Exclusive Breast-Feeding Is Safer Than Mixed Feeding For Infants Born to HIV-Positive Mothers

Breast-fed infants who are also given solid foods or milk from formula are at higher risk of HIV infection than those who are exclusively breast-fed, according to a study of mother-to-child transmission of HIV in KwaZulu Natal, South Africa.[1] Infants who receive such mixed feeding are more likely than those exclusively breast-fed to acquire HIV infection (hazard ratio, 10.9). Among infants who are exclusively breast-fed, those whose mothers have CD4 cell counts of fewer than 200 cells or 200–500 cells per microliter have elevated risks of getting infected (3.8 and 2.4, respectively) or not surviving HIV-free for six months after birth (4.0 and 2.3, respectively). Other factors associated with increased risk are a maternal age of 20–30, an infant birth weight of less than 2,500 g and labor lasting more than 12 hours.

The risk of mother-to-child transmission of HIV through breast-feeding in resource-poor countries has not been adequately examined, and there is some confusion regarding the recommendation of infant feeding options. Therefore, researchers conducted a nonrandomized intervention cohort study to assess the probabilities of HIV transmission and HIV-free survival associated with exclusive breast-feeding and other types of infant feeding during the first six months after birth.

Between 2001 and 2005, the study enrolled 1,372 HIV-infected women aged 16 or older who were attending antenatal clinics in KwaZulu Natal. Antenatal CD4 cell counts were measured, and women were counseled about feeding options; those who chose to use formula were given a six-month supply. All women were provided with a single dose of nevirapine after enrollment or 28 weeks of gestation to be taken during delivery, and another dose to be given to the infant soon after birth. Following birth, counselors and clinic nurses supported mothers in their preference to breast-feed exclusively or to practice replacement feeding. (Exclusive breast-feeding was defined as receiving only breast milk, though water or formula was allowed on a total of no more than three days during the study period; replacement feeding was defined as receiving formula, with or without other liquids or solids.) Mothers reported feeding practices to independent monitors every week for six months; infants were tested monthly for HIV infection. Cumulative HIV transmission and infant mortality were determined using survival analyses, and regression analyses were used to assess associations between infection and mortality and various maternal and infant variables.

The median maternal age of HIV-infected mothers was 25. At the time of birth, 83% breast-fed exclusively, 8% practiced replacement feeding and 3% practiced mixed feeding (giving breast milk with formula, other liquids or solids); information was missing for the remaining women. Women who breast-fed exclusively were more likely than those who practiced replacement feeding to live in rural areas (45% vs. 30%) and were less likely to be urban dwellers (18% vs. 32%); equal proportions lived in semiurban areas (37–38%). Mothers' CD4 cell counts differed by feeding type: A higher proportion of women who practiced replacement feeding than of those who breast-fed their baby exclusively had counts of fewer than 200 cells per microliter (21% vs. 10%), and a lower proportion had counts of more than 500 cells per microliter (30% vs. 41%).

Of the 1,034 exclusively breast-fed infants for whom HIV test results were available, 175 were diagnosed as HIV-positive before six months of age; survival analysis found cumulative infection rates of 14% by six weeks and 20% by six months. Four percent of breast-fed infants who were uninfected at six weeks of age were infected by six months. Among exclusively breast-fed infants, estimated mortality at three months was 6%; among the infants given replacement feeding from birth, estimated mortality at three months was 15%.

Infants who received mixed feeding during their first six months were at higher risk of HIV infection than those who had breast-fed exclusively (hazard ratio, 10.9). Among the latter infants, transmission risk was associated with maternal CD4 cell counts: In a multivariate analysis, those whose mothers had counts of fewer than 200 cells or 200–500 cells per microliter had a higher risk of HIV infection (3.8 and 2.4, respectively) than those whose mothers had counts of more than 500 cells per microliter. Other factors associated with an elevated risk of infection were having a mother aged 20–30 versus one younger than 20 (1.9), having a birth weight of less than 2,500 g versus a weight of more than 3,500 g (1.8) and being born after labor that lasted more than 12 hours versus less than four hours (2.2). In contrast, infants delivered by cesarean section rather than vaginally had a lower risk of infection (0.5).

