

Thai Men Who Patronize Prostitutes Place Their Wives at Risk of HPV-Associated Cervical Cancer

For Thai women, infection with human papillomavirus (HPV) type 16 or 18 is the most important factor in the progression of precancerous cervical lesions to invasive cancer; the risk of cancers associated with these viral types rises with decreasing age at first intercourse and with increasing numbers of pregnancies.¹ The great majority of women with cervical cancer have had intercourse only with their husbands, and their risk of cancer is strongly related to the frequency of their husbands' visits to prostitutes as young men; according to the investigators, most are therefore likely to have acquired carcinogenic types of HPV from their husbands.² These are the major findings of three interrelated studies—two involving women with cervical cancer and one involving commercial sex workers in Bangkok and husbands of a subgroup of women with cervical cancer and controls from the first two studies.

All participants in the first two studies were recruited from Siriraj Hospital in Bangkok. Women with newly diagnosed precancerous lesions or invasive cervical cancer were eligible if they had been admitted to the hospital between September 1991 and September 1993, had been born after 1929 and had lived in Thailand for at least one year before their interview. These women were matched to other hospitalized women without either of these cervical abnormalities, on the basis of date of admittance to the hospital, five-year age-group and area of residence. Investigators interviewed all participating women to obtain information regarding their use of contraceptives, sexual behavior, medical history, tobacco and alcohol use, and socioeconomic status. Blood samples and cervical scrapings were analyzed to detect markers for sexually transmitted diseases and to identify specific types of HPV. For the third study, the investigators interviewed and obtained biologic samples from a subset of the husbands of women with invasive cancer and of control women, as well as commercial sex workers in one brothel and one massage parlor in Bangkok.

Cofactors in HPV-Related Cervical Cancer

To investigate risk factors for specific types of invasive cervical cancer, the investigators analyzed data from 232 women with invasive cervical cancer and 291 controls.³ They also examined tissue samples from cases to classify tumors as either squamous or adenomatous. They then compared women with each type of tumor to controls, and compared cases with each of two strains of HPV (HPV-16 and HPV-18) to controls with no evidence of HPV. All odds ratios were adjusted for age using logistic regression analysis.

Women with squamous and adenomatous cancers were much more likely than controls to be infected with a carcinogenic type of HPV (79% and 76% vs. 3%). HPV-16, the most common carcinogenic type in this sample, occurred nearly twice as often in women with squamous tumors as in those with adenomatous tumors (60% vs. 33%), and was rare among controls (2%). HPV-18 was much more strongly associated with adenomatous cancers (43%) than with squamous ones (14%), and was not detected in any of the controls. Women with squamous and adenomatous cancers did not differ significantly with regard to any other risk factors.

The risk of both tumor categories increased as age at first intercourse declined: For example, compared with women who had first had sex at age 24 or older, those who had done so at ages 17–18 had three times the odds of developing an HPV-16-related tumor (odds ratio of 3.1) and more than four times the odds of having an HPV-18-related tumor (4.6). Women's pregnancy history also influenced their risk: Those who had experienced three or four pregnancies had a higher risk of developing both types of tumors than did women who had been pregnant only once or twice (odds ratios of 2.1 for HPV-16-related tumors and 4.1 for HPV-18-associated tumors).

Women with a Pap smear in the previous 12 months were at much lower risk for both HPV-16-related and HPV-18-related tumors (odds ratios of 0.2 and 0.1, respectively) than were women who had

never had a Pap smear, while women who had ever had a chest X ray were at lower risk (0.6 and 0.4) than those who had not. The odds of HPV-16-related cancer were significantly lower for women who had ever attended school (0.5) or used an IUD (0.4) than for women without those characteristics. Among women who had been pregnant, those with a history of spontaneous abortion had an elevated risk of HPV-18-related cancer (2.2).

Each of the associations with HPV-16-related cancer remained after the effects of other factors had been accounted for; the number of women with HPV-18-related tumors was too small to permit a similar analysis. No significant association was observed between either tumor category and number of sexual partners; use of oral contraceptives; smoking; or prior infection with herpes simplex virus types 1 or 2, syphilis or hepatitis B.

The investigators note that the association between early age at first intercourse and HPV-16-related and HPV-18-related tumors may be confounded by the sexual habits of the women's husbands and that the reduced risk of cancer related to HPV-16 observed among IUD users is probably the result of cervical cancer screening at the time of IUD insertion or removal. They also point out that school attendance and chest X rays are most likely markers for important protective socioeconomic factors that have yet to be identified. The investigators conclude that "the similarity in risk factors for cervical carcinomas with HPV-16 and HPV-18 DNA provides strong evidence that the same cofactors operate to enhance the carcinogenicity of these two viral types."

