

Long-Term Pill Use, High Parity Raise Cervical Cancer Risk Among Women with Human Papillomavirus Infection

Use of oral contraceptives for five years or more appears to raise the risk of cervical cancer among women infected with human papillomavirus (HPV). The odds of developing cervical cancer are nearly tripled among women who used the pill for 5–9 years and quadrupled among those who relied on the pill for 10 years or more, compared with the odds among never-users.¹ An HPV-positive woman's likelihood of developing cervical cancer is also associated with the number of times she has given birth. Compared with those who have never borne a child, HPV-infected women who have had 1–2 births have twice the odds of developing cervical cancer, and those who have given birth seven or more times have four times the odds.²

Oral contraceptive use and high parity long have been thought to be tied to the development of cervical cancer, yet past research into these associations has been hindered by a lack of information about whether women were infected with HPV, one of the main immediate causes of cervical cancer. A series of studies by the International Agency for Research on Cancer (IARC) included assessments of women's HPV status and thus provide an opportunity to investigate the independent role of reproductive factors in the development of cervical cancer.

Data and Analyses

The IARC sponsored case-control studies of invasive cervical cancer between 1985 and 1997 in eight countries (Brazil, Colombia, Morocco, Paraguay, Peru, the Philippines, Spain and Thailand). In addition, in two countries (Colombia and Spain), research was conducted on the occurrence of carcinoma in situ. All of the studies followed similar protocols. Cases (women with cervical cancer) and controls (women recruited either from the same hospital or from the same region as the cases) were interviewed in person. Interviewers collected detailed information on participants' background characteristics, sexual and reproductive behavior, contraceptive history, smoking habits, history of sexually transmitted diseases, Pap smear history and hygienic practices. HPV

infection was diagnosed through analysis of cervical cells collected from participants.

Data from these studies were pooled, yielding a total of 1,853 women with cervical carcinoma (either invasive or in situ) and 1,916 controls. HPV was detected in tissue samples from 1,676 cases and 255 controls; all subsequent analyses were focused on these women. The investigators used logistic regression to control for the effects of study center, age, education, smoking, lifetime number of sexual partners, age at first intercourse, Pap smear history, and pill use or parity (depending on the factor being studied).

Pill Use and Cervical Cancer

Roughly one-third of both cases and controls who were HPV-positive had ever used oral contraceptives; the average duration of use was 6.1 years. The data suggest that ever-users of oral contraceptives were slightly more likely than never-users to have developed cervical carcinoma (odds ratio, 1.4), although this increase was not statistically significant.

Among women who had used oral contraceptives for no more than four years, the odds of cervical cancer were no different from those among never-users. However, women who had taken the pill for 5–9 years had a significantly elevated risk of cervical cancer (odds ratio, 2.8), and those who had done so for 10 or more years had even further increased odds (4.0).

Compared with never-users, women who began taking oral contraceptives before age 20 or in their early 20s had elevated odds of cervical neoplasia (odds ratios, 2.9 and 1.7, respectively), while those who did so later had no increased risk. When the investigators examined duration of use and age at first use together, they found that women who had used the pill for five or more years were at similarly elevated risk regardless of whether they began using oral contraceptives before or after age 25. This finding leads them to comment that cancer risk is “more likely to be determined by duration of oral contraceptive use than by age at first use.”

Current pill users and women who had used

the pill in the preceding 1–5 years had increased risks of cervical carcinoma (odds ratios, 2.6 and 4.7, respectively), but use in the more distant past was not associated with the risk of disease. The effect of recency of use, however, depended on duration of use. For women who had used the pill for less than five years, the only effect was a marginal increase in risk among those who had used it within the previous five years. By contrast, longer-term users had an elevated risk of cancer that persisted for up to 14 years after they discontinued use.

Parity and Cervical Cancer

More than nine in 10 women with cancer and controls had given birth. Regardless of their cancer status, study participants had had about five births each, and the median age at first birth was 20–21 years. Cervical cancer risk rose steadily as a woman's number of births increased. Compared with nulliparous women, those who had borne one or two children had 1.8 times the odds of developing cancer; odds ratios were 2.6–2.8 for those who had had 3–6 births and 3.8 for those with seven or more births. Likewise, cervical cancer risk was closely linked to age at first birth; the odds ratio was highest among women who gave birth at age 16 or younger (4.4), and then ranged from 2.5 among those who initially delivered at ages 17–19 to about 2.2 among those who did so at age 20 or older.

