

FERTILITY IN MEN EXPOSED PRENATALLY TO DIETHYLSTILBESTROLALLEN J. WILCOX, M.D., PH.D., DONNA D. BAIRD, PH.D., CLARICE R. WEINBERG, PH.D.,
PAIGE P. HORNSBY, PH.D., AND ARTHUR L. HERBST, M.D.

Abstract Background. Prenatal exposure to diethylstilbestrol causes infertility in male mice and has been associated with malformations of the genital tract in men. However, little is known about the fertility of men who have been exposed prenatally to diethylstilbestrol.

Methods. In 1950 through 1952, 1646 pregnant women were enrolled in a randomized, placebo-controlled clinical trial of diethylstilbestrol at Chicago Lying-in Hospital. We interviewed men who were born to the women during that study about their fertility.

Results. Four decades after their birth, we were able to trace 548 of the surviving sons (68 percent). Ninety percent consented to be interviewed (253 who had been exposed to diethylstilbestrol in utero and 241 who had not been exposed). Congenital malformations of the genitalia were reported three times as often by the diethylstilbestrol-exposed men as by the sons of the women in the placebo group. Within the exposed group, malformations

were reported twice as often among those exposed to diethylstilbestrol before the 11th week of gestation as among those exposed later ($P=0.05$). Men with genital malformations were nonetheless as fertile as other men. The diethylstilbestrol-exposed men (with or without genital malformations) had no impairment of fertility by any measure, including whether they had ever impregnated a woman, age at the birth of their first child, average number of children, medical diagnosis of a fertility problem, or length of time to conception in the most recent pregnancy of the female partner. Finally, diethylstilbestrol-exposed men had no impairment of sexual function, as indicated, for example, by the frequency of intercourse or reported episodes of decreased libido.

Conclusions. High doses of diethylstilbestrol did not lead to impairment of fertility or sexual function in adult men who had been exposed to the drug in utero. (N Engl J Med 1995;332:1411-6.)

DIETHYLSTILBESTROL is an orally active synthetic estrogen that for many years was thought to prevent complications of pregnancy. Between the late 1940s and the early 1970s, diethylstilbestrol was prescribed for 2 million to 3 million women in the United States during pregnancy.¹ In 1971, diethylstilbestrol was found to be associated with the development of clear-cell adenocarcinoma of the vagina and cervix in young women whose mothers had been given diethylstilbestrol during pregnancy.² The use of diethylstilbestrol in pregnancy was subsequently banned. Since then, women exposed prenatally to diethylstilbestrol have been found to have an increased risk of reproductive difficulties, including infertility, miscarriage, preterm delivery, and fetal or infant death.^{1,3,4}

At least 1 million men in the United States from 30 to 45 years of age were exposed prenatally to diethylstilbestrol.¹ The effects of the drug on their ability to reproduce are unknown. Male rodents exposed prenatally to diethylstilbestrol have an excess prevalence of malformations of the genitalia and infertility.⁵⁻⁷ In men, an excess rate of minor malformations of the genitalia has been associated with prenatal exposure to diethylstilbestrol.⁸ Fertility problems in men have been suspected,⁸⁻¹⁰ but the evidence has been inconclusive.

In the early 1950s, a randomized clinical trial of diethylstilbestrol during pregnancy was carried out at the University of Chicago.¹¹ We traced and interviewed

men whose mothers participated in that trial and compared the fertility of men who were exposed to diethylstilbestrol prenatally with the fertility of men whose mothers received the placebo.

METHODS

In 1950 through 1952, Dieckmann and his colleagues at Chicago Lying-in Hospital conducted a clinical trial of the efficacy of diethylstilbestrol in preventing complications of pregnancy.¹¹ Pregnant women were invited to enroll in this double-blind, placebo-controlled study at their first prenatal visit. The women were randomly assigned to the treatment or placebo group. Women in the treatment group received daily doses of diethylstilbestrol that increased gradually from 5 mg at the 7th week of pregnancy to 150 mg at the 34th and 35th weeks. To verify compliance, phenol red was added to all pills and monitored in the women's urine.