Among infants who had breast-fed exclusively, the risk of not surviving HIV-free for six months after birth was similar to the risk of infection. Those whose mothers had counts of fewer than 200 cells or 200–500 cells per microliter had a higher risk of not surviving HIV-free (hazard ratios, 4.0 and 2.3, respectively) than those whose mothers had counts of more than 500 cells per microliter. An elevated risk was also found for infants whose mothers were aged 20–30 (1.5), who had a birth weight of less than 2,500 g (1.9) and who were born following labor that lasted more than 12 hours (2.3). Infants delivered by cesarean section were at lower risk of not surviving HIV-free for six months than those delivered vaginally (0.5).

According to the researchers, their findings on mother-to-child transmission of HIV confirm that exclusive breast-feeding is safer for infants of HIV-positive women than mixed feeding for the first six months after birth. Furthermore, the researchers believe that these findings "warrant revision of the present UNICEF, WHO, and UNAIDS infant feeding-guidelines," which recommend that HIV-infected women feed their infants commercial or home-prepared formula rather than breast milk when possible.—*J. Thomas*

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In Tanzania, Use of Multivitamins Reduces Risk Of Low Birth Weight and Maternal Anemia

Pregnant, HIV-negative Tanzanian women who are given multivitamins have reduced risks of some adverse perinatal and postnatal outcomes but not others, according to a double-blind, randomized trial.[1] Compared with their counterparts given a placebo, women given multivitamins were less likely to deliver infants with a low birth weight (relative risk, 0.8) or a small size for gestational age (0.8) and were themselves less likely to have anemia postpartum (0.9). However, the risks of fetal death, preterm birth and maternal death were unaffected.

Pregnant women visiting prenatal clinics in Dar es Salaam, Tanzania, during 2001–2004 were eligible for the trial if they had a fetal gestational age of 12–27 weeks and tested negative for HIV. Participants received either a daily multivitamin or a daily placebo from enrollment until six weeks after delivery. The multivitamins contained niacin, folic acid and vitamins B_1, B_2, B_6, B_{12}, C and E in amounts providing, on average, 6–10 times the recommended dietary allowance for several of the B vitamins and vitamin C, and two times that for vitamin E. In addition, both groups received iron and folic acid supplements, as well as malaria prophylaxis. Social, demographic and obstetric information was collected and laboratory tests were performed at enrollment; thereafter, the women were examined monthly and received standard prenatal care. Midwives attended deliveries and weighed and measured infants. Outcomes were compared between groups according to the intended treatment.

Analyses were based on 8,428 women and their infants. On average, the women were 25 years old and the fetal gestational age was 21 weeks at enrollment. The majority of women had 5–7 years of education (67%) and had previously had at least one live birth (55%). About two-thirds were anemic (having a hemoglobin level of less than 11 g/dl). On average, the women took 88% of the pills they were given up to delivery and 80% during the entire trial, with no difference between the multivitamin and placebo groups.

Women in the multivitamin group had a lower incidence of low-birth-weight births (those with a birth weight less than 2,500 g) than did their counterparts in the placebo group (8% vs. 9%); the difference corresponded to a 20% reduction in risk (relative risk, 0.8). The result was similar when the analysis was restricted to singleton births. In addition, the average birth weight was higher in the multivitamin group, although only modestly so (3,148 g vs. 3,083 g).

Compared with women in the placebo group, those given multivitamins had a lower incidence of small-for-gestational-age births, defined as deliveries of infants with a birth weight below the 10th percentile for gestational age (11% vs. 14%); the decrease in risk was 20% (relative risk, 0.8). Average gestational age was older in the multivitamin group as well, but the difference was again small (39.5 vs. 39.4 weeks).

The two groups had statistically indistinguishable incidences of preterm birth, defined as birth before 37 weeks (17% in each group), a finding that did not change when the analysis was restricted to singleton births. The groups also had nearly identical rates of extremely preterm birth, defined as birth before 34 weeks (5–6%); fetal death, defined as death at any time before delivery (4–5%); perinatal death, defined as death between 28 weeks' gestation and one week after delivery (6–7%); postnatal death, defined as death during the first six weeks after delivery (3% each); and maternal death, defined as death at any time up to six weeks postpartum.

