

## Most Refined Analysis to Date Confirms Link Between Third-Generation Pills and Venous Thromboembolism

Confirming the findings that touched off the 1995 “pill scare,” an analysis of a large British database shows that use of oral contraceptives containing a “third-generation” progestogen (desogestrel or gestodene) is associated with a higher risk of venous thromboembolism than use of pills containing levonorgestrel.<sup>1</sup> As further evidence of this association, the researchers found that subsequent to the pill scare, when British women’s use of third-generation formulations dropped sharply, the number of venous thromboembolisms occurring among oral contraceptive users was lower than would have been expected if use had not changed.

Since 1995, when a British advisory committee warned that third-generation pills are a poor choice for women at risk of venous thromboembolism, the question of whether these pills pose a greater risk than earlier versions has been the subject of intense controversy, and research on the issue has produced conflicting results. However, this analysis overcomes a number of methodological problems of previous work and has been called perhaps “the most important paper yet published on this vexed subject.”<sup>2</sup>

The researchers used Britain’s General Practice Research Database to identify women aged 15–39 who received pill prescriptions between January 1993 and December 1999. In all, the analyses include nearly 400,000 person-years of oral contraceptive use, roughly evenly divided between pills containing levonorgestrel and those containing third-generation progestogens. The investigators conducted a cohort analysis to compare the risk of venous thromboembolism in the periods leading up to the pill scare (January 1993 to October 1995) and immediately thereafter (January 1996 to December 1999); they also conducted a case-control analysis to compare the risks associated with the different types of pills.

### *Cohort Analysis*

In the years preceding the pill scare, third-generation pills accounted for 63% of oral contraceptive use among British women.

In the later period, however, only 18% of pill use involved these preparations. The decline occurred in all age-groups but was especially steep among younger women. For example, 82% of teenage pill users in 1993–1995 took third-generation pills, compared with 11% in 1996–1999; among women in their late 30s, by contrast, the proportions were 56% and 18%, respectively.

A total of 106 women in the study population developed venous thromboembolism—42 users of oral contraceptives containing levonorgestrel and 64 users of third-generation pills. Seventy-one of these women were in the earlier cohort and 35 in the later one. During both periods, the crude incidence of venous thromboembolism was higher among women using third-generation pills (37–41 cases per 100,000 person-years) than among those using pills with levonorgestrel (20–23 per 100,000).

After adjusting the data for women’s age, the analysts calculated incidence ratios to compare the risks by pill type and by cohort. They found that for the two periods combined, the risk of venous thromboembolism was twice as great for women taking third-generation pills as for those using pills containing levonorgestrel (incidence ratio, 1.9). Furthermore, the incidence of venous thromboembolism associated with each type of pill was the same in both periods.

In additional analyses, the researchers calculated the number of venous thromboembolisms that would have been expected in 1996–1999 if the age-specific distribution of types of pill used had not changed. These results show that in the absence of the shift to levonorgestrel, 44 pill users would have developed venous thromboembolism—nine more than actually did.

### *Case-Control Analysis*

For the case-control analysis, each woman who had venous thromboembolism was matched with up to six women who were the same age, went to the same physician and were using the pill at the time that the

woman with venous thromboembolism received her diagnosis; data were available for 569 controls. The researchers performed conditional logistic regression analyses to assess the risks associated with each type of pill, adjusting for body mass index, smoking, duration of pill use and switching of pill types.

In these analyses, women taking third-generation pills had twice the odds of venous thromboembolism of those using pills containing levonorgestrel (odds ratio, 2.3). According to the researchers, the difference between the results in the cohort and case-control analyses is attributable to the additional adjustments for confounding factors in the latter.

The results were similar in the years preceding the pill scare (2.2) and immediately thereafter (2.8). They also were similar for pills containing gestodene (1.9) and those with desogestrel (2.0–2.8, depending on the estrogen dose). High body mass and smoking were associated with increased risks of venous thromboembolism, and the analysts found evidence that doctors may have taken these factors into account when deciding which type of pill to prescribe after 1995.

### *Conclusion*

As the researchers note, a number of studies have yielded conflicting results regarding the association between venous thromboembolism and the use of third-generation oral contraceptives. In particular, a widely publicized analysis based on the same database used in this study found no difference in the incidence of the condition before and after the pill scare, leading to the conclusion that third-generation pills were associated with no higher risk than pills containing levonorgestrel.<sup>3</sup> However, the researchers contend that several features of their methodology improve on the approach of the earlier study: For example, they restricted the analysis to third-generation pills and formulations containing levonorgestrel (rather than including all combined oral contraceptives), and they more adequately con-

trolled for important confounding factors.