Women were enrolled no later than the 20th week of pregnancy; those in the treatment group received a mean total dose of 12,200 mg of diethylstilbestrol. Since the highest doses were administered late in pregnancy, the stage of pregnancy at which women entered the study had little influence on the total dose: 95 percent of the women in the treatment group received between 11,500 mg and 12,600 mg of diethylstilbestrol.

A total of 848 male babies were born during the original study (Table 1). Two decades later, when diethylstilbestrol had been identified as a transplacental carcinogen, the University of Chicago attempted to trace all participants and their offspring. Of the 827 sons who survived infancy, 693 were found. Interviews and clinical examinations of 615 of these men were carried out between 1974 and 1976.¹² No further contact was made with the men until 1991, when we sought their participation in this study. Our research protocol was approved by the institutional review boards of the National Institute of Environmental Health Sciences and the University of Chicago.

We were unable to locate 15 percent of the 693 sons whose whereabouts had ever been known since birth; 26 others (4 percent) had died, and 12 (2 percent) had requested that they be excluded from any future follow-up. Of the 548 men we contacted, 1 was incompetent to be interviewed and 53 others (10 percent) declined to participate. Our study group thus consisted of 494 men, who made up 62 percent of the 801 survivors of the original cohort and 74 percent of the 667 men who had not died or been lost to follow-up before 1975 (Table 1).

From the Epidemiology Branch (A.J.W., D.D.B.) and the Statistics and Biomathematics Branch (C.R.W.), National Institute of Environmental Health Sciences, Research Triangle Park, N.C.; the Health Sciences Center, University of Virginia, Charlottesville (P.P.H.); and the Department of Obstetrics and Gynecology, University of Chicago, Chicago (A.L.H.). Address reprint requests to Dr. Wilcox at the Epidemiology Branch, NIEHS, Research Triangle Park, NC 27709.

Table 1. Follow-up Status of the University of Chicago Cohort of Males Exposed Prenatally to Diethylstilbestrol and Unexposed Males, Born in 1951 or 1952.

| CATEGORY | EXPOSED | UNEXPOSED | TOTAL |
|------------------------------|---------|-----------|-------|
| No. of males born 1951–1952 | 425 | 423 | 848 |
| Died in infancy | –14 | –7 | –21 |
| Lost to follow-up, 1952–1975 | –63 | –71 | –134 |
| No. ever located since birth | 348 | 345 | 693 |
| Lost to follow-up, 1975–1992 | –47 | –60 | –107 |
| Died during follow-up | –17 | –9 | –26 |
| Requested no further contact | –6 | –6 | –12 |
| Declined to participate* | –25 | –29 | –54 |
| No. of study participants | 253 | 241 | 494 |

*Includes one man who was not competent to complete the interview.

Of these 494, 365 (74 percent) reported that they had ever impregnated a woman. We requested permission to contact the female partner who had most recently become pregnant, so that we could collect more detailed information about that pregnancy. The partner's name and telephone number were provided by 312 men (85 percent). Of those women, 305 (98 percent) consented to be interviewed.

Trained female interviewers carried out structured telephone interviews with the men and their female partners. Fifty-one percent of the men still lived in Illinois; the remainder lived in 39 other states and 8 foreign countries. The exposure status of the men was not known to the interviewers. Interviews with the men and their partners lasted an average of 25 and 20 minutes, respectively.

The length of time to conception in the most recent pregnancy was analyzed with use of a discrete-time analogue of the Cox proportional-hazards model.¹³ Confidence intervals for differences in percentages were based on binomial standard errors.

RESULTS

We interviewed 494 men (253 who were exposed to diethylstilbestrol prenatally and 241 who were not exposed), all between the ages of 38 and 41 years. These men represented 64 percent of the surviving males of the original University of Chicago cohort who were exposed in utero and 59 percent of the unexposed males. The large number of sons lost to follow-up between 1952 and 1992 (26 percent of the exposed males and 31 percent of the unexposed males) raises the possibility of selection bias among those who actually participated. To address this question, we compared the men who participated in our study with all the rest of the original group. No differences were found in their mothers' mean age at delivery or in the week of pregnancy during which diethylstilbestrol treatment was begun.