Progression to Invasive Cancer

To investigate risk factors for progression from precancerous lesions to invasive cervical cancer, the investigators analyzed data from 190 women with invasive squamous-cell cancer and 291 matched controls, and from 75 women with precancerous lesions and 124 matched controls.⁴ They compared cases to controls to determine the factors

associated with each type of cervical abnormality. They then examined the risk of invasive disease associated with each factor in relation to the risk of precancerous lesions to identify factors associated with progression to invasive cancer. All logistic regression results were adjusted for age.

The women with invasive cancer and their controls were somewhat older (median age, 43–45 years) than the women with precancerous disease and their controls (37–38 years). The proportions of women with invasive and precancerous disease reporting vaginal bleeding were similar (65% and 63%), as were the proportions reporting no specific symptoms (33% and 31%). Women with precancerous lesions were much more likely than controls to be infected with any type of HPV (77% vs. 10%), any carcinogenic type of HPV (57% vs. 6%), HPV-16 (38% vs. 5%) or HPV-18 (8% vs. 1%).

Women with invasive disease were significantly more likely than those with precancerous lesions to test positive for any HPV type (odds ratio of 2.7), any cancer-causing type of HPV (3.5), HPV-16 (4.2) or HPV-18 (4.0), indicating that HPV infection is a significant factor in the progression to invasive disease. No factor other than HPV infection had a significantly stronger association with invasive cancer than with precancerous lesions.

The Role of Husbands and Sex Workers

More than 90% of the women with cervical cancer and the controls participating in these studies reported only one lifetime sexual partner. To investigate the possible role of husbands in women's risk for HPV and cer-

vical cancer, investigators interviewed and obtained serum samples from the husbands of 50 of the 175 women with squamous-cell cervical cancer who reported one lifetime sexual partner, and the husbands of 98 of the 272 monogamous controls.⁵ Penile scrapings were obtained from 57 husbands of women with precancerous lesions or invasive disease and 68 husbands of controls. The association found in previous research between Thai men's sexual contact with prostitutes and their wives' risk of cervical cancer was confirmed in this study and suggests that the men acquire carcinogenic HPV from prostitutes and transmit the infection to their wives.

To determine the prevalence of carcinogenic HPV and high-grade precancerous lesions among commercial sex workers, the researchers interviewed and obtained blood samples and cervical smears and scrapings from 170 female massage parlor workers and 84 female brothel workers in Bangkok.

Women whose husbands reported more than 280 lifetime visits to prostitutes had more than three times the risk of invasive disease among women whose husbands reported no visits (odds ratio of 3.2). The husband's annual number of visits before the age of 30 and his use of condoms less than 10% of the time during these visits were also associated with an elevated risk of invasive cancer.

On average, the brothel workers interviewed were much younger than massage parlor workers (median age of 19 vs. 30 years) and were more likely to be infected with each of nine carcinogenic types of HPV tested. For example, among 20–24-

year-old women, the prevalence of HPV-16 was 18% for brothel workers and 10% for massage parlor workers.

High-grade precancerous lesions were found in 8% of brothel workers and 4% of massage parlor workers. Women who had high-grade lesions were more likely than those who did not to test positive for HPV-16 (odds ratio of 19.2).

While acknowledging that the response rate among husbands was low, the investigators note that their findings are consistent with those from studies with higher response rates and provide "direct evidence for the role of husbands as vectors of HPV transmission from prostitutes."—A. Hirozawa

References

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Female Condoms Remain Structurally Sound After Being Washed and Reused as Many as Seven Times

The female condom can be washed and reused several times and still meet structural standards set by the U.S. Food and Drug Administration (FDA), according to a study conducted in South Africa.¹ When women washed, dried and relubricated female condoms up to seven times, the devices continued to meet FDA requirements with respect to the amount of pressure they could withstand and the strength of their seams. Five holes were detected in the 295 condoms used, but these were not associated with the number of times the condom was used.

A sample of 50 women—predominantly commercial sex workers and clients at an inner-city sexually transmitted disease clinic—were enrolled in the study and instructed in how to clean a female

condom for reuse. (The procedure consisted of rinsing the condom; washing it for 60 seconds with liquid detergent; rinsing it; patting it dry with clean tissues or towels, or air-drying; and relubricating it with vegetable oil just before reusing.) Participants were given a condom and asked to use, wash and reuse it, and return it to the study site for laboratory testing. If the condom was found to be structurally sound, the women were asked to repeat the cycle with a new condom, reusing it twice; the cycle was repeated until the women washed a single condom seven times (i.e., used it a total of eight times).

Laboratory analyses of the used condoms tested the devices' water leakage, the maximum pressure they could withstand before bursting and the tensile

strength of the seams. Results were compared both with FDA standards for new condoms and with results for a sample of 20 unused condoms from the same production batch from which the study condoms were drawn.

