² High viral load and low CD4 cell counts were associated with the development of resistant variants. The K103N was the most common mutation detected and nevirapine-resistant mutations faded from detection within 12–24 months in 11 evaluable women. No comparable results are yet available for subtype C, the most common subtype in the high-prevalence areas of southern Africa. The long-term impact of the selection of nevirapine-resistant virus on future treatment options and subsequent pregnancies is not known, but current international recommendations are that this concern should not delay the implementation of nevirapine-based mother-to-child-transmission programmes.

Elective caesarean section

Several studies have shown that caesarean section before the onset of labour reduces the risk of MTCT. In a large meta-analysis of over 8500 mother-infant pairs, elective caesarean section reduced the risk of transmission by over 50% compared with vaginal delivery.¹³ Transmission was reduced from 7.3% to 2% in women in the analysis who had elective caesarean section and had received long-course antiretroviral treatment. Elective caesarean section reduced transmission by more than half in a randomised trial in Europe.¹⁴ This potential benefit has to be balanced against

PANEL 1. RISK FACTORS ASSOCIATED WITH INCREASED OVERALL RISK OF MOTHER-TO-CHILD TRANSMISSION OF HIV^{15,16}

	Strong evidence	Intermediate evidence	Limited evidence
Maternal factors	High viral load Immuno-deficiency Viral characteristics Advanced disease HIV infection acquired during pregnancy or breastfeeding	Chorioamnionitis Anaemia Vitamin A deficiency Sexually transmitted infections Smoking	Frequent unprotected sexual intercourse Multiple sexual partners Drug use involving injection
Obstetric factors	Vaginal delivery (compared with elective caesarean section)	Invasive procedures	Episiotomy
Infant factors	Prematurity Breastfeeding	Lesions of skin and/or mucous membranes (oral thrush)	

the risk to the mother: postoperative morbidity has been reported above-average in HIV-infected women, especially infective complications. There is also little information about the additional benefit of elective caesarean section in women receiving highly active antiretroviral therapy with very low viral loads. In contrast, elective caesarean section for reducing MTCT will not be an accessible option in most developing countries, where resources to perform the operation are not available and the prevalence of HIV is very high.

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Combined oral contraceptives, human papillomavirus, and cervical cancer

Olav Meirik

The relation between combined oral contraceptives (COCs) and cervical cancer has been under investigation for several decades. COCs are among several factors that are statistically associated with cervical cancer, and until recently the results were difficult to interpret because the underlying cause of the disease was unknown. It is now established that oncogenic human papillomavirus (HPV) is necessary for development of practically all squamous cervical cancers.¹ This scientific advance has allowed studies and analyses that tell us much more about the relation between COC use and cervical cancer.

Human papillomavirus infections

About 120 HPV types have been identified, but only some of these are responsible for squamous carcinoma (and the less common adenocarcinoma of the cervix).^{1,2} Two HPV types, 16 and 18, accounted for about 70% of the HPV types associated with cervical squamous carcinoma in a large multi-country study.¹ Oncogenic HPV types are also related to other epithelial cancers.² Some different HPV types cause warts of the hands and genitals. Genital HPV infection is predominantly transmitted sexually and affects a large proportion of sexually active young adults; use of the male condom provide some protection.³ The majority of genital HPV infections are transient, the virus being cleared or controlled by the immune system;^{4,5} however, a small proportion become persistent and some of these lead to gradual malignant transformation of cells in the cervix.² The early stages of the cell transformation, cervical

intraepithelial neoplasia, can be detected by cervical cytological examination and treated surgically.

Why some HPV infections become persistent and cause malignant change has yet to be discovered. Immunological factors are involved; people with HIV infection or receiving immunosuppressive treatment are at increased risk of cervical cancer.⁵ Multiparity, smoking, and COC use are other risk factors, and genital herpes simplex and chlamydia infections have been implicated. Genetic variation within oncogenic HPV types seems also to determine risk of progression to cancer.^{2,5}

COCs and cervical cancer

New information on COCs and risk of cervical cancer comes from reanalysis of data from ten case-control studies (conducted in Brazil, Colombia, Morocco, Paraguay, Peru, the Philippines, Spain, and Thailand) coordinated by the International Agency for Research on Cancer (IARC) in Lyon, France.⁶ Eight of these studies included incident cases of invasive squamous carcinoma and two carcinoma-in-situ. Information on risk factors came from face-to-face interviews. COCs were not distinguished from other hormonal methods, but use of hormonal contraceptives other than COCs was rare in all countries except Thailand, where depot-medroxyprogesterone acetate was common. The main reanalyses were restricted to women whose cervical scrapes were HPV DNA positive by polymerase chain reaction (PCR) and included 1676 cases and 255 controls (90% and 13% of all cases and controls, respectively). The analyses used logistic regression with adjustment for confounders such as study centre, age, education, parity, and sexual and cervical-smear history.