In order to pursue the possibility that some unknown factor differentially influenced the entry of exposed and unexposed men into our study, we compared the biologic and demographic characteristics of the exposed and unexposed men. The two groups were nearly identical in height, weight, education, income, race or ethnic group, smoking status, and age at first marriage. The men exposed to diethylstilbestrol were slightly more likely than the unexposed men to be married at the time of the interview (75 percent vs. 69 percent, $P=0.12$).

We assessed differences between the exposed and unexposed men that might affect their fertility. Twelve percent of the men in each group reported that they had at some time been given a diagnosis of a sexually transmitted disease. However, the men exposed to diethylstilbestrol reported substantially more medically diagnosed genital malformations (15 percent, vs. 5 percent among the unexposed men; $P<0.01$). The most common malformations in these men were epididymal cysts and hypoplastic testes, described in previous reports of the clinical examination of men from this cohort.^{9,13}

We further divided the exposed men into two groups: those whose mothers' diethylstilbestrol treatment had started within 10 weeks and 6 days of their last menstrual periods, and those whose treatment started at 11 completed weeks of gestation or later. The prevalence of reported malformations was twice as high among the men with early exposure as among those whose exposure began later ($P=0.05$) (Table 2). Even so, men with malformations of the genitalia were no different from all the other men in the percentage who had ever fathered a child, the age at the birth of their first child, the total number of children, or any other measure of fertility.

Finally, we compared all the exposed and unexposed men (regardless of the presence or absence of malformations) in terms of a variety of end points related to fertility (Table 3). The reported rate of physical development during adolescence, age at first intercourse, frequency of intercourse, and sexual activity with male partners were similar in the two groups. The diethylstilbestrol-exposed men were more often concerned about possible infertility than the unexposed men and were slightly more likely to have sought medical advice because of problems with fertility. However, an actual medical diagnosis of male infertility was reported no more often by exposed than by unexposed men.

Other problems related to infertility were actually less common among the men exposed to diethylstilbestrol. Fewer of the exposed men reported being child-

Table 2. Reported Genital Abnormalities According to Diethylstilbestrol-Exposure Status and Timing of Diethylstilbestrol Treatment.

| SITE OF ABNORMALITY* | EXPOSED (N = 253) | | UNEXPOSED (N = 241) |
|------------------------------------|--------------------------------------|-------------------------------------|------------------------|
| | <11 WEEKS' GESTATION (N = 154) | ≥11 WEEKS' GESTATION (N = 99) | |
| | <i>percent</i> | | |
| Testicles | 10 | 8 | 5 |
| Epididymis | 3 | 1 | 0 |
| Other | 6 | 2 | 1 |
| Total with any genital abnormality | 18 | 9 | 5 |

*Some men reported more than one abnormality.

less, and fewer reported that it had taken more than a year for their partners to achieve pregnancy, that they had ever sought medical treatment for problems of erection or ejaculation, or that they had had decreased sex drive for at least three months. Conception while using birth control is an indirect measure of a couple's fertility; thus, the more fertile the couple the more likely they are to conceive accidentally. There were more exposed men than unexposed men who reported pregnancies conceived while they were using some method of birth control.

A sensitive measure of a couple's fertility is the length of time to conception — that is, the number of menstrual cycles from the time the couple stops using contraception until conception occurs.¹³ Of the 305 women we interviewed, 82 (30 percent of the partners of exposed men and 21 percent of the partners of unexposed men) were unable to give useful data on the length of time to their most recent pregnancies because the pregnancies had been unplanned or the use of birth control had been sporadic. The remaining 223 women (119 partners of exposed men and 104 partners of unexposed men) provided usable information. Figure 1 shows the cumulative percentage of the group that was pregnant at each cycle after the discontinuation of birth-control measures. No difference between the partners of the exposed and those of the unexposed men is apparent.