Three-quarters of the women used liquid detergent to wash the condoms, as they had been instructed to do; the rest used bar soap or, in one instance, soap powder. Three in five women air-dried the condoms, and 99% relubricated the devices before reuse, primarily with baby oil, sunflower oil or petroleum jelly.

Five holes were detected in the 295 condoms used, for a breakage rate of 2%. In three cases, the women had noticed the holes and told clinic staff about them when they returned the condoms for test-

ing; the other two holes were found during the water leakage test. The holes were detected after various numbers of reuses, with no clear trend related to the number of times a condom was washed. Moreover, the investigators note that four of the holes were in the part of the condom that lies outside the vagina and that is twisted during removal of the device.

Regardless of the number of times a condom was washed, test values for burst and seam strength were above minimum FDA standards. Comparisons of reused and new condoms showed no differences in results for seam strength and minor variations for pressure.

The researchers comment that “although occasional holes result from the repeated handling of the condom, these are not sufficiently common to make the practice [of washing and reusing female condoms] unacceptable.” Their overall conclusion is that “while it is preferable to use a new female condom or male condom, a reused female condom may be an acceptable next choice in situations where this is not possible.”—*D. Hollander*

Reference

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Risk of HIV Transmission Is Raised by High Viral Load, Presence of Genital Ulcers

On average, each time a monogamous, heterosexual couple in which one partner is HIV-positive has intercourse, the probability that the virus will be transmitted to the uninfected partner is 0.11%, according to an analysis of data from rural Rakai, Uganda.¹ The probability rises significantly as the infected partner's viral load (the amount of virus in the blood) increases, and it is elevated if the HIV-positive partner has genital ulcers. Although some researchers have hypothesized that viral subtype is a factor in HIV infectivity, no such relationship was evident in this population.

The data on which the analysis was based came from an AIDS prevention study conducted in 1994–1998, for which researchers gathered information from more than 15,000 men and women aged 15–59. At follow-up visits every 10 months, participants were asked to provide blood and urine samples, and women were asked for a self-collected vaginal swab; all samples were tested for HIV and a variety of

other sexually transmitted diseases (STDs). In addition, participants completed interviews in which they were asked about their background characteristics and sexual behavior, including their number of partners, use of condoms and usual frequency of intercourse with each partner.

At the end of the study, the investigators identified couples in which one partner had been HIV-positive and the other HIV-negative at enrollment. To assess the probability of infection associated with various factors, they used data from the 174 couples in which both partners reported that they were monogamous and that the uninfected partner was monogamous throughout follow-up.

In 77 couples, the woman had been infected with HIV at enrollment, and in 97, the male had been the infected partner. The HIV-positive men and women had a median age of 29 and a median viral load of 12,476 copies per mL. By the end of the study, 27% of infected women and 18% of infected men had transmitted the virus to their partners. Participants reported having intercourse an average of 8.9 times per month; a high level of agreement between partners' reports supports the reliability of this information.

Using Poisson regression, the investigators estimated rate ratios of HIV transmission, controlling for the HIV-infected partner's sex, age, viral load, and STD symptoms and diagnoses. These calculations revealed no significant difference between men and women in the risk of transmission. While rate ratios also did not vary significantly by age, results of chi-square testing showed a significant trend toward a lower risk of transmission as an infected partner's age increased.

The risk of transmission climbed sharply and steadily as viral load increased: Compared with men and women whose viral load was less than 1,700 copies per mL, those with a viral load of 1,700–12,499 copies per mL were 16 times as likely to transmit the virus (rate ratio, 16.1); the rate ratio rose to 27.7 for individuals with a viral load of more than 38,500 copies per mL. An infected individual with genital ulcer disease was at increased risk of transmitting the virus (2.6), but no other STD-related factors were associated with the risk.

Overall, the probability of HIV transmission was 0.11% per act of intercourse. The probability was higher for individuals younger than 30 (0.13–0.17%) than for those aged 30 or older (0.06–0.09%), and it rose as viral load increased (from 0.01% at the lowest level to 0.23% at the highest). The age pattern was the same regardless

of viral load, and the viral load pattern was the same regardless of age. Similarly, the probability of transmission was higher among those with genital ulcers (0.41%) than among those without (0.11%), and this pattern held across levels of viral load. Infected women appeared to be more likely than infected men to transmit the virus (0.13% vs. 0.09%); the researchers note that while this difference was not statistically significant, it is consistent with incidence data from Rakai and with findings on transmission in other developing countries. No difference in the probability of transmission was detected between the two virus subtypes that are responsible for the HIV epidemic in Uganda.