Type of delivery also appears related to cervical cancer: The few women who had given birth only by cesarean section had a risk of cervical cancer no different from that among women with no lifetime births. However, the odds of cervical neoplasia were elevated among women who had delivered only vaginally (2.6) or both vaginally and via cesarean section (2.2). In contrast, the only association seen between a history of abortion (either induced or spontaneous) and cervical cancer was a significantly reduced likelihood of cancer among women who had had two or more abortions (odds ratio, 0.6).

When the researchers restricted their analy-

sis to women with at least one birth and controlled for the effects of age at first full-term pregnancy, the overall number of full-term pregnancies still predicted cervical cancer risk: Compared with women who had had 1–2 births, those who had borne three or four children had 1.5 times the odds of disease; the odds ratio climbed to 2.3 among women with seven or more lifetime births. This relationship was more pronounced among women whose cancer was diagnosed before age 45 than among those who found out later that they had cancer.

Women whose first full-term pregnancy occurred 5–14 years previously had elevated odds of cervical cancer (1.7), while those who had first given birth 15 or more years before had no increase in their cancer odds. By contrast, in analyses controlling for the effects of number of full-term pregnancies, age at first full-term pregnancy was no longer associated with cervical cancer risk.

Finally, the investigators examined the combined effects of parity and oral contraceptive use; for all comparisons, nulliparous women who had never used the pill are the reference group. Regardless of women's history of pill use, increasing parity was associated with increased cancer risk. For never-users of oral contraceptives, odds ratios rose from 1.8 for those who had had 1–2 births to 3.4 among those who had borne five or more children. Results were similar for women who had used the pill for less than five years, with odds ratios increasing from 1.9 to 2.6. Among those who had taken oral contraceptives for longer durations, however, the differentials were much sharper; the odds ratio was 4.9 for those with 1–2 lifetime births, 6.0 for those with 3–4 births and 11.8 for those who had given birth five or more times.

Conclusions

The researchers who analyzed pill use and cervical carcinoma comment that the relationship they found between the two suggests that oral contraceptives promote “some step in the process of HPV-related cervical carcinogenesis.” However, they find no evidence that pill use promotes HPV infection: An examination of all controls in the pooled data showed no association between oral contraceptive use and HPV infection.

As for the findings on parity and cervical cancer, the researchers responsible for those analyses observe that the lack of association between abortion and cancer “provides some hint that events related to the second and third trimesters of pregnancy or to delivery might

be relevant” to cervical cancer development. They cite changes in hormonal levels late in pregnancy that might increase the likelihood of cervical carcinoma.

The author of a commentary published along with the studies observes that they had several shortcomings, including wide confidence intervals in some of the analyses and reliance on just one assessment of HPV status (making it difficult to know how recently infection had occurred). Nevertheless, he notes that the most important aspect of the studies is that because they were restricted to women infected with HPV, they suggest that observed associations between cervical cancer and parity or pill use are not related to differences in levels of HPV infection. Confirmation of these results, the author argues, will bring about “wider acceptance that high parity and long-term use of oral contraceptives can act as cofactors in the genesis of cervical cancer.”³—*M. Klitsch*

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HIV-Related Stigma Falls, But Some Misperceptions About Transmission Persist

The level of stigmatization associated with HIV and AIDS has been declining within the United States, but the proportion of the public who hold misperceptions about how HIV is transmitted is rising. A national telephone survey of adults has shown that the odds of supporting the quarantine of people with AIDS decreased by 15% per year between 1991 and 1999.¹ Likewise, the odds that respondents would avoid contact with people who have AIDS or harbored negative feelings toward them decreased annually by about 10%. During the same period, however, the odds of believing that HIV infection could be contracted by being sneezed or coughed on rose significantly.

By interviewing nationally representative samples of adults in 1997 and 1999, re-

searchers were able to estimate the prevalence of stigmatizing opinions and wrongly held beliefs about HIV and AIDS among the American public. They also compared the results with those from a similar survey they conducted in 1991 to examine trends in the public's attitudes toward HIV and AIDS during the decade. Of the 1,309 interviewees in 1997 and 669 interviewees in 1999, 55% were female and about 80% were non-Hispanic white; the average age was 44–45, and the median educational level was some college or other post-secondary schooling.