Six weeks after delivery, relative to their counterparts given placebos, women given multivitamins had a lower incidence of anemia (19% vs. 22%), corresponding to a 10% lower likelihood of this outcome (relative risk, 0.9). There was a difference, albeit a small one, in average hemoglobin level as well (12.1 vs. 11.9 g/dl). The women in the multivitamin group were also less likely to have a CD4+ immune cell count below the median baseline value (775 cells/mm^3) at that time (31% vs. 38%), translating to a risk reduction of 20% (relative risk, 0.8). Average CD4+ values were modestly higher in this group (924 vs. 888 cells/mm^3).

Discussing the findings, the researchers point out that many developing countries already routinely provide iron and folic acid supplements to pregnant women and could add micronutrients at the recommended dietary allowance level for an increase in cost of roughly 20%. They note that the multivitamin-associated risk reductions observed in HIV-negative women were smaller than those previously observed in HIV-positive women in the same setting, and concede that it is unclear if multivitamins will have the same effects in populations that have less access to prenatal care than the trial population. Nonetheless, given the observed benefits and the low cost of this intervention, "multivitamins should be considered for all pregnant women in developing countries," they recommend.—*S. London*

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In Rural Area of Zimbabwe, Casual Sex May Explain Early Sex–HIV Risk Link

In Zimbabwe's rural Manicaland Province, having premarital sex before age 18 is positively associated with men's and women's lifetime number of partners, number of recent partners and number of current sexual relationships, but also with consistent condom use.[1] Early first sex is also associated with an increased risk of HIV infection for women; this relationship is significant when the number of years of sexual activity is taken into account, but not when the number of lifetime partners is controlled for. Males' age at first sex is not associated with their risk of acquiring HIV infection. These are among the details about timing of sexual debut, its determinants and its consequences provided by results of a survey conducted in 1998–2000.

The survey was carried out among a population-based sample of men aged 17–54 and women aged 15–44. Researchers conducted face-to-face interviews with participants, who wrote their responses to sensitive questions on cards that they dropped into a locked box. Free HIV counseling, as well as treatment for other sexually transmitted infections, was offered in each of the 12 communities involved. Analyses were based on data from 4,138 men and 4,948 women who provided consistent information about their age and their age at first sex.

Eighty-three percent of men and 81% of women in the sample were sexually experienced. The median age at first sex was 19 years for men and 18 for women. Results of chi-square tests for trends suggest that the median for men declined over the 30 years preced-

ing the survey; the median for women was stable for 20 years but appears to have increased during the last 10 years before the survey.

In one set of analyses, the researchers calculated hazard ratios to estimate associations between sexual experience among those younger than 25 and a wide range of socioeconomic characteristics and AIDS knowledge. At the multivariate level, few significant associations emerged. Among young men, students and those who were unemployed were less likely than manual laborers to have had sex (hazard ratios, 0.6 and 0.9, respectively), members of traditional churches were more likely than Anglicans to be sexually experienced (1.4), and the likelihood of sexual experience was greater among minority tribes than among the Manyika, the predominant group (1.3). Among young women, students, those in skilled occupations and those who listened to the radio daily had a reduced likelihood of being sexually experienced (0.2–0.8), as did 15–19-year-olds who had completed their primary education (0.7). Members of minority tribes and women who had previously lived in an urban area or in a different rural area had an increased likelihood of being sexually experienced (1.3–1.5).

The next set of analyses used linear and logistic regression to determine the association between sexual debut before age 18 and selected outcomes related to sexual behavior: numbers of lifetime partners (with and without adjustment for number of years of sexual activity), partners in the past month, sexual encounters in the past two weeks and current relationships; consistent condom use in the past two weeks; and divorce. For both males and females who had first had sex before age 18 outside marriage, the coefficients were positive and significant for all outcomes except divorce (which was nonsignificant). These results indicate that individuals who had early premarital sex subsequently engaged in more sexual activity than others, but also that they were more likely to protect themselves by using condoms. Fewer results were significant for men and women whose first intercourse had occurred before age 18 within marriage, and the magnitude of the associations was smaller.