While previous studies have examined the probability of HIV transmission per act of intercourse in the United States, Europe and Thailand, the researchers note that theirs was the first to do so in Sub-Saharan Africa, and their overall finding was similar to those from the earlier work. Given this similarity and the fact that different strains of HIV are prevalent in these various settings, the investigators conclude that the rapid spread of the virus in parts of Africa is unlikely to be attributable to characteristics of a particular subtype that facilitate transmission. Commenting on the association they found between the probability of transmission and viral load (which is consistent with results of other research indicating increased transmission among people with compromised immune systems), they suggest that interventions aimed at lowering viral load could reduce transmission.—*D. Hollander*

Reference

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In Kenya, the Risk of Poor Birth Outcomes Is Highest For a Woman's First Child

Birth order is the most consistent predictor of poor birth outcomes in Kenya, where women having their first child are about twice as likely as others to deliver prematurely, have a baby who is smaller than average and require a cesarean section. Other key factors influencing the odds of having a premature birth are related to the extent to which women use prenatal care services, while women's nutritional status is one of the most important factors in their infant's size at birth;

the odds of cesarean section, meanwhile, are affected by women's socioeconomic status and contraceptive practice. These are among the chief findings of an analysis of data from the 1993 Kenya Demographic and Health Survey.¹

The survey gathered information on women's background characteristics, as well as on pregnancies and births that occurred during the previous five years. A total of 5,295 births for which complete information was available were included in the analyses of factors associated with adverse birth outcomes. According to the women's accounts, 4% of these births were premature, 5% of the deliveries were by cesarean and 15% of the infants were smaller (i.e., weighed less) than average.

In bivariate analyses, the researchers identified a wide array of factors related to women's socioeconomic background, reproductive history, health care, nutritional status and biological characteristics that were associated with the risk of poor birth outcomes. They then used multilevel regression analysis to estimate the independent effects of these factors on women's odds of having a premature birth, a smaller-than-average baby or a cesarean section.

A woman's use of prenatal care and the quality of services played a large role in her risk of having a premature birth. Women who visited a prenatal care provider only once or twice had considerably higher odds of this outcome than those who made seven or more visits (odds ratio, 5.1). Furthermore, those who had at least one tetanus shot (which suggests good-quality care) had substantially reduced odds of delivering prematurely (0.3). The odds also were lower among women who delayed care until the second or third trimester (0.5 and 0.2, respectively) than among those who first saw a provider in the first trimester, a result that the researchers note probably reflects early initiation of care by women with pregnancy complications.

A number of other factors also were strongly associated with the risk of premature delivery. The odds of this outcome were significantly elevated among women having a first birth (2.3), those having a multiple birth (7.0) and those who were members of the Luo (as compared with the Kikuyu) ethnic group (7.1). Relative to residents of the Central Province, women who lived in Nairobi or Nyanza Province had sharply lower odds of delivering prematurely (0.3 and 0.2, respectively).

Some of the same factors affected women's likelihood of bearing a baby

who, by their report, was smaller than average. The odds of this outcome were elevated among women having a first birth (1.8) or a multiple birth (3.1), and were reduced among those who had had at least one tetanus injection (0.6). Region of residence again played a role; women from the Western Province had increased odds of bearing a small infant (1.8). In addition, women who bore a girl were more likely than mothers of boys to say that the baby had been small (1.8), and those who scored low on a scale assessing women's weight for their height (an indication of poor nutrition) had elevated odds of this outcome (1.5).

For the final outcome examined, cesarean delivery, women having a first birth were again at greater risk than those who had given birth before (odds ratio, 2.2). The odds of this outcome were almost doubled (1.5–1.9) among women of high (as opposed to medium) socioeconomic status, those aged 30–34 (compared with those in their early 20s) and those who had ever used a modern contraceptive (as opposed to those who had never practiced family planning). Compared with women whose height was in the range of 150–160 cm, shorter women had elevated odds of cesarean delivery (2.5), and taller women had reduced odds (0.7). The increased risks among women of high socioeconomic status and those who had used modern methods of contraception, the authors note, are not surprising, since these women were more likely than others to have had access to—and to have used—appropriate health facilities.

At the district level, the probability of cesarean delivery varied significantly. On average, cesarean deliveries occurred less frequently than would be expected in districts in the Western, Nyanza and Coast Provinces, and more frequently than expected in Nairobi and the Central Province districts.

The investigators note that their data are limited, since they reflect women's perceptions of their birth outcomes, rather than objective measures. Nevertheless, the researchers conclude that the findings point up the need for integrated maternal health programs that include prenatal and delivery care, as well as nutrition interventions. Furthermore, the analysts stress, it is "crucial" that women having a first birth get appropriate care, given their increased odds of all three adverse outcomes studied. And since regional variations were apparent for each outcome, it is also important for programs to be "sensitive to regional disparities."—*D. Hollander*

Reference

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Perceptions of Peer Behavior Predict Whether Peruvian Adolescents Have Had Sex

Peruvian secondary school students' perceptions of their peers' sexual activity is one of the most consistent predictors of their own behavior, according to results of a survey conducted in nine cities.¹ For example, males who said that many of their friends had had sex were more likely than those who thought that none had done so to be sexually experienced and to have had multiple partners in the past three months; however, they also were more likely than others to have used a condom at first intercourse. Self-esteem and socioeconomic status also play an independent role in determining whether young people will engage in risky or protective sexual behavior, but students' knowledge of reproductive health issues is not a factor.