The prevalence of extreme attitudes toward people with AIDS decreased significantly throughout the decade: Some 29–34% of respondents endorsed the segregation or public naming of people with AIDS in 1991, whereas 12–16% did so in 1999. The odds of supporting these punitive policies, as estimated by logistic regression analysis, decreased by 15% and 9%, respectively, each year. The prevalence of anger, fear or disgust toward people with AIDS also fell during the decade: The proportions of respondents harboring these negative feelings decreased from 27–35% in 1991 to 15–20% in 1999, corresponding to reductions in odds of 8–10% per year. From 1997 to 1999, the proportions supporting the mandatory testing of immigrants and of people at risk of getting AIDS decreased significantly—from 78% to 74% and from 74% to 64%, respectively. In addition, the odds of agreeing that most people with AIDS are responsible for having their illness decreased by 9% each year from 1997 (54% of respondents) to 1999 (48%). However, between 1991 and 1999, the proportion of respondents agreeing that people with AIDS have gotten what they deserve grew from 20% to 25%.

From 1991 to 1997, the proportion of those interviewed who believed that HIV could be spread by kissing an infected person on the cheek decreased significantly, from 17% to 13%. In contrast, respondents commonly answered incorrectly about the risk of HIV infection from other types of contact: From 1991 to 1999, the proportion of those believing that infection could be contracted by sharing a glass remained at about one-half, and the proportion believing that infection could be acquired by donating blood was roughly one-third. Moreover, the likelihood of wrongly replying that HIV could be transmitted by using public toilets or through coughing and sneezing was significantly higher at the end of the decade (41% and 50%, respectively) than at

the beginning (34% and 46%); the odds of giving these responses increased annually by 4% and 15%, respectively. The researchers show that the high level of misperception about HIV transmission is not due to public mistrust of scientists and doctors: At the end of the decade, the majority of respondents trusted these professionals to tell the truth about AIDS (70%) and believed them when they said that AIDS is not spread by casual contact (87%).

In 1997 and 1999, roughly one-quarter of those surveyed said they would feel uncomfortable if they worked in the same office or if their child attended the same school as someone with AIDS, or if they shopped in a local grocery store knowing that the owner had AIDS. Although the odds of avoiding people with AIDS in these three hypothetical situations decreased during the decade by 8–10% each year, three in 10 respondents in 1999 still would avoid shopping in a store if the owner had AIDS. The researchers comment that discomfort toward people with AIDS “might well translate into avoidance or discrimination in

some real-world interactions.”

The investigators note that although “overt expressions of stigma” seem to have decreased during the past decade, more covert forms remain. They warn that fear of people with AIDS and public support for punitive policies persist, calling these trends “disturbing.” According to the researchers, the findings have at least two implications for public health. First, AIDS educational efforts need to communicate more effectively how HIV is not transmitted. Second, public health policy should address the persistence of stigma to reduce its harmful effects on people with AIDS and to improve the success of programs and policies aimed at preventing HIV transmission. The authors conclude that “eradicating AIDS stigma remains an important public health goal for effectively combating HIV.”—*T. Lane*

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Not All Infants Born to Women with Preeclampsia Are Low-Birth-Weight; Gestational Age Is a Key Factor

Infants born at term to mothers with preeclampsia have similar birth weights, on average, to those of infants born to women who do not experience this condition; however, infants born preterm to mothers with preeclampsia weigh significantly less than those born to women with normal blood pressure during pregnancy, according to a retrospective cohort study of births in Canada.¹ Similar results were found in analyses comparing women who experienced gestational hypertension with normotensive mothers. Sixty-one percent of women with preeclampsia gave birth at term; thus, most infants born to women with the disorder had normal birth weights for their gestational age.

The study was based on the medical records of 97,270 women who delivered at 35 hospitals in Alberta between July 1991 and December 1996. Women who had used antihypertensive drugs before pregnancy and those who had multiple births, preexisting chronic hypertension, diabetes, gestational diabetes, cardiovascular disease or chronic renal disease were excluded, because these characteristics are associated with both preeclampsia or gestational hypertension and birth weight. The final sample consisted of 87,798 births.

Women were classified as having gestational

hypertension or preeclampsia by their blood pressure and urine protein level. Gestational age was based on the date of the mother’s last menstrual period, and was verified by first-trimester or early second-trimester ultrasound. Analyses of variance compared the mean birth weights of infants born to mothers with gestational hypertension or preeclampsia with the mean birth weights of infants born at the same gestation to normotensive women. Linear regression analyses were used to control for the confounding effects of maternal smoking, maternal age, parity, obesity, prior spontaneous and induced abortion, prior births of infants who were small or large for gestational age, anemia and premature rupture of membranes.

Eight percent of women in the overall population were aged 19 or younger, 54% were 20–30 and 37% were older than 30. Sixty percent had had previous births, and 27% had smoked during pregnancy. The incidence of hypertensive disorders was low: Four percent of women experienced gestational hypertension, and 2% experienced preeclampsia. Nine percent of births occurred preterm (i.e., at less than 37 weeks’ gestation), and 7% of newborns were low-birth-weight (i.e., less than 2,500 g). Sixty-one percent of women with

preeclampsia gave birth at term.