A commentary accompanying the study concurs about the strength of this study. "As well as answering the previous report," the commentator writes, "it provides vital evidence on several controversial matters."<sup>4</sup>—*D. Hollander*

## References

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3. Farmer RDT et al., Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research database, *BMJ*, 2000, 321(7259):477–479.
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## Preteenage Relationship With an Older Partner May Lead to Early First Sex

More than half of sixth graders surveyed in Northern California have never had a serious romantic relationship, but about a third have had a same-age boyfriend or girlfriend, and one in 10 have had a boyfriend or girlfriend two or more years their senior.<sup>1</sup> Those who have been involved with an older person are more likely than others to be sexually experienced and to have experienced unwanted sexual advances; they also are more likely to perceive that their peers have had sex or approve of doing so.

The survey, conducted in 1997, included 2,829 urban, ethnically diverse sixth graders in 19 middle schools. On average, the students were about 11.5 years old; their ages ranged from 10 to 13 years. Fifty-six percent of the sixth graders had never had a serious romantic relationship, 35% had had a boyfriend or girlfriend less than two years older than they, and 9% had been involved with someone at least two years older.

In analyses of variance and bivariate logistic regression analyses, students who had had an older boyfriend or girlfriend differed from both those who had never had a relationship and those who had been involved with someone their age. They were significantly more likely to be Hispanic and less likely to be culturally assimilated; they had less-educated mothers and lower educational aspirations than the students in the other groups. Sixth

graders who had had an older boyfriend or girlfriend also were the most likely to say that their friends were sexually active or wished to be, and the most likely to have experienced unwanted sexual advances. Females in this group were more likely than others to have already menstruated. On most measures, results for students who had had a same-age boyfriend or girlfriend were between those for their peers who had not had a relationship and their peers who had been involved with someone older.

Four percent of the students—5% of the boys and 3% of the girls—reported that they had had sexual intercourse. Those who had ever had a romantic relationship were more likely to have had sex than were those who had never had a boyfriend or girlfriend. Additionally, the greater the age difference between students and their oldest boyfriend or girlfriend, the more likely it was that they had had sex: In all, 1% of those who had never had a romantic attachment had had sex, compared with 6% of those with a same-age boyfriend or girlfriend and 19% of those with an older boyfriend or girlfriend. (The researchers emphasize that the survey did not ask students the age of their sexual partner; therefore, one cannot assume that the oldest boyfriend or girlfriend was also a sexual partner.) For boys, the proportions are similar to the overall pattern; among girls, however, the proportion who had had sex reached 39% among those who had been involved with someone five or more years their senior.

Finally, the researchers conducted multivariate logistic regression analyses to assess which characteristics had independent effects on sixth graders' likelihood of having initiated sexual activity. Boys who had had a same-age girlfriend were significantly more likely than those who had never had a girlfriend to be sexually experienced (odds ratio, 3.1); the odds were further elevated for boys who had had an older girlfriend (4.7). The odds of sexual initiation also were heightened for boys who had experienced unwanted sexual advances (2.2) and increased as peers' acceptance of sexual activity grew (4.3). The more acculturated boys were, the less likely they were to have begun having sex (0.6).

Girls also had significantly elevated odds of sexual initiation if they had been romantically involved with someone their age (6.1) or, especially, with someone older (11.9). Again, peer norms that encouraged sexual activity were associated with increased odds of sexual initiation (2.3). In

addition, girls' odds of having had sex declined as their grades increased (0.8).

According to the authors, sixth graders who have had a boyfriend or girlfriend are at "substantial risk" for early sexual activity. This is of particular concern, the researchers comment, not only because sixth graders are developmentally too young to have sex, but also because young girls with older boyfriends may be at particular risk for HIV, other sexually transmitted diseases and unplanned pregnancy. The consequences for Hispanic girls are especially troubling, since Hispanic adolescents have lower rates of contraceptive use and higher birthrates than teenagers in other ethnic groups.