The survey was conducted in late 1998 as part of an evaluation of Peru's national sexuality education program, launched in 1996. In all, 6,962 students from 38 schools participated. Schools and students were selected through two-stage cluster sampling in Lima and eight other cities that represent the country's major ecological regions (coast, mountains and jungle).

Female students outnumbered males by almost two to one because a disproportionate number of all-female schools were included; the researchers note that since they analyzed females and males separately, this disparity does not affect the results. One-third of participants were from Lima, and the rest were distributed about equally among the other regions. Two-fifths of students (mostly 13–14-year-olds) were in their first two years of secondary school; the remainder (who were typically 15–18 years old) were in their last three years.

Respondents completed a questionnaire that explored their knowledge of and attitudes toward issues covered in the sexuality education program, as well as a wide array of background and psychosocial characteristics. All students were asked if they had ever had sex; those in the upper three grades also were asked the number of partners they had had in the last three months and whether they had used condoms at first and last intercourse. The researchers conducted bivariate analyses to

identify factors that were significantly related to students' sexual behavior and condom use, and then used a variety of multivariate techniques to isolate the independent effects of these factors.

The bivariate analyses yielded several striking findings—particularly that students' knowledge of reproductive health risks and how to avoid them, perceptions of gender roles, and frequency of attendance at religious services were not associated with their sexual behavior or condom use. According to the researchers, the lack of an association for the first two of these factors probably reflects that participants uniformly reported themselves to be highly knowledgeable about reproductive health and quite “modern” with respect to gender role norms; the finding on religion, the investigators add, is more difficult to explain.

Sexual Behavior

Seventeen percent of all respondents—32% of males and 7% of females—had ever had sex. Results of a hazard regression analysis indicate that students' perceptions of their peers' behavior (regardless of the accuracy of those perceptions) were a strong predictor of whether they had had intercourse: Participants who said that a few or many of their friends had had sex were at least twice as likely as others to be sexually experienced themselves (hazard ratios, 2.0–2.3 for males and 2.5 for females); for males, the perception that many friends had been involved in a pregnancy also raised the likelihood of sexual experience (1.7).

Self-esteem was another key factor determining young people's sexual behavior: For both males and females, respondents who felt that they were always or almost always important to those they lived with were less likely to have ever had sex than were those who thought this was never the case (hazard ratios, 0.5–0.8). In addition, the likelihood of being sexually experienced was elevated for young men who said that they were almost always leaders among their friends (1.3) and was reduced among young women who always told friends when they disagreed with them (0.7).

Most background characteristics were not associated with students' having initiated sexual intercourse. However, women of high socioeconomic status were less likely than those in the lowest stratum to be sexually experienced (0.6), and men who lived in jungle areas were considerably more likely than residents of Lima to have had intercourse (2.6).

Overall, 5% of respondents (10% of males and 2% of females) had had intercourse in the three months before the survey. More than half of these young men (54%) had had two partners or more during that time, but nearly all of the women (91%) had had only one. The number of females with recent sexual experience was too small for further analysis, but the researchers assessed the determinants of multiple partners among males, using tobit regression analysis. Once again, peer norms and self-esteem played a substantial role in men's behavior: Males who perceived their friends to be sexually experienced or to have been involved in a pregnancy were more likely than others to have had multiple partners in the past three months (coefficients, 1.1–2.2), as were those who were almost always leaders among their friends (0.5).

Young men from the highest socioeconomic level and those who worked had an increased likelihood of having had more than one partner (coefficients, 0.6–0.8), and the likelihood of this behavior rose with age (0.8). Males living in the jungle were at greater risk of having had multiple partners than were their counterparts from Lima (1.9).

Condom Use

Among sexually active students, 38% of males and 26% of females said that they had used a condom at first intercourse; 63% and 42%, respectively, reported having used one at last intercourse. The researchers used logit regression analysis to examine the determinants of condom use, again excluding women because of the small number with sexual experience.

Men from the middle and high socioeconomic tiers were significantly more likely than those with low socioeconomic status to have used a condom at first intercourse (odds ratios, 1.6–2.2), and those who lived with neither parent were significantly less likely than those from two-parent households to have done so (0.3).

Only one factor related to perceptions of peers' behaviors influenced condom use at first intercourse: Men who reported that many of their friends were sexually experienced were significantly more likely than those who reported no sexually experienced friends to have used a condom at first sex (1.8). The investigators point out that this finding of a protective influence stands in contrast to the findings on sexual activity, which suggest that males' perceptions that their friends were sexually active led to risky behavior. A plausible explanation, they note, is that

young males anticipating their first intercourse were advised to use a condom by more experienced peers.