Finally, logistic regression was used to measure associations between age at first sex and the likelihood of acquiring HIV infection. In multivariate models controlling for the number of years of sexual activity, women who had initiated intercourse at ages 12–16 were significantly more likely than those whose sexual debut had been at age 21 or later to become HIV-infected (odds ratio, 1.6). Age at first intercourse was not a significant predictor of HIV risk for males in this model or for either gender in a model that controlled for the lifetime number of partners.

Because the survey was cross-sectional, the researchers note, the data do not imply "that early sexual debut leads to a spiral of decline and riskier sexual behavior." The investigators conclude that delaying sexual debut would have only a limited effect on lifetime HIV risk at the population level because "the casual nature of...sexual activity rather than...early sexual debut appears to be what leads to...infection" among individuals in Manicaland who begin their sexual lives at a young age.—*D. Hollander*

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Herpes Simplex Infection Increases HIV Risk for Men Who Have Sex with Men

In a randomized, controlled study of an HIV prevention intervention conducted among high-risk men who have sex with men, HIV infection rates were elevated among those who acquired herpes simplex virus type 2 (HSV-2) during follow-up, particularly within six months of the herpes diagnosis.[1] The risk of herpes, in turn, was elevated among black men and among men who engaged in certain risky behaviors; it was not reduced among those who participated in the intervention.

The study, which was carried out in six U.S. cities from 1999 to 2003, recruited HIV-negative men who were at least 16 years old, had had anal sex with a man in the year before enrollment and were not in a mutually monogamous relationship of two or more years' duration with an HIV-negative partner. Participants who were assigned to the intervention received individualized counseling in 10 hour-long sessions over 4–6 months, followed by quarterly maintenance sessions; those assigned to the control group received standardized pretest and posttest counseling and semiannual HIV tests. At six-month intervals, participants completed audio computer-assisted self-interviews about their sexual risk behavior since the previous interview, and provided blood samples for HIV and herpes testing. HSV-2 infections acquired during follow-up were categorized as recent incident at the visit at which they were detected, remote incident at visits within the next 24 months and prevalent at all subsequent visits. The analyses were based on the 3,909 participants for whom valid HSV-2 tests were available (91% of the cohort). These men were about evenly divided between the intervention and control groups; in both, the median follow-up time was 36 months.

Twenty percent of men in the analytic sample had HSV-2 infection when they entered the study, 75% were seronegative throughout the study and 4% acquired the virus during follow-up; the incidence of HSV-2 did not differ between the intervention and control groups. After conducting univariate regression analyses to identify potential predictors of herpes infection, the researchers performed multivariate hazard analyses to assess independent associations. These calculations confirmed that the likelihood of acquiring HSV-2 was similar for those assigned to the intervention and controls. Black men were significantly more likely than whites to become infected during follow-up (hazard ratio, 1.9), and those who reported having had unprotected receptive anal intercourse five or more times since the previous interview were more likely to do so than were those who said they had not engaged in this behavior (2.6). The likelihood of HSV-2 acquisition also was raised among men who, in the last six months, had had an HIV-positive male partner (1.6) or had had six or more partners (1.5).

Overall, the rate of HIV acquisition during follow-up was 1.9 per 100 person-years. Rates were significantly higher, however, among participants with herpes infection—6.9 per 100 person-years among those with recent incident infection, 6.8 per 100 among those with remote incident HSV-2 and 2.7 per 100 among those with prevalent infection. In analyses controlling for study arm, study site, age, race and a variety of risky behaviors, men with recent incident HSV-2 infection and those with prevalent infection were significantly more likely than those who remained free of HSV-2 to acquire HIV (hazard ratios, 3.6 and 1.5, respectively). Remote incident herpes infection was associated with an increase in the likelihood of HIV acquisition in the univariate analysis, but not in the multivariate analysis.

Twenty participants acquired both HSV-2 and HIV during follow-up; seven had the HSV-2 diagnosed before the HIV, and 13 had both in-

fections detected at the same visit. No herpes infections were detected after an HIV diagnosis, because participation in the study ended if a man tested positive for HIV. The researchers note that distinguishing between a causal association and simultaneous acquisition of the two infections "is very difficult and would require very frequent HSV-2 and HIV testing."