In univariate analyses, infants born preterm to women with preeclampsia weighed, on average, 179–464 g less than those born preterm to women with normal blood pressure during pregnancy; after adjustment for all potentially confounding variables, preterm infants of preeclamptic mothers weighed between 224 g and 665 g less than others, and the differences were statistically significant. Infants born before 37 weeks’ gestation to women experiencing gestational hypertension weighed, on average, 190–434 g less than those born before 37 weeks to normotensive women; in multivariate analyses, the average difference ranged from 55 g to 485 g. There were no significant differences between the birth weights of infants born at term to women experiencing gestational hypertension or preeclampsia and the birth weights of infants of women with normal blood pressure. In analyses taking into account women’s parity, no significant differences were found in the effects of preeclampsia and gestational hypertension on birth weight.

The researchers note that the finding that most babies born to preeclamptic women at term have normal fetal growth cannot be reconciled with the currently held belief that preeclampsia is caused by reduced blood flow through the placenta to the fetus. Instead, they suggest that preeclampsia is likely the result of multiple factors, and that there may be at least two types of preeclampsia: one that restricts fetal growth and often leads to preterm delivery and one that does not produce these effects. The researchers recommend that further research be done to determine “whether there is a difference between these two possible subtypes of preeclampsia in terms of onset and severity.”—*J. Rosenberg*

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Circumcision May Lower Risk of Both Acquiring And Transmitting HPV

Circumcised men are less likely than uncircumcised men to have penile human papillomavirus (HPV) infection, and female partners of men who engage in risky sexual behavior have a reduced likelihood of having cervical

cancer if the man is circumcised. According to a multinational study conducted by the International Agency for Research on Cancer (IARC), the odds that circumcised men had penile HPV infection were about 60% lower than the odds that uncircumcised men had this diagnosis.¹ Among monogamous women who had a partner reporting six or more lifetime sexual partners, the odds of having cervical cancer were reduced by about 60% if the partner had been circumcised.

Acknowledging that cervical cancer is the second most common cancer among women worldwide and that nearly all cases may be caused by HPV, the IARC Multicenter Cervical Cancer Study Group sought to investigate how circumcision affects the risks of genital HPV infection in men and cervical cancer in their partners. The researchers conducted a total of seven case-control studies between 1985 and 1993 in Spain, Colombia, Brazil, Thailand and the Philippines. They used a standardized questionnaire to interview women who had newly diagnosed, histologically confirmed cervical carcinoma in situ or invasive cervical cancer, as well as age-matched women without these forms of cancer. The investigators also enrolled each woman's partner with whom she had had regular intercourse for at least six months before the study. These men were administered a similar questionnaire and were tested for penile HPV infection.

The analyses were based on 1,913 male respondents—977 partners of women with cervical cancer and 936 partners of control women. Roughly half of the men were aged 38–56, about one-quarter were 37 or younger and the remainder were 57 or older. The women were distributed about equally among the three age-groups 36 or younger, 37–48, and 49 or older. Nineteen percent of the men reported that they were circumcised.

Medical examination of about two-fifths of the men showed that 95% had reported their circumcision status correctly. Circumcised men had a marginally significantly higher educational level than did uncircumcised men; they also were less likely to report genital washing after intercourse but more likely to have good genital hygiene. The two groups of men were no different in the following characteristics: age, age at first sex, number of lifetime partners, whether they had had sex with a prostitute, whether they had used a condom with the regular partner, the frequency of condom use with prostitutes and the current partner's number of lifetime partners.

Of the 847 uncircumcised men who had valid results in tests for penile HPV infection, 20% were positive for the virus, whereas only 6% of the 292 circumcised men with valid test results had the infection. The presence of HPV was consistently less prevalent among circumcised men than among uncircumcised men when the two groups were stratified according to the various characteristics. After the analysts made adjustments for potentially confounding factors (including study location), logistic regression analysis showed that the odds of penile HPV infection for circumcised men were about 60% lower than those for uncircumcised men, whether the circumcision status was self-reported or medically confirmed (odds ratio, 0.4 for each). Furthermore, men who had had six or more lifetime partners were more likely than those who had had five or fewer partners to have a diagnosis of penile HPV infection (odds ratio, 2.0).