Finally, one measure of self-esteem was associated with increased odds of having used a condom at first intercourse. Students who said that they almost always needed guidance when they had a problem were significantly more likely than those reporting that they never needed guidance to have used a condom the first time they had sex (1.6).

Findings regarding condom use at most recent intercourse were essentially the same as those for use at first intercourse. A notable exception is that whereas a young man's perception that many of his friends were sexually experienced was associated with increased odds of use at first sex, it was associated with decreased odds of use at last sex. In the researchers' view, this result may point to changing effects of peer norms as young men become more sexually experienced, or it may reflect that the number of males reporting recent intercourse (250) was too small to yield reliable results.

Conclusion

In light of their findings, the researchers emphasize that programs directed solely at improving young people's knowledge of reproductive health “may not be sufficient to avert teens' risk-taking in settings presenting a large number of other risk factors.” Rather, they suggest, expanding programs' focus “to target some of the contextual factors that influence adolescent behavior is likely to enhance [their] impact.”—*D. Hollander*

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A First Pregnancy May Be Difficult to Achieve After Long-Term Use of an IUD

Women who have never given birth and have used an IUD for an extended period of time face decreased fertility when they try to conceive, according to a prospective study conducted in England and Scotland.¹ Thirty-nine percent of nulliparous women who discontinued IUD use to become pregnant gave birth within 12 months, compared with 54% of those who stopped using a barrier method; the proportion was significantly lower among women who had used an IUD for 78 months or more (28%) than for those who

had used one for a shorter period (45%). The association between extended IUD use and decreased fertility remained after other factors that affect fertility were taken into account.

To investigate the relationship between IUD use and subsequent fertility among nulliparous women, the researchers analyzed data from 558 women who had stopped using an oral contraceptive, IUD or barrier method in order to conceive. These women had been recruited between 1982 and 1985 as part of a larger prospective study at 17 family planning clinics, and were followed up on an annual basis through 1994. Study participation was restricted to white British citizens who had never given birth, were either married or in a stable living situation with a male partner, and were using an oral contraceptive or IUD at the time of enrollment. The researchers assessed return to fertility by calculating the length of time between a woman's first discontinuation of contraceptive use in order to conceive and a term birth; they excluded from their analyses women who were lost to follow-up, did not have a term birth or resumed contraceptive use.

At the time that the women discontinued contraceptive use in order to conceive, 29% had been using an IUD, 28% oral contraceptives and 43% a barrier method. (A small number of women using the rhythm method were included in the barrier category.) Some women had recently switched methods, however: Three months prior to stopping contraceptive use, 43% had been using oral contraceptives, 33% an IUD and 24% a barrier method.

Women who had been using an IUD at the time they discontinued practicing contraception were slightly older (mean age, 27.7 years) than women using oral contraceptives or barrier methods (26.0 years for each). In addition, they were more likely to be current or former smokers (54%) than were users of other methods (41–48%), and were more likely to have a history of miscarriage, abortion or ectopic pregnancy (25% vs. 13–17%). Women using barrier contraceptives were the most likely to have a history of two or more gynecologic or other selected illnesses (9%, compared with 3–4% of pill or IUD users). Social class, as measured by the husband's occupation, was lower for women using oral contraceptives (47% had husbands working in manual occupations) than for women using other methods (33–34%); however, social class based on the woman's occupation was similar across groups.

Overall, women who had been using a

barrier method achieved conception most quickly. Twelve months after stopping use, 54% of these women had given birth, compared with 39% of IUD users and 32% of those who had been taking oral contraceptives. However, 18 months after discontinuation of use, fertility was more similar among the three groups: Seventy-six percent of barrier method users, 70% of pill users and 67% of IUD users had given birth.

Duration of oral contraceptive use had no impact on fertility. However, women who had switched from oral contraceptives to a barrier method within three months before attempting to conceive were more likely to become pregnant within 12 months (54%) than were those who attempted to conceive immediately after discontinuing oral contraceptives (32%). Among women who had had an IUD, those who had used it for 78 months or longer were significantly less likely to give birth within 12 months (28%) than were those who had used it for a shorter period (46%). Too few women had switched from an IUD to a barrier method shortly before conceiving to permit analysis of the effect of such a change.

When women were classified on the basis of the contraceptive method they had used three months before attempting to conceive, fertility did not differ significantly across groups. Again, duration of use was not related to the rapidity with which pregnancy occurred among women who had taken oral contraceptives, but longer use of an IUD was associated with delayed conception. When women were classified according to whether they had ever or never used an IUD, duration of use was linked to fertility decline in a similar fashion. (Only 28 women had never used oral contraceptives; therefore, meaningful comparisons could not be made between ever- and never-users.)