Given that the behavioral intervention was not associated with a reduced risk of HSV-2 acquisition, the researchers stress the need for studies to evaluate other prevention approaches, including education, counseling and potential vaccines. Furthermore, they conclude that HSV-2 infection is an important risk factor for HIV acquisition in this population and therefore "appears to be an important target for HIV prevention interventions."—*D. Hollander*

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In France, Over-the-Counter Emergency Contraception Increases Access, Not Risk

Increases in the use of emergency contraception have little apparent effect on indirect indicators of women's risky sexual behavior, according to a study of two cross-sectional surveys of women in France.[1] Use of emergency contraception rose between 1999 and 2004, following the May 1999 introduction of a dedicated product that was almost immediately available in French pharmacies with no prescription requirement; however, researchers found no increase in the proportion of women who had ever had intercourse, no decrease in the age at first sex and no increase in the proportion of young women at risk for unintended pregnancy. The use of modern contraceptives increased in the first five years of emergency contraception's over-the-counter status, and among women at risk for unintended pregnancy, levels of contraceptive use and use of effective methods did not diminish.

The data came from two large-scale, household-based health surveys of 12–75-year-olds, conducted in 1999 and 2004. Analyses were restricted to the 4,166 women in 1999 and 7,490 in 2004 who were between the ages of 15 and 44 and had responded to questions on sexual activity, STIs, contraceptive use and abortion. Relevant questions were the same in the two surveys. The researchers used a variety of logistic regression techniques to examine differences between survey years in women's emergency contraception use, sexual experience, contraceptive use and experience of abortion.

In late 1999 (six months after the introduction of the dedicated over-the-counter emergency contraceptive pill), 10% of sexually experienced women reported that they had ever used emergency contraception. By 2004, the proportion had risen to nearly 17%, and increases were significant for all age-groups but the oldest (40–44). Women aged 15–24 experienced an increase in emergency contraception use of 17 percentage points, while use among women aged 25 or older increased only five percentage points between 1999 and 2004.

In 2004, most women (60%) who had ever used emergency contraception had last obtained the drug from a pharmacy with no prescription. Further reflecting women's preference for obtaining emergency contraception directly from a pharmacy, 85% of women who had used the method in the last year had gotten it without a prescription. Older women had sought a prescription more commonly than their younger counterparts had (48% of 40–44-year-olds, compared with 12% of women younger than 40).

Despite the increase in emergency contraception use, the availability of the drug apparently encouraged little change in women's sexual activity or risk for unintended pregnancy. The proportion of women who had ever had sex did not change, with the exception of a small but significant decline among women aged 35 or older. Age at first intercourse did not change in any age-group.

The proportion of women younger than 25 who were at risk for unintended pregnancy (sexually active in the 12 months prior to the survey, currently with a partner, able to conceive and not trying to become pregnant) did not change between 1999 and 2004. The proportion of women aged 25 or older who were at risk exhibited a slight upswing, which was attributable to an increase from 72% in 1999 to 80% among those aged 40–44. Among those at risk for unintended pregnancy, the proportion who used contraceptives, either consistently or sporadically, remained stable among women younger than 25 years old (94% in 1999 and 96% in 2004), and decreased slightly but significantly among older women (from 95% in 1999 to 93% in 2004). However, the researchers point out, the increase in risk and decrease in contraceptive use cannot be attributed to use of emergency contraception, as only a small proportion of women older than 25 (9–21%, depending on specific age-group) reported having used emergency contraception in 2004.

Among women using any contraceptive, the proportion using the most effective methods increased from 84% in 1999 to 87% in 2004, while the proportion using other methods decreased from 16% to 14%. These changes were mainly attributable to a substantial shift among 18–19-year-olds from condom use to pill use: In 1999, 22% of 18–19-year-olds used condoms and 77% used the pill; in 2004, 12% of 18–19-year-olds used condoms, while 88% were pill users. Among the youngest women in the sample (15–17-year-olds), contraceptive use did not change between 1999 and 2004.

Overall, 17% of women in 1999 and 16% of women in 2004 reported having had an abortion. The proportion decreased from 20% to 17% among women aged 25 and older, but was 7% in both years among younger women.