Analysis of the effect of circumcision status on the prevalence of cervical cancer suggested that circumcision may reduce the likelihood of cervical cancer in the men's current partners (odds ratio, 0.7); however, this result was not statistically significant. Circumcision status did not affect the odds that women had cervical cancer, regardless of women's age, age at first sex, educational level, number of lifetime partners or condom use. When the researchers limited their analysis to the 1,420 monogamous women, they found that the odds of having cervical cancer were reduced by about 60% among women with a partner who reported six or more lifetime sexual partners and had been circumcised (0.4).

The investigators also studied the effect of circumcision on the risk of cervical cancer according to males' level of risky sexual behavior. They classified males who reported six or more lifetime partners and an age at first sex of below 17 as having a high risk, those reporting five or fewer partners and an age at first sex of at least 17 as having a low risk, and the remainder as having an intermediate risk. Circumcision of low-risk men did not reduce women's risk of cervical cancer (odds ratio, 1.6). However, circumcision was linked to reductions in the risk of cervical cancer as the men's sexual behavior got riskier (odds ratios for women whose circumcised partners had intermediate and high risk were 0.5 and 0.2, respectively).

The authors of an accompanying editorial point out that the strengths of this study are its size, the HPV detection method used (polymerase chain reaction assay) and the general-

izability of the findings because of the multiple study locations.² They note, however, that some confounding factors are difficult to measure accurately and control for, such as frequency of genital washing and genital hygiene. Furthermore, although the investigators focused on monogamous women, they cannot exclude the possibility that women with cervical cancer had been infected with HPV by an earlier, unreported partner; hence, the association between circumcision and the risk of cervical cancer may have been underestimated.

The researchers suggest that circumcision may reduce the risk of acquiring and transmitting HPV and hence the risk of cervical cancer. They propose that circumcision reduces the vulnerability of the penis to HPV infection: In uncircumcised men, the inner surface of the foreskin offers a portal of entry for HPV when it is exposed, by way of tiny ulcers and abrasions that occur during intercourse. The editorialists emphasize that circumcision itself does not protect against cervical cancer: The protective effect relates only to a reduction in the likelihood of genital infection with oncogenic HPV in men. Regarding other potential health benefits of circumcision, the investigators recommend that "further study is needed to determine whether routine circumcision can reduce the risks of HIV and HPV infections and other sexually transmitted diseases."—*T. Lane*

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Jail-Based Syphilis Services Can Benefit Both Arrestees And the Larger Community

Programs offering routine testing and treatment for syphilis in jails can help prevent transmission of the disease by identifying infected individuals and treating them before they return to the community, a study conducted in Louisiana demonstrates.¹ One percent of arrestees who were tested for syphilis upon entering a parish jail between 1994 and 1998—nearly 500 individuals—were found to have a previously undetected infection, and 61% of these men and women received treatment

while incarcerated. Trends in prevalence over the study period were similar to those in the surrounding community, suggesting that jail-based programs could be a means for monitoring community-level infection rates.

The program, designed as a response to a statewide syphilis epidemic, was launched in 1994 at the jail serving the metropolitan Baton Rouge area. Participation is not required, but arrestees are offered the opportunity to be tested for syphilis within 24 hours of their arrival at the facility; likewise, treatment is offered to infected individuals, but is not mandatory. Researchers analyzed program data for the period from July 1994 through December 1998 to assess the program's effectiveness in detecting untreated cases of syphilis and its value to community-level surveillance, as well as to examine the population at greatest risk of infection.

During the study period, more than 50,000 men and women were booked into the jail; 76% underwent syphilis testing. Most of those who were not tested either refused or were freed on bond before the test could be administered. Arrestees who were tested were predominantly male (84%) and black (73%), with a median age of 29 years. In all, 494 cases of syphilis were detected among individuals who had no history of the disease, for an overall prevalence rate of 1.3% among those tested. Prevalence was more than twice as high among women and black arrestees as among men and whites (odds ratios, 2.4 and 2.6, respectively); it rose as arrestees' age increased. Sixty-one percent of infected individuals were treated before release; those who did not receive treatment in jail were followed up by disease intervention specialists to ensure that they obtained treatment once they returned to the community.

Over the course of the study, the prevalence of early syphilis (defined as primary, secondary or early-latent infection) declined by 68%. At the same time, the prevalence in East Baton Rouge Parish, as reported by laboratories and health care providers, fell by 79%. (Cases of early syphilis identified in the jail program made up a substantial proportion of those in the community overall—between 15% and 31% each year between 1995 and 1998.) The researchers note that the prevalence monitoring data from the program are less likely than the case-reported data from the parish to be biased by underreporting, and they therefore conclude that “in areas where case reporting is weak and jail screening coverage high, monitoring prevalence among arrestees can be a useful way to monitor syphilis trends independently of other [dis-

ease] control program activities.”