In initial log-rank and proportional hazards analyses of individual factors, a number of factors were associated with delayed fertility at a significance level (p-value) of .10 or less: contraceptive method used; duration of IUD use; maternal age; social class, based on the husband's occupation; smoking history; and history of gynecologic and other illnesses. The researchers conducted a multivariate proportional hazards analysis to assess the independent effects of each of these factors on fertility.

According to the multivariate results, women who had taken oral contraceptives and those who had used an IUD for 42–78 months were less likely to give birth dur-

ing follow-up than were those who had used a barrier method (relative hazard of 0.7 for each group). There was an even more dramatic decline in fertility among women who had used an IUD for 78 months or more: These women were only half as likely as barrier method users to bear a child (0.5). Older maternal age, lower social class, and a history of multiple gynecologic and other diseases were also associated with decreased fertility (0.2–0.5).

Because the types of commonly used IUDs have changed and infection screening has improved since the time that these women were recruited into the study, the researchers warn that their results "should be extrapolated to present day practice with extreme caution." Nevertheless, they conclude that "long-term use of an intrauterine device by a nulliparous woman increases the risk of impairment of fertility to a clinically important extent," and cite the well-established link between IUD use and pelvic inflammatory disease, a known cause of infertility. They conclude that "intrauterine devices should be used sparingly in nulliparous women and, in particular, that use for many years should be avoided." —A. Hirozawa

Reference

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Short Anti-HIV Treatment Okay for Infant If Mother Receives Standard Regimen

The standard zidovudine regimen given to expectant mothers and their newborn children is no more effective in preventing perinatal transmission of HIV-1 than regimens in which the course of treatment for either the mothers or their infants is abbreviated, according to a randomized trial conducted in northern Thailand.¹ When both mothers and infants receive abbreviated zidovudine treatment, however, the transmission rate is more than double the rate for mother-infant pairs receiving the standard regimen (11% vs. 4%).

To determine whether the standard regimen of zidovudine could be shortened without increasing the risk of mother-to-child HIV transmission, researchers recruited 1,437 HIV-infected women at 27 rural and provincial hospitals in northern Thailand between June 1997 and Decem-

ber 1999. The women, who were enrolled at 28 weeks of gestation, agreed to feed their infants formula rather than breast milk, which could be a vehicle for HIV transmission. Participants were randomly assigned to four treatment groups. Women assigned to the standard regimen received oral zidovudine starting at 28 weeks' gestation and continuing through delivery; the drug was administered to their infants for the first six weeks after their birth. The second group tested abbreviated regimens for both mother and child: Women were given zidovudine from 35 weeks of gestation through delivery, and their infants received zidovudine for only three days following birth. The third regimen called for the standard treatment for the mother and the shortened treatment for the child; in the fourth, only the mother's treatment was shortened. Analysis was based on the participants' assigned regimen rather than on their actual compliance.

The characteristics of the participating women were similar across treatment groups: Eight in 10 were aged 20–30 years, six in 10 had had only one child, more than nine in 10 had no symptoms of HIV infection or AIDS, and none had previously received antiretroviral drugs. Compliance was excellent among women in all groups: More than nine in 10 took at least 80% of the prescribed zidovudine doses. CD4 counts were lower for women who enrolled later in the study than for those who enrolled earlier.

An interim analysis of mother-infant pairs enrolled before December 4, 1998,

showed that HIV transmission was significantly higher when both mother and child received shortened treatment (11% vs. 4%); the investigators therefore discontinued assignments to that treatment group. The infants of women who had been assigned to that group on or after the cutoff date but had not yet delivered were given the standard regimen and excluded from the efficacy analysis.

The HIV transmission rates for the group in which only the mother received abbreviated treatment and the group in which only the infant received abbreviated treatment did not differ significantly from the rate for the group receiving the standard treatment (9%, 5% and 7%, respectively). An analysis adjusting for time of enrollment (i.e., before or after randomization was limited to three groups) produced similar, non-significant results, as did analyses using HIV transmission or infant death within six months of birth as their endpoint.

The investigators then collapsed the four groups into two, comparing the transmission rate for mothers who received the standard regimen to the rate among mothers who received the abbreviated regimen. They found that mothers who received abbreviated treatment with zidovudine were more than twice as likely as those who received the standard treatment to transmit HIV to their infant (5% vs. 2%). The results did not change after adjustment for time of enrollment.

No women dropped out of the study because of zidovudine intolerance or toxicity. The risk of maternal death, stillbirth or serious complications for women re-

ceiving the short course of zidovudine did not differ significantly from the risk for women receiving the standard regimen. The four groups of infants had similar rates of health problems and death.

According to the investigators, their results provide clear evidence that pregnant women should be given the long regimen whenever possible. They suggest that a three-day course of treatment is appropriate for infants whose mothers are treated with zidovudine starting at 28 weeks' gestation, but recommend the long regimen for infants whose mothers start treatment late in pregnancy.