According to the researchers, France's "introduction of a dedicated product that was almost immediately available in pharmacies with no prescription requirement" had no negative influence on women's sexual behaviors. The researchers imply that instead of substantiating "concerns about the negative impact of easier access to [emergency contraceptive pills] on sexual risk-taking and regular contraceptive use," the policy did little more than allow women greater access to a needed drug.—*H. Ball*

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In South Africa, Some HIV Risk Factors Also Predict Intimate Partner Violence

Among young rural South African women, having experienced intimate partner violence is strongly associated with certain risk factors for HIV infection, according to an observational analysis.[1] Women who had experienced such violence were more likely than others to have had at least three sexual partners in the past year (odds ratio, 2.1), to have had sex recently (1.8) and to have a more educated partner (1.5)—all factors also associated with elevated

odds of HIV infection. Intimate partner violence was associated with increased odds of HIV infection before these HIV risk factors were taken into account, but not afterward.

Researchers analyzed information collected from sexually experienced women aged 15–26 years who lived in rural villages in the Eastern Cape province of South Africa and were participating in a trial of a behavioral intervention to prevent HIV infection. Most of the women were recruited from schools and lived with their families. At the start of the trial, they completed a questionnaire and gave a blood sample for HIV testing. The questionnaire asked about intimate partner violence (physical and sexual), as well as social and demographic factors, knowledge and attitudes about sexual and reproductive health and HIV, adverse childhood events (including sexual abuse), substance use, characteristics of the current or most recent main sexual partner, and sexual activity and practices.

The 1,295 women studied were 19 years old, on average. About 12% were infected with HIV, and 27% had experienced intimate partner violence, defined as more than one episode of physical or sexual violence perpetrated by an intimate partner. In an unadjusted analysis, relative to their counterparts who had not experienced such violence, women who had were more likely to be HIV positive (odds ratio, 1.6).

In a first bivariate analysis comparing HIV-positive and HIV-negative women, the positive women were older (20 vs. 19 years), and a larger proportion had ever been pregnant (34% vs. 20%). On average, the age difference between women and their partners was greater in the HIV-positive group (four vs. three years); moreover, larger proportions of HIV-positive women had partners who were at least three years older than they were (62% vs. 45%), who had at least a high school education (54% vs. 32%) and who earned money (45% vs. 35%). Women in the positive group had also had more partners in the past year (two vs. one), and a larger proportion had had at least three partners during that time (22% vs. 9%) and had been sexually active in the past three months (90% vs. 72%).

In a second bivariate analysis comparing women with and without a history of intimate partner violence, larger proportions of those who had experienced such violence had had a casual sexual partner (35% vs. 17%) and transactional sex with a casual partner (16% vs. 6%) or a main partner (28% vs. 20%). In addition, larger proportions of the women who had been assaulted by intimate partners had had sex in the past three months (82% vs. 71%) and three or more partners in the past year (19% vs. 7%). They also had higher mean scores on a variable measuring the experience of adverse events in childhood.

In a multivariate analysis assessing risk factors for HIV infection, women's odds of being HIV positive increased with each year of age (odds ratio, 1.4). In addition, four sex- and partner-related factors increased their risk of being positive—having at least three sexual partners in the past year (2.5), having had sex in the past three months (3.4), having a partner who was at least three years older (1.7) and having a partner with at least a high school education (1.9). Women who had experienced intimate partner violence did not have elevated odds of HIV infection in this adjusted analysis.

In a set of multivariate models testing associations between selected variables and the four sex- and partner-related HIV risk factors, women who had experienced intimate partner violence were more likely to have had at least three sexual partners in the past year (odds ratio, 2.1), to have had sex in the past three months (1.8) and to have a partner with at least a high school education (1.5). Other factors associated with an increased risk of having at least one of the four HIV risk factors included younger age (1.3), adverse childhood experiences (1.4), a greater number of years since sexual initiation (1.2–1.3), higher socioeconomic status (1.2), more egalitarian attitudes toward gender relations (1.4), having had transactional sex with a casual partner (1.9) and having been pregnant (1.9). On the other hand, women were less likely to have certain of these HIV risk factors if they were older (0.8), had higher resistance to peer pressure to have sex (0.7) and had a less controlling partner (0.8).