Use of COCs for less than 5 years in HPV-positive women was not related to any increased risk of squamous cervical cancer or carcinoma-in-situ (odds ratio [OR] 0.7 [95% confidence interval 0.5–1.0]). For women having used COC between 5 and 9 years the risk was increased 2.8-fold (95% CI 1.5–5.4). The highest risk was observed for women who had used COCs for 10 or more years, among whom the OR was 4.0 (95% CI 2.1–7.8). Age at starting COCs was not significantly associated with cervical cancer when adjusted for duration of use. Women who had taken COCs for 5 years or more continued to be at excess risk of cervical cancer up to 15 years after stopping use. Data on risk more than 15 years after stopping were sparse but it still seemed to be increased. Presence of HPV DNA in the cervical cells from the control women was not associated with COC use, indicating that use of COCs is not related to HPV infection.

The reanalysis relied on data that were collected for research questions other than those asked in the current study. The study therefore has some weaknesses – such as incomplete ascertainment of the type of hormonal contraceptive and a suboptimal number of controls. The risk estimates (ORs) in some subgroups are based on very few controls and may be imprecise. Overall, however, the findings largely concur with those of previous work specifically investigating the relation between use of COCs and risk of squamous cervical cancer; differences are that the ORs are higher than in most previous studies and the continued excess risk long after stopping COCs is contrary to other studies.⁷

The association between COC use and cervical cancer has potentially large public health implications. Cervical cancer is the third most frequent cancer in women worldwide and the second most frequent among women in developing countries;⁸ in 1994 some 93 million women worldwide were using oral contraceptive pills.⁹ In most developed countries cervical cancer incidence declined from 1973 to 1991, probably because of cytological screening.¹⁰ In some of a few Asian and Latin American countries that have been studied, the incidence was also declining, maybe because of decreasing parity.

Implications for family planning

The Reproductive Health and Research department at WHO recently reviewed the findings of the IARC study at an expert meeting and recommended no changes in oral contraceptive prescribing practices or use, pending results of new studies in progress.¹¹ The experts noted that, among women who use oral contraceptives, the number of cervical cancers that result from this use is likely to be very small and that cervical cancer can be prevented through appropriate screening practices. Where screening is available, COC users should use the same services as other women. In countries that do not offer screening, pregnancy morbidity and mortality are often high and COCs are one of the few contraceptive methods widely available. Since high parity is a risk factor, COC use may reduce cervical cancer risk attributable to parity. For most women, the risk of maternal mortality from non-use of contraception in these settings would probably far exceed any additional risk of cervical cancer from COC use.

Some tests for cervical HPV infection are available and methods for screening are being developed,¹² but many years will pass before these are affordable and systematically manageable in public health services in developing countries. Prophylactic vaccines against oncogenic HPV are under development but are unlikely to become generally available in this decade.⁴

The research by IARC and others demonstrates that the risk of cervical cancer is limited to women with persistent cervical infection of oncogenic HPV and that, among women with such infections, COC use for more than 5 years is one of several factors that increase the risk of the disease. The great majority of women in the world do not have access to health services where persistent cervical HPV infections can be diagnosed. For the time being, therefore, current best clinical practices and counselling must be provided in family planning and reproductive health services, but governments and research funding institutions have an obligation to allocate resources to accelerate development of screening methods and vaccines for oncogenic HPV infections.

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IMAP meeting, May 2002

During this meeting, the International Medical Advisory Panel (IMAP) combined its statements on injectable contraceptives, contraceptive implants, and steroidal oral contraception into a single statement, which will be published later this year. The Panel also responded to matters referred by the Central Secretariat, the Regions, FPAs, and volunteers.

Third-generation pills and risk of thromboembolism/myocardial infarction

Use of combined oral contraceptive pills (COCs) increases the risk of venous thromboembolism (VTE) 3–6 times but the absolute risk of death from this cause is still very low. COCs containing the newer progestogens desogestrel and gestodene may carry a slightly greater risk of VTE (1.6 fold) than COCs containing levonorgestrel. The absolute risk of VTE attributable to use of COCs rises with increasing age, obesity, recent surgery, and certain forms of thrombophilia. In Caucasian women, the baseline risk of VTE is 5 per 100 000 women years and this increases to 60 per 100 000 during pregnancy; in women using pills containing levonorgestrel the risk is 15 per 100 000 and in those using desogestrel or gestodene it is 20–30 per 100 000. There are no similar data in non-Caucasian women. IMAP recommends that, for young healthy women, combined pills containing levonorgestrel should be the first choice.