This study also demonstrates the significant role that older boyfriends and girlfriends play in early sexual initiation. Preadolescent relationships with older partners, according to the researchers, "are particularly risky because they are associated with unwanted sexual advances and peer norms encouraging sexual activity." The authors conclude that "interventions are needed that provide young people with a sense of their personal power, the ability to state feelings and needs, and an ability to set limits and personal boundaries." They also emphasize the need to "alert young people to the special risks of relationships with older partners."—*J. Liebmann-Smith*

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## Vertical HIV Transmission: Risk Grows with Duration Of Membrane Rupture

For every hour that elapses after an HIV-infected pregnant woman's membranes rupture, the risk that the virus will be transmitted to her offspring rises by 2%, according to a meta-analysis involving data on nearly 5,000 deliveries.<sup>1</sup> Moreover, among women with AIDS, the risk of transmission increases steeply as the time since rupture of the membranes grows—from 8% at two hours to 31% at 24 hours.

To test the a priori hypothesis that the longer the membranes have been ruptured, the higher the risk of vertical transmission, the researchers pooled data from 15 prospective cohort studies conducted in Europe and North America. They included only deliveries (vaginal or cesarean) that occurred after the onset of labor

or within 24 hours after the membranes ruptured; cesarean sections performed before labor and before rupture of membranes were excluded. The analyses are based on 4,721 deliveries, which occurred between 1982 and 1990.

In univariate analyses, the duration of ruptured membranes was significantly associated with the risk of transmission. Twelve percent of women whose membranes were ruptured for less than one hour transmitted HIV to their infants, and the proportion rose to 19% among those whose membranes were ruptured for more than 12 hours. Other significant factors were the year of delivery, whether antiretroviral therapy was used, the mother's AIDS status, her CD4 percentage (an indicator of the severity of her illness), and the child's birth weight and gestational age. Only one factor that the researchers examined—the mode of delivery—was not related to the risk of vertical transmission at the univariate level.

The researchers used logistic regression to calculate odds ratios estimating the strength of the association between the length of time membranes were ruptured and the infant's HIV status, controlling for the mother's CD4 percentage, mode of delivery, receipt of antiretroviral therapy and the infant's birth weight. According to the results, each one-hour increase in duration of ruptured membranes represented a 2% increase in the risk of transmission (odds ratio, 1.02). Further analyses using additional variables produced similar odds ratios.

As in the univariate analysis, the mode of delivery was the only factor that did not contribute to the risk of vertical transmission. The risk was significantly elevated for women with low CD4 percentages (odds ratios, 1.9–2.3) and those whose infants weighed less than 2,500 g at birth (1.8); it was reduced if the woman, her infant or both received antiretroviral therapy (0.3–0.6).

Finally, an examination of interactions between the duration of membrane rupture and the other variables suggested that the probability of vertical transmission was affected by an AIDS diagnosis. For women with AIDS, this probability was 8% if the duration of membrane rupture was two hours, and it rose to 31% if the membranes were ruptured for 24 hours.

According to the researchers, the large number of deliveries included in their analyses allowed them to examine the relationship of duration of membrane rupture to vertical HIV transmission in greater detail than was previously possible. They

suggest that future studies incorporate information on maternal viral load and investigate the relative importance of duration of ruptured membranes among HIV-infected women receiving various antiretroviral treatments.—*J. Tomarken*

## Reference

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## Among Teenagers Treated For Chlamydia, Two-Year Reinfection Rate Nears 20%

Nearly one in five teenage women who have had a chlamydial infection are reinfecting within two years, according to an analysis of data from Washington State.<sup>1</sup> Women aged 15–19 are four times as likely as 30–44-year-olds to develop one repeat infection and five times as likely to be reinfecting at least twice. Furthermore, teenagers are less likely than older women to seek care from the same facility each time they have a chlamydial infection.

Chlamydia is the most common bacterial infection in the United States, and repeat infections increase the risk of long-term complications such as pelvic inflammatory disease, infertility and ectopic pregnancy. Therefore, factors leading to repeat infections need to be identified and addressed. To this end, analysts examined data from a population-based sexually transmitted disease (STD) registry in Washington, which provided information on 32,698 women aged 10–44 who were treated for an initial chlamydial infection during the years 1993–1998. They assessed the proportion of women with at least one repeat infection (defined as a urogenital or rectal infection that occurred at least 30 days after appropriate treatment for the initial infection) and used logistic regression models to analyze predictors of repeat infections.