Using data on 125 arrestees in whom early syphilis was diagnosed in 1995–1997 and 385 uninfected controls, the researchers examined the characteristics associated with syphilis in this jail population. The findings indicated that among women, those who had syphilis were significantly more likely than controls to have been arrested for prostitution (odds ratio, 7.0). Among men, a syphilis diagnosis was associated with increased odds of felony theft (4.3). No other charges (including possession of substances and previous incarceration) were associated with syphilis risk, and these two accounted for only small proportions of infected individuals (13% of females and 12% of males). Therefore, the investigators observe, cause of arrest is not a valid criterion for determining whom to screen for the disease in jail-based programs.

The researchers conclude that jail-based programs are useful as public health interventions and as tools for monitoring disease trends. Noting that “serologic screening has been a cornerstone of syphilis control in the United States,” they recommend that control strategies involve “targeted serologic screening programs” not only in jails, but also in other community-based settings, such as drug treatment centers and emergency rooms.—*D. Hollander*

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Prenatal Cocaine and Opiate Use Are Linked to a Wide Variety of Health Hazards

Women who use cocaine or opiates during pregnancy are at elevated risk of a number of high-risk conditions and behaviors.¹ Data collected at four clinical centers in the United States indicate that compared with women who were not exposed to these substances during pregnancy, those who used them were more likely to be infected with syphilis, gonorrhea, hepatitis or HIV; to have psychiatric or emotional disorders; and to have experienced pregnancy-related bleeding. These women also were significantly more likely than others to have used tobacco, alcohol or marijuana while pregnant.

As part of a large research study of the toxic

effects of drug use during pregnancy on the health of the woman and the fetus, investigators collected data on women who gave birth between May 1993 and May 1995 at large medical facilities in Florida, Michigan, Rhode Island and Tennessee. Women were not eligible to participate if they were younger than 18, had evidence of psychosis or had been institutionalized because of emotional problems or mental retardation; if the newborn was unlikely to survive; or if there was a multiple gestation. In addition, potential participants were excluded at all centers if they refused to give consent and at some centers if they could not be interviewed in their preferred language.

Specially trained staff interviewed women about their social and demographic characteristics and their history of drug use, both prior to and during the pregnancy. To encourage the women to report honestly, each site had obtained a certificate of confidentiality from the National Institute on Drug Abuse exempting the research staff from requirements that they report prenatal drug exposure to state child protection services. The researchers defined drug use during pregnancy on the basis of the women's report during the interview or the detection of drug metabolites in the infant's meconium (the contents of the first bowel movements following birth).

The analyses are based on a cohort of 8,627 mother-infant pairs. Half of the participants (50%) were black, 35% were white and 15% were of some other race. Forty-nine percent were aged 18–25, 44% were 26–35 and the remaining 8% were 36–49. Unmarried women—either never-married (60%) or divorced (2%)—substantially outnumbered currently married women (38%), and the majority of participants had their delivery covered by Medicaid (64%). Sixty-seven percent had more than a high school education, and 51% had worked in the preceding year. Nearly all (95%) received prenatal care.

Thirteen percent of study participants had ever used cocaine, and 59% of these had used cocaine during their pregnancy. Additionally, 2% had ever used an opiate, and 58% of these had done so during the pregnancy.

Women who had used drugs while pregnant were substantially more likely to be black than were nonusers (76% vs. 48%) and were older, on average (30 vs. 26 years). Moreover, 93% of those who had used cocaine or opiates had also drunk alcohol or smoked cigarettes or marijuana while they were pregnant, compared with only 42% of nonusers.

In analyses controlling for the effects of differences by study site, the odds of a number of conditions or infections were significantly elevated among women exposed to cocaine or opiates during pregnancy: a positive HIV test (odds ratio, 8.2); syphilis (6.7); hepatitis (4.8); psychiatric, nervous or emotional illness (4.0); and gonorrhea (1.9).

Drug use during pregnancy also was associated with some delivery complications or treatments needed during pregnancy or labor. In particular, women who had used substances were substantially more likely than nonusers to have been hospitalized as a result of violence during pregnancy (odds ratio, 18.9). They also were significantly more likely than others to have been prescribed psychoactive drugs during pregnancy (2.8), to have experienced bleeding problems (2.3 for placental abruption and 1.9 for placenta previa) and to have had prolonged rupture of the membranes (1.8). Although the great majority (77%) of women who had used drugs received prenatal care, they were less likely than nonusers to have done so (odds ratio, 0.1). On the other hand, women exposed to cocaine or opiates were less likely than unexposed women to experience preeclampsia (odds ratio, 0.6) and to need anesthetics during their hospitalization (0.6).