The authors of an accompanying editorial, however, observe that the findings have little significance for countries where "zidovudine prophylaxis has been largely superseded by prophylaxis with a combination of antiretroviral agents."² They also question the feasibility and effectiveness of a long maternal zidovudine regimen in countries with limited resources, noting that "initiation of treatment at 28 weeks of gestation not only is more costly in terms of drugs but also requires earlier and more frequent antenatal care and thus necessitates a strong health care infrastructure."—A. Hirozawa

References

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Pregnant Women Experiencing Job-Related Fatigue Face Elevated Risk of Premature Membrane Rupture

Working women pregnant with their first child who report occupational fatigue run a greater risk of preterm premature rupture of membranes than their counterparts who do not work outside the home or who work outside the home but do not experience occupational fatigue.¹ The risk of preterm premature rupture of membranes increases significantly as the number of sources of occupational fatigue increases—from 2% among women not working outside the home to 7% among those who report four or five sources of fatigue on their job. In addition, the number of hours worked per week is significantly associated with preterm premature rupture of membranes in working women pregnant with their first child. Similar associations are not apparent among working women

who have given birth previously.

To determine the relationship between occupational fatigue and spontaneous preterm birth (subdivided into spontaneous preterm labor, preterm premature rupture of membranes and indicated preterm delivery), researchers analyzed data from the Preterm Prediction Study. The prospective study, which was conducted at 10 locations in the United States between October 1992 and July 1994, included women who were 22–24 weeks pregnant at enrollment and had a singleton gestation and intact membranes.

Researchers obtained detailed socioeconomic, medical and obstetric data from each woman through interviews and by reviewing medical records. They also asked each participant to complete a nurse-administered questionnaire about her cur-

rent employment, the number of hours she worked per week and sources of occupational fatigue. The questionnaire asked about five specific sources of job-related fatigue: posture (standing for more than three hours daily); work with industrial machines; physical exertion; mental stress (doing repetitive or boring work); and working-environment stress (working in a cold, wet or noisy area). Participants were followed up until they delivered, and outcome data were collected.

The analyses include data on 2,929 women—1,218 who had not given birth before (nulliparous women) and 1,711 who had had at least one previous birth (multiparous women). Participants were predominantly black and low-income (62–63%); about one-third had less than

12 years' schooling. More than half had symptoms that suggested preterm labor, three in 10 smoked during pregnancy and one-quarter had vaginal bleeding within the first two trimesters. Overall, 14% of the women delivered preterm (before 37 weeks' gestation). Preterm premature rupture of membranes occurred in 5% of pregnancies and accounted for 33% of all deliveries before 37 weeks' gestation.

In univariate analyses, preterm premature rupture of membranes was linked to each of the five sources of occupational fatigue for nulliparous women; relative risks, when these women were compared with their counterparts who did not work outside the home, ranged from 2.6 to 3.1. Furthermore, the absolute risk grew significantly as the number of sources of occupational fatigue increased: from 2% among women not working outside the home to 7% among those reporting 4–5 sources of fatigue. No other category of preterm delivery was associated with job-related fatigue among women pregnant with their first child. However, these women also showed a statistical link between preterm premature rupture of membranes and the number of hours

worked per week: The risk of this outcome ranged from 2% for women not working outside the home to 9% for women working more than 40 hours per week.

Results of multivariate analyses that took into account women's socioeconomic background and clinical characteristics confirmed that nulliparous women who reported job-related fatigue had a significantly elevated risk of experiencing preterm premature rupture of membranes. The risk was more than doubled for those who worked with industrial machines (odds ratio, 2.2) and was nearly doubled for those reporting other sources of fatigue (1.6–1.7).

Occupational fatigue was not associated with any of the categories of spontaneous preterm delivery for multiparous women at the univariate level and therefore was not examined in multivariate analyses. The researchers initially speculated that this lack of association might reflect that women who have previously borne children preterm might limit their work activities during subsequent pregnancies. However, they found no significant demographic differences between women with and those without a history

of preterm delivery, and the same proportion of women in both groups (41%) worked during the study pregnancy.

According to the researchers, the major strength of their study is that it considers the individual components of occupational fatigue in relation to the various categories of spontaneous preterm delivery. They acknowledge, however, that its results may not be generalizable to the general obstetric population and that the findings are limited by deficiencies in the questions asked.

Commenting on their findings, the researchers observe that it remains to be seen why occupational fatigue is associated with an increased risk of preterm premature rupture of membranes only among nulliparous women. Given the "obvious public health importance" of such an association, they conclude that "studies to determine which nulliparous women may be at risk and why multiparous women appear able to avoid this risk need to be designed."—*J. Ochs*

Reference

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