Forty-eight percent of the women were younger than 20 when they were first infected, 62% were white and 47% lived in an urban setting. Not-for-profit and public clinics (mainly family planning, STD, reproductive health and jail clinics) were used by approximately 41% of the women. Screening detected 45% of initial infections; at least 36% of women had sought care because they were experiencing STD symptoms. Four percent also had gonorrhea or another STD at the time of their first chlamydia diagnosis.

During the follow-up period, which ranged from six months to six years, 15% of women had at least one repeat infection, and 3% had two or more (range, 2–8). The median time to first repeat infection was approximately 11 months. In initial analyses, age was the predominant factor in predicting repeat infections. The rate of repeat infection within one year was highest (16%) among 10–14-year-olds and second-highest (11%) among 15–19-year-olds. In all, 6% of women younger than 20 were reinfecting within six months, 11% within one year and 17% within two years. By contrast, for those aged 20 and older, reinfection rates were 4–10% in the two years after treatment.

Several other characteristics appeared to be modestly associated with an increased risk of repeat infection: being black or American Indian, obtaining care from a facility other than a family planning clinic, seeking services because of symptoms of or exposure to an STD, having gonorrhea at the time of the initial diagnosis and having a long interval between infections. Women living in nonurban areas appeared to have a reduced risk of repeat infection.

Results of the multivariate analyses confirmed that age is the strongest predictor of repeat chlamydial infection. When length of follow-up and type of clinic were taken into account, 10–14-year-olds were six times as likely as women between the ages of 30 and 44 to have at least one repeat infection and 12 times as likely to develop two or more repeat infections (odds ratios, 6.3 and 11.6, respectively). Older teenagers also had considerably higher odds of repeat infection than women aged 30–44 (3.5–4.5). Odds were roughly doubled for women in their early 20s but were not significantly elevated for those aged 25–29.

Nonwhite women, women who were coinfecting with gonorrhea and those who had visited their provider because of STD symptoms had modestly elevated odds of repeat infection (odds ratios, 1.2–2.0). Residents of rural areas were considerably less likely than city dwellers to acquire a repeat infection (0.3); odds were also significantly reduced for those living in areas classified as semirural (0.5) or semiurban (0.8).

The researchers also examined where women sought care for consecutive episodes of chlamydia. They found that only 36% had both their initial and their first repeat infection diagnosed at the same clinic, and only 50% received both diagnoses from the same type of provider.

Adolescents had the lowest rates of continuous care. Only 29% of 10–14-year-olds and 33% of older teenagers visited the same clinic for care of their first two infections, compared with 39–51% of adults. Similarly, the proportions visiting the same type of provider ranged from less than half of teenagers to three-quarters of women aged 30–44.

The analysts point to two important issues that are highlighted by their findings. First, the significant number of repeat chlamydial infections in adolescents indicates a serious public health problem; the rate of repeat infection even among older women also is of concern. Second,

since women seek treatment at different kinds of sites, follow-up and epidemiological evaluations of repeat infections may be difficult.

One strategy the researchers suggest for addressing these problems is increased screening for chlamydial infection. For teenagers, screening as often as every six months could be beneficial because of the high incidence of repeat infections within this time period; for older women who have been infected, annual screening may be advantageous. Counseling also may be effective in reducing subsequent infections, especially among adolescents with a previous STD. And because adolescent

women may acquire a repeat infection from untreated partners, the analysts stress the need for ensuring that infected partners receive treatment before teenagers resume having intercourse. "For the risk of long-term sequelae to be reduced," the analysts conclude, "more frequent screening for chlamydia must be accompanied by enhanced efforts to prevent repeat chlamydial infection."—J. Tomarken

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## Well-Baby Care Visits Create Opportunity to Screen New Mothers for Abuse During Postpartum Period

Six percent of North Carolina mothers were physically abused during pregnancy in 1997 and 1998 and 3% were the victims of abuse during the first three and one-half months postpartum, according to the results of a statewide representative survey.<sup>1</sup> Most of the perpetrators of that violence were the woman's husband or partner (67–76%). Women who were abused after giving birth seldom sought medical care for their injuries. Nearly all women took their infants for well-baby visits, however, which creates an opportunity for pediatricians to screen postpartum women for physical abuse.

Women who had recently had a live birth were recruited by mail or telephone between July 1997 and December 1998 to participate in a population-based survey, which used the North Carolina birth certificate data file as the sampling frame. (The data collection was part of a larger, ongoing project, the North Carolina Pregnancy Risk Assessment Monitoring System, or PRAMS.) Three-quarters of the women invited to participate in the survey responded, and nearly all of these (2,630 women) answered all questions concerning physical abuse in the year before pregnancy, during pregnancy and since delivery. On average, the women were 3.6 months postpartum when they completed the survey.