Some of these findings differed by type of substance used. When the researchers restricted analyses to women who had used only cocaine (which does not usually involve injection with a needle), they found that odds ratios for most problems did not differ much from overall results. However, when they focused on women who had used opiates only (which usually involve needle use), they found that the odds of hepatitis were further elevated (odds ratio, 7.2), while the odds of HIV infection and syphilis were no longer significant. In addition, the odds of chronic hypertension became significantly elevated (3.0), as did the odds of needing medication for pain or sedation during delivery-related hospitalization (2.6). The odds of bleeding problems in this subgroup were nonsignificant.

The authors comment that their findings of an increased risk of hospitalization, particularly because of violence, “have far-reaching implications,” and note that “physicians who are caring for women who admit to drug use, particularly cocaine use, should have a high index of suspicion for exposure to violence and abuse.” They also observe that their findings support those of previous studies suggesting a link between drug use and bleeding com-

plications such as hemorrhage before delivery, but they draw attention to the “relative rarity” of these complications, even in such a high-risk population, and attribute this to the women’s greater-than-expected use of prenatal care. It is important, they conclude, to ensure the availability of “early, comprehensive prenatal care for [drug]-exposed women to prevent or treat the identified health hazards that accompany drug exposure.”—*M. Klitsch*

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Risk of Low or Very Low Birth Weight Rises After Assisted Reproduction

Infants conceived with the use of assisted reproductive technology (ART) are more likely than infants in the general population to have low or very low birth weight, a large population-based study reveals.¹ The increased prevalence of low or very low birth weight among babies conceived using procedures in which eggs and sperm are handled outside the body (including embryo transfer) can be partially explained by the relatively high proportion of multiple births resulting from these procedures. An additional factor, however, is that singletons conceived through these techniques have almost a doubled risk of having low or very low birth weight, even if they were the only fetus present during pregnancy.

By obtaining data reported to the Centers for Disease Control and Prevention by institutions that had treated infertility with ART, researchers were able to study nearly all such procedures performed in the United States between 1996 and 1997 for women aged 20–60. They identified 42,463 infants born alive who were conceived through a total of 136,972 ART procedures, and they analyzed the prevalence of low birth weight (2,500 g or less) and very low birth weight (less than 1,500 g), as well as factors such as the woman’s age, number of previous births, type of ART used, whether ART had been used before and cause of infertility. The researchers calculated expected numbers of infants with low and very low birth weight from data on 3.4 million infants in the general population born in 1997 to women aged 20 or older. The expected numbers were

adjusted for maternal age and number of previous births, and were used to estimate standard risk ratios for low and very low birth weight.

Compared with the whole group of women who had used ART, women who gave birth to live infants were more likely to be younger than 35, to have had previous deliveries, to have used fresh (rather than frozen) embryos and not to have used ART before—characteristics linked to higher ART success rates. Singletons and babies from twin births each accounted for 43% of infants conceived by ART. Twelve percent of infants were from triplet births, and the remainder were from births of four or more babies. The proportion of infants who had low birth weight increased from 13% among singletons to 55% among twins, 92% among triplets and nearly 100% among infants from births of four or more babies. The rate of low birth weight was higher among singletons if ultrasound scanning during early pregnancy had detected more than one fetal heart (18–50%) and among twins if scanning had detected more than two fetal hearts (61–90%). Furthermore, the proportion of very-low-birth-weight infants increased with the number of babies per delivery, ranging from 3% among singletons to 67% among infants from births of four or more babies.

The numbers of singletons conceived with ART who had low and very low birth weight were nearly twice the predicted numbers (risk ratio, 1.8 for each). When the singletons were categorized by whether they were born at term (at least 37 weeks’ gestation) or preterm, the risk of low birth weight was again elevated for both groups—2.6 and 1.4, respectively. The risk of low birth weight at term remained elevated when analyses were limited to pregnancies during which the ultrasound scan showed one fetal heart (2.6), procedures that used donated eggs and healthy sperm (1.9), cases of paternal infertility (2.9) and surrogate births (1.7). In contrast, preterm singletons conceived with ART had moderately elevated risks of low birth weight if one fetal heart had been detected during pregnancy (1.3) or if donated eggs and healthy sperm were used (1.5). Twins conceived through ART were no more likely than those in the general population to have low birth weight, whether they were delivered at term or earlier.