As regards myocardial infarction (MI), women without risk factors such as smoking, diabetes, or hypertension do not put themselves at extra risk by taking a COC. However, COC use does increase the likelihood of MI in women with risk factors – especially those over 35 years. Data are at present too limited and inconsistent to indicate how COCs containing desogestrel or gestodene compare in this respect with those containing levonorgestrel.

Oral contraceptives and the risk of cervical cancer

Reviewing the paper by Moreno and others discussed by Dr Meirik on p 3 of this *Bulletin*, IMAP concluded that the findings do not justify routine testing for human papillomavirus DNA testing or an alteration to routine cervical screening practice.

New implants

IMAP recommends that Jadelle, the two-rod levonorgestrel-releasing implant, be added to the IPPF commodities list. The lifespan of Jadelle is 5 years; its efficacy and side-effects are similar to those of Norplant, but it is easier to insert and remove.

Implanon, a single-rod implant releasing the progestogen etonogestrel, has a lifespan of 3 years and high contraceptive efficacy. This implant may also be added to the commodities list. Although data on this product are much less extensive than those for Norplant and Jadelle, existing information on safety and efficacy is reassuring, and insertion and removal are easy.

In countries where Norplant is already available, a change to Jadelle would require little retraining of providers. Implanon insertion requires a different technique, and additional training would be necessary.

Yasmin and Diane

Yasmin contains the progestogen drospirenone, an analogue of spironolactone. More information on its safety profile, especially regarding thromboembolism, is needed before this pill can be recommended for distribution by IPPF. Diane is indicated mainly for treatment of acne and hirsutism. It is expensive, and not a first-choice contraceptive product.

News

Sex education for adolescents

In the June *Bulletin* Nancy Williamson, discussing sex and HIV programmes for young people, referred to the ten characteristics of a successful programme identified by Kirby. Since then, an important paper has been published from Scotland – a country with a high rate of teenage pregnancy. Wight and his co-workers¹ assessed the SHARE programme (Sexual Health and Relationships: Safe, Happy and Responsible) in 25 non-Catholic schools, randomising them to SHARE or usual sex education. The SHARE programme includes active learning, information sheets, and development of skills through interactive video and role-play; it has all ten of the characteristics favoured by Kirby. The measured outcomes (self-reported) were exposure to sexually transmitted infections, use of contraceptives at first intercourse, and unwanted pregnancy. The special intervention improved knowledge of sexual health but made no obvious difference to sexual activity or sexual risk-taking up to age 16. A possible explanation for these disappointing results is that existing teaching methods in these Scottish schools were already influencing adolescent behaviour to the maximum achievable. The results of a similar but bigger study in Tanzania, in which end-points include laboratory tests for HIV, are anxiously awaited.

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Contraceptive advice during pregnancy

The postpartum period seems an ideal opportunity for promoting and delivering contraception, and many developing countries run special programmes to offer advice at this time. But is this really the best moment for such advice? A Cochrane report,¹ based on studies conducted in the Lebanon, Nepal, and Peru, concluded that there was no strong evidence for the efficacy of such services in preventing unplanned pregnancies; and a group in the UK² suggested that the antenatal period – when women are not distracted by the needs of their new baby – might be a better time to discuss contraception. This proposal has now been assessed in a randomised controlled trial. Antenatal advice on postpartum contraception was compared with standard practice in three centres in Scotland (Edinburgh), China (Shanghai), and South Africa (Cape Town). 500 women were recruited in each centre and followed up for one year after childbirth. The intervention consisted of a 20-minute one-to-one interview with an 'expert' family planning nurse sometime between the 24th and 36th week of pregnancy. Conclusions from this trial are largely negative. The only obvious effect of the antenatal counselling was in Edinburgh, where significantly more women in the intervention group chose to be sterilised. At the end of one year, more than 79% of women in all centres were using contraception – in China, mainly condoms, natural methods, or withdrawal; in South Africa mainly depot-medroxyprogesterone. The antenatal intervention made no difference in terms of continuation rates or pregnancy rates. Rather, pregnancy rates were related to the type of contraception, being highest in China where, in the year of follow-up, 11% of the women had a termination.

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