The survey instrument asked whether the woman had been physically abused (i.e., whether she had been pushed, hit, slapped or hurt in some other way) and who had perpetrated that violence (a current or former husband or partner, another family member, multiple persons, a friend or someone else). Women who had been the victim of abuse after delivery were

asked whether injury had resulted and if they had sought medical care for it. The researchers calculated odds ratios to determine whether the woman's socioeconomic characteristics were related to the likelihood of abuse and whether previous physical abuse was associated with the likelihood of subsequent abuse.

The majority of women surveyed were aged 20 and older (85%), had graduated from high school (78%), were married (67%) and had had other children (57%). Overall, nearly 7% had been abused in the year before they became pregnant, 6% had been the victim of violence during their pregnancy and 3% had been physically hurt since their baby was born. The perpetrators of the violence were most commonly former or current intimate partners (67–76% of perpetrators, depending on the timing of the abuse).

Seventy-seven percent of the women who had been abused since giving birth reported that the abuse had led to physical injury. Some 73% said they had experienced pain the day after the abuse, and 57% had suffered sprains and bruises, while 6–9% reported more serious injuries (e.g., internal or permanent injuries, weapon wounds and broken bones). Only 23% of all women who were injured, however, received related medical care.

Women did take their babies for medical attention, however: Nearly all women, regardless of whether and when they had experienced abuse, had taken their infant for a well-baby visit. Women had made an average of three such visits during the postpartum period covered by the survey, and the majority (71%) had used private physicians for their baby's care.

Women who had been abused in any of

the three time periods that the survey asked about were significantly more likely than those who had never been abused to be unmarried, to be poor, to be younger than 20 and to have not graduated from high school. There were no significant differences in women's socioeconomic characteristics, however, by the timing of abuse (i.e., in any of the eight categories created by the yes-no responses to abuse in each of the three times asked about).

Moreover, the researchers found that previous violence was strongly associated with subsequent violence. For example, physical abuse in the year before pregnancy significantly raised the likelihood of abuse during pregnancy (odds ratio, 67.6); similarly, women who suffered physical abuse during pregnancy had significantly increased odds of being victimized again in the first few months postpartum (odds ratio, 38.0). Conversely, the absence of physical abuse protected women from violence; that is, women who were unharmed before or during pregnancy were at significantly decreased odds of suffering physical abuse once their baby was born (odds ratios, 0.01–0.02).

The researchers acknowledge that because of several limitations, their study could underestimate the true prevalence of physical abuse during the period surrounding pregnancy and childbirth. These limitations include the significant socioeconomic differences between respondents and nonrespondents; the sensitive nature of the topic; the absence of questions on psychological abuse; and the exclusion of women whose pregnancies did not result in a live birth. The researchers assert that the encouraging finding of nearly universal well-baby care creates an

important opportunity for intervention. They recommend that pediatricians be trained to screen postpartum women for abuse and that physicians be educated about the long-term nature of domestic violence.

The investigators' recommendations are seconded in a related editorial that advocates building questions on physical abuse into standard forms used in routine well-baby care.<sup>2</sup> The editorial authors assert that pediatricians could actively prevent child abuse and further domestic violence by screening battered mothers who happen to come into their practices. They conclude that pediatricians and other health professionals involved in caring for infants should focus on filling the gap in screening for physical abuse during the immediate postpartum period, because "it is the right thing to do."—*L. Remez*

## References

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## Maternal Exposure to Weed, Rodent Killers Raises Risk Of Congenital Heart Defect

Exposure to certain pesticides during the first trimester of pregnancy increases a woman's risk of bearing an infant with a severe congenital heart defect that disrupts oxygenation of the blood. An analysis involving more than 1,800 infants with congenital heart defects indicates that early maternal exposure to rodenticides nearly quintuples the risk, while exposure to herbicides almost triples the risk.<sup>1</sup>

The researchers used a subset of data from a case-control study conducted from 1981 through 1989 to identify genetic and environmental risk factors for congenital heart defects. That subset, which includes 1,832 infants with congenital heart defects and 771 infants without such defects, provides detailed information on the type and frequency of pesticide exposure and its timing in relation to conception.