The authors estimate that conception using ART accounted for fewer than 1% of all infants born in 1997 to women aged 20 or older, but for 3–4% of those with low or very low birth

weight. They note that although the use of ART results in a higher rate of multiple birth, which carries a high risk of low birth weight, ART itself does not seem to increase that risk. However, because singletons conceived by this technology—even if they were born at term and the pregnancy had involved a single fetus—have an increased risk of low birth weight, the investigators conclude that “infants from both singleton and multiple births must be considered in assessing the effect of assisted reproductive technology on the rate of low birth weight in the United States.”—*T. Lane*

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Chlamydia Rates in Public Clinics: Repeat Infections Exceed New Diagnoses

Repeat infection with chlamydia appears to be a substantial problem among clients of public sexually transmitted disease (STD) clinics, and continued exposure to the same infected partner may be a key factor, according to analyses of data from a Denver clinic.¹ Among men and women who had at least two chlamydia tests, those who were infected at the time of their first visit had a significantly higher rate of infection at a subsequent visit than those who initially tested negative (23.6 vs. 10.0 infections per 100 person-years). In multivariate analyses, the risk of repeat infection was not associated with the acquisition of new partners, but was increased among clients who reported at their first visit that they never used condoms (odds ratio, 1.7).

The study included 3,568 men and women who had two or more chlamydia tests at least 30 days apart between January 1997 and June 1999 at a large public STD clinic. Using the clinic's database, researchers gathered information on clients' demographic characteristics, risk behaviors, clinical and laboratory find-

ings, and treatment. For each client, they created a record based on data from the first visit that included a laboratory test for chlamydia and from the next visit at which an infection was diagnosed (or, for those who tested negative at all subsequent visits, the last visit during the study period). They categorized incident infections (i.e., those occurring between tests) as new if the client had initially tested negative or as repeat if the initial test had detected chlamydia infection.

Members of the study cohort were, on average, about 30 years old; most (59%) were male. Some 38% were black, 32% white, 27% Hispanic and 4% members of other racial or ethnic groups. The follow-up interval averaged 335 days.

Fourteen percent of clients tested positive for chlamydia at their first visit, and 11% tested positive at a subsequent visit. About two-thirds of each group received treatment before their laboratory results confirmed a diagnosis of chlamydia—either because they had clinical signs of infection (nongonococcal urethritis or epididymitis in men; mucopurulent cervicitis or pelvic inflammatory disease in women; or gonorrhea in either) or because they had a partner with suspected or confirmed chlamydia infection. While the proportion of clients treated because of clinical diagnosis was essentially the same for those with baseline and incident infections (54% and 58%, respectively), clients with incident infections were significantly less likely than those who tested positive at baseline to be treated because of their partner's known or suspected condition (13% vs. 23%).

In all, 11.7 incident infections occurred per 100 person-years of follow-up. The rate was significantly higher among clients with a repeat infection (23.6 per 100 person-years) than among those who were newly infected (10.0 per 100); repeat infections accounted for about one-quarter of all incident cases of chlamydia. Results of logistic regression analyses showed that a different set of risk factors predicted the incidence of new and repeat infections.

The odds of new infection were significantly higher among men than among women (odds ratio, 1.5) and were higher among blacks than

among whites (1.8). Compared with people aged 30 and older, younger men and women had a sharply higher risk of new infection: Odds ratios increased steadily from 2.5 among those in their late 20s to 6.8 among teenagers. A history of STDs was associated with a doubling of the odds of new infection (1.8), as was inconsistent condom use (2.2). Finally, clients who reported at their follow-up visit that they had a new partner and did not use condoms had a higher risk of new infection than those who said either that they did not have a new partner or that they had a new partner but they used condoms at least some of the time (1.9).

Age was associated with the incidence of repeat infection as well, but the effect was not as strong as it was for new infection: Men and women in their late 20s had no greater risk than those aged 30 or older, and the odds of repeat infection were roughly doubled for both clients in their early 20s and teenagers (odds ratio, 2.2 for each group). Only two other factors were predictive of the incidence of repeat infection: Clients who had said at their first visit that they never used condoms had a higher risk than those who had reported any condom use (1.7), and clients who had received treatment at their initial visit because their partner had chlamydia or a related condition had a lower risk than those who had not (0.5).

While the researchers acknowledge that they were not able to determine whether repeat infections resulted from continued exposure to the same untreated partner or from contact with new partners, they contend that the multivariate results suggest “a pattern of unprotected intercourse with the source partner continuing after the first infection and thus increasing the risk for repeat infection.” Therefore, they conclude that their findings “point to the need for the establishment and evaluation of partner services for persons with identified chlamydial infection.”—*D. Hollander*

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