Taken together, the researchers assert, the results suggest that certain risky sexual behaviors—having more frequent sex and having more partners—mediate the association between intimate partner violence and HIV infection among young rural South African women. These results, they write, add to the evidence linking gender-based violence and HIV infection, and support the contention that whether it is direct or indirect, "there is an underlying, enduring, and strong association between experience of intimate partner violence and HIV risk practices." In conclusion, they say, "This suggests that undertaking efforts to promote gender equity and reduce levels of intimate partner violence are of critical importance for HIV prevention."—*S. London*

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Lowest-Dose Birth Control Pills Provide the Greatest Ovarian Cancer Protection

Oral contraceptive use has a well-established association with a reduced risk of ovarian cancer; new evidence from a population-based U.S. case-control study suggests that pills with the lowest hormonal content offer the greatest protection.[1] The odds of ovarian cancer were reduced by up to 80% among pill users, depending on the oral contraceptive formulation. Furthermore, the lower the dose of one particular progestin, the lower the risk of ovarian cancer. If all women had used some type of birth control pill, an estimated four in 10 malignancies might have been avoided; if all had used low-dose pills, that proportion would have been almost three-quarters.

Using data from two rapid-response systems, researchers identified residents of Hawaii and Los Angeles aged 18 and older in whom ovarian cancer was diagnosed between 1993 and 2005; they obtained information about tumor stage, grade and histology from pathology and surgical reports. A control group of women aged 18 or older with no history of ovarian cancer was randomly selected from among respondents to an annual household survey in Hawaii and by random digit dialing in Los Angeles. Participants completed interviews covering demographic, socioeconomic, health-related and contraceptive information; interviewers used monthly calendars and pictures of various oral contraceptives to help women provide detailed information about their reproductive history and pill use.

The analyses included 745 women with cancer and 943 controls. In both groups, women were, on average, about 56 years old; the vast majority were Asian or white. Women with cancer had had significantly less education and fewer pregnancies than controls, and were more likely to have a family history of ovarian cancer. They were significantly less likely to have been sterilized, to be premenopausal and to be using combined hormone therapy.

A total of 868 women (317 women with cancer and 551 controls) had ever used combination oral contraceptives and provided the information necessary for the researchers to determine the potency (low vs. high) of each hormonal component. Forty percent of ever-users had taken pills with a low concentration of estrogen (0.035 mg or less of ethinyl estradiol), and 10% had taken pills with a low concentration of progestin (less than 0.3 mg of norgestrel). These women had used oral contraceptives more recently than those who had used higher potency formulations, but they had used the pill for longer durations.

In analyses controlling for a wide range of potentially confounding variables, ever-use of oral contraceptives was associated with significantly reduced odds of ovarian cancer (odds ratios, 0.5 overall; 0.6 in analyses adjusted for duration of use). Associations were found for women who had taken pills with high doses of both hormones (0.6), low doses of both (0.2), or a low dose of estrogen combined with a high dose of progestin (0.5); differences among pill formulations were not statistically significant. The researchers estimate that use of any combined oral contraceptive might have averted 42% of ovarian cancers and that use of pills with low doses of estrogen and progestin might have prevented 73% of malignancies.

A similar pattern was observed in analyses restricted to women with invasive ovarian cancer. Compared with women who had never used the pill, ever-users had 46% lower odds of invasive cancer; significant reductions were found regardless of pill formulation. Both the overall results and those for invasive cancer were essentially the same for women younger than 55 (the only ones exposed solely to low-dose pills) as for the entire cohort.

A final set of analyses examined the ovarian cancer risk in relation to ever-use of monophasic pills containing the progestin norethindrone. These calculations showed a significantly reduced risk of disease associated with use of any such oral contraceptive (odds ratio, 0.6). The risk was dramatically lower among women who had used pills with 0.4–0.5 mg of norethindrone (0.1) than among those whose pills had contained 10 mg of the progestin; it decreased significantly as the dose of norethindrone declined.

The researchers acknowledge a number of shortcomings of their study, including the possibility of nonresponse bias and reliance on participants' recall. However, they also point to some distinctive strengths—particularly, that the cohort included enough women providing detailed information about pill use to permit important subgroup analyses. Noting that declines in ovarian cancer rates in the United States are partly attributable to oral contraceptive use, the researchers conclude that studies involving larger numbers of women are needed so that the association between low-dose pill use and ovarian cancer risk can be better understood.—*D. Hollander*

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