The analysis included infants with congenital heart defects who were born in the Baltimore-Washington area in 1987–1989

\*Because of the transposition, the aorta carries deoxygenated rather than oxygenated blood out of the heart to be distributed throughout the body.

and treated at one of the region's six pediatric cardiology centers, as well as a random sample of infants without heart defects born in the area during that period. Interviews conducted with the children's parents, generally before the children's first birthday, covered socioeconomic and demographic data, family history of congenital heart and other defects, and maternal and paternal exposure to environmental contaminants.

After a preliminary analysis indicating that heart defects as a group are not associated with pesticide exposure, the researchers focused on one type of malformation that was twice as common among infants whose mothers had been exposed as among those whose mothers had not been exposed. In this malformation, called transposition of the great arteries, the aorta arises from the right instead of the left ventricle, while the pulmonary artery originates in the left instead of the right ventricle; as a result, the body's supply of oxygenated blood is disrupted.\* In addition to the 66 infants with transposed arteries, 114 infants had other abnormalities affecting the flow of blood from the heart; these infants made up a second comparison group.

The three groups were similar in race, age and exposure to most environmental contaminants. However, the families of infants with transposed arteries were more likely than those of controls to be of low socioeconomic status (74% vs. 60%). In addition, the mothers of such infants were more likely than those of control infants to have been exposed to solvents (6% vs. 2%), and the fathers were more likely to have been exposed to pesticides (62% vs. 45%).

Exposure to a pesticide of any kind was reported by 44% of the mothers of infants with transposed arteries, 26% of the mothers of those with other abnormalities affecting the flow of blood out of the heart and 27% of the mothers of infants without heart defects. Small proportions in each group (6–11%) reported exposure occurring at least once a week. The most common mode of exposure for all three groups was by hand-held spray (14–21%), but the greatest difference among groups was for exposure to pellets, to powder or to poison disguised as food (3–11%). Bivariate analysis indicated significant associations between transposed arteries and exposure to chemical rodent killers (unadjusted odds ratio of 3.5) or weed killers (3.7). The use of pellets, powders or food imitators was the only mode of exposure associated with the malformation (4.0). No overall trend was evident ac-

ording to frequency of exposure, although too few women had been exposed once a week or more for meaningful analysis. None of these factors had significant effects on the risk of other abnormalities affecting the flow of blood from the heart.

After adjustment for socioeconomic and demographic characteristics, medical history and paternal pesticide exposure, a logistic regression analysis found that infants whose mother had been exposed to weed killers or rodent killers had significantly elevated odds of being born with transposed great arteries (2.8 and 4.8, respectively). Exposure to rodent killers did not affect a woman's risk of bearing a child with other malformations affecting the flow of blood from the heart. No women whose children had such defects reported exposure to herbicides during the first trimester or the three months preceding conception.

An examination of the effect of the timing of pesticide exposure in relation to conception revealed that maternal exposure to a pesticide of any kind during the first trimester of pregnancy or the preceding three months significantly increased the risk that an infant would be born with transposed arteries (odds ratio of 2.1); exposure before or after that period had no effect. When the analysis focused on specific types of pesticides, however, rodenticide exposure and herbicide exposure had significant effects when they occurred 4–6 months before conception (6.1 and 4.7, respectively) or during the six months centering on conception (5.1 and 3.6, respectively).

The researchers note that currently available weed, insect and rodent killers use more than 600 pesticide chemicals in as many as 50,000 formulations and that they were not able to determine the specific chemicals to which women were exposed. They were, however, able to identify chemical categories (such as anticoagulants, the predominant chemicals used in rodenticides) that call for further examination, and they stress the need to examine the effects of pesticide exposure in larger samples. Nevertheless, they conclude that transposition of the great arteries "is associated with environmental pesticide exposure during the periconceptional period of pregnancy."—*F. Althaus*

## Reference

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## In Clinical Use, Low-Dose Medical Abortion Method Proves Highly Successful

A medical abortion regimen designed to reduce the rate and severity of side effects by using a lower-dose drug combination than is typically used in Europe is highly effective, especially for nulliparous women and women who seek abortion during the first seven or eight weeks of pregnancy, according to a retrospective study conducted in Edinburgh, Scotland.<sup>1</sup> The researchers, working in a routine clinic setting, found that 96% of women given 200 mg of oral mifepristone followed by 0.5 mg of vaginal gemeprost had a complete abortion without surgical intervention. The likelihood of complete abortion was significantly higher among women who had never given birth than for their parous counterparts, and it declined as the length of gestation increased.

The study was based on data for women who sought abortions at an Edinburgh clinic in 1995–1999. Women who were interested in medical abortion were first counseled and given a medical examination. Gestational age was based on a clinical assessment, with ultrasound used for confirmation in cases of uncertainty. Subsequently, women were given 200 mg of oral mifepristone and asked to return to the clinic in 48 hours. At that time, 0.5 mg of gemeprost was inserted into the vagina. (The standard regimen uses 600 mg of mifepristone and 1 mg of gemeprost.) Nursing staff monitored the women for up to six hours and recorded any passage of fetal tissue. Analgesia was given as requested.

Women returned for a follow-up visit 10–14 days later. A diagnosis of complete abortion was made at follow-up on the basis of the amount of bleeding and pain since treatment, a physical examination of the uterus and, for women who had not passed fetal tissue at the previous visit, a vaginal ultrasound examination. Abortion-related complications, such as bleeding or pelvic infection, were also assessed and treated at this time.

Initially, 3,161 women who obtained medical abortions were studied. Twelve women were excluded because their complete records were not available, and another 310 were excluded because they did not return for follow-up, leaving a total of 2,839 women included in the analyses. On average, the women were 26 years old; 48% had given birth. Most sought their abortion within the first eight weeks of pregnancy: 51% before 49 days' gestation

and 32% at 50–56 days. Sixteen percent were 57–63 days pregnant, and 1% were at longer gestations. One-fifth had had a previous abortion.

Overall, 96% of women had a complete abortion after treatment with the drugs and did not require any surgical procedure; in these instances, the researchers considered the method a success. Abortion failures fell into two categories: For 2% of women, the abortion was incomplete (i.e., fetal tissue was still detected in the uterus), while for 1%, the pregnancy was ongoing (i.e., a fetal heartbeat was still detectable) at follow-up. In cases of failure, women underwent surgical evacuation of the uterus.

In bivariate analyses, women who obtained their abortion during the first 49 days of gestation had a higher rate of complete abortion (97%) than those whose abortion occurred later (95%); the results were similar when the researchers compared women who had an abortion within 56 days with those who had the procedure later. Additionally, women who had never given birth were more likely to have a complete abortion (98%) than were parous women (95%). Complete abortion also was more likely among younger women and women who had not had a previous pregnancy termination than among their respective counterparts.

In multivariate analyses using logistic regression, parity and gestation remained significant as predictors of completed abortion after medical therapy. Nulliparity was more strongly associated with the probability of successful medical pregnancy termination ( $p < .001$ ) than was short gestation ( $p = .01$ ). These analyses also showed that women with no children were less likely than parous women to have an incomplete abortion ( $p = .04$ ) or an ongoing pregnancy ( $p < .001$ ), and that the likelihood of ongoing pregnancy rose as gestation increased ( $p < .001$ ).

Seven in 10 women required analgesics, and the proportion was significantly higher among nulliparous women (81%) than among parous women (59%). Gestational age was not associated with analgesic use. Abortion-related complications were rare: Fewer than 1% of women suffered severe hemorrhage, and 6% were given antibiotics during the two weeks following the abortion. The occurrence of complications was not associated with any characteristics examined.

The researchers point out that the proportion of women who failed to attend follow-up visits (10%) was higher than the proportion found in other prospective

studies; but they add that this proportion is more likely reflective of what happens in a routine clinical setting. Given the increased fetal and maternal risks from an ongoing pregnancy and incomplete abortion, respectively, the researchers mention that this lack of follow-up after medical pregnancy termination “demands persistent attention.”

The researchers conclude that the reduced-dose regimen used in the study is effective and safe. They observe that the difference in medical abortion success between nulliparous and parous women was unexpected, and suggest that it reflects differences in early pregnancy between these two groups. Moreover, they note that clinicians can use parity, along with gestation, as criteria when trying to predict the likelihood of a successful medical abortion.—A. Brochert

### Reference

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## Job-Related Fatigue During First Pregnancy May Cause Early 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.<sup>1</sup> 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 con-

ducted at 10 locations 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 current 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

1. Newman RB et al., Occupational fatigue and preterm premature rupture of membranes, *American Journal of Obstetrics and Gynecology*, 2001, 184(3):438–446.