The length of time to conception can be adjusted for possible confounding factors by expressing the out-

Table 3. Fertility-Related End Points among Men Exposed Prenatally to Diethylstilbestrol and Unexposed Men.

| VARIABLE | EXPOSED (N = 253) | UNEXPOSED (N = 241) | 95% CI FOR DIFFERENCE* |
|--|----------------------|------------------------|---------------------------|
| Timing of physical maturation (%) | | | |
| Earlier than average | 9 | 9 | -5 to 5 |
| About average | 71 | 73 | -10 to 6 |
| Later than average | 20 | 18 | -5 to 9 |
| Mean age at first intercourse (yr) | 18.4 | 18.6 | — |
| Any male sex partner as an adult (%) | 3 | 3 | -3 to 3 |
| Ever married (%) | 88 | 82 | 0 to 12 |
| Ever fathered children (%) | 72 | 61 | 3 to 19 |
| Mean age at birth of first child (yr) | 28.7 | 28.6 | — |
| Mean total no. of children† | 2.2 | 2.2 | — |
| Ever concerned about fertility (%) | 24 | 15 | 2 to 16 |
| Ever examined by a doctor for a fertility problem (%) | 10 | 8 | -3 to 7 |
| Ever had a diagnosed fertility problem (%) | 1 | 1 | -2 to 2 |
| Ever sought medical help for problems (%) | | | |
| With erection | <1 | 3 | -5 to 0 |
| With ejaculation | 0 | 2 | -4 to 0 |
| Frequency of intercourse (per month) | 10.1 | 9.6 | — |
| Any decrease in sex drive lasting more than three months (%) | 6 | 11 | -10 to 0 |
| Partner ever took longer than a year to become pregnant (%) | 12 | 15 | -10 to 4 |
| Most recent pregnancy due to a failure of birth control (%) | 12 | 6 | 0 to 12 |

*The approximate confidence intervals (CI) in percentage points for the difference between the groups (exposed group - unexposed group).

†Includes only men with children.

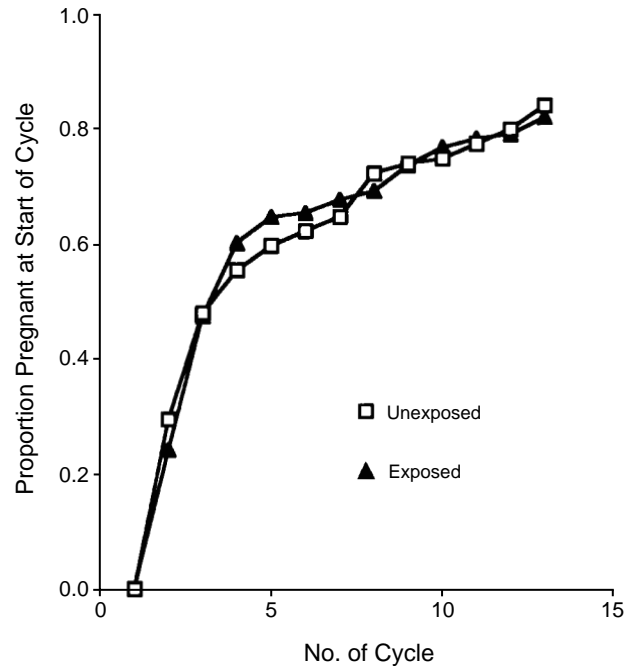


Figure 1. Cumulative Probability of Conception per Menstrual Cycle for 119 Couples in Which the Man Was Exposed Prenatally to Diethylstilbestrol and 104 Couples in Which the Man Was Unexposed.

come in terms of fecundability (the chance of conception per menstrual cycle).¹⁴ When the fecundability of exposed and unexposed couples is compared as a ratio, a value of less than 1 indicates lower fertility among the exposed men and their partners. The fecundability ratio was slightly but not significantly lower for the exposed men (0.9; 95 percent confidence interval, 0.7 to 1.2). We adjusted this ratio for possible confounding by the frequency of intercourse, alcohol consumption or smoking by the man or his partner, caffeine consumption by the partner, and other factors. The resulting fecundability ratio was unchanged (0.9; 95 percent confidence interval, 0.7 to 1.1). Among exposed men, the timing of the first exposure to diethylstilbestrol had no effect on fecundability. Finally, fecundability was not reduced in men with malformations of the genitalia, regardless of their exposure status.

DISCUSSION

The effects of diethylstilbestrol on the human fetus might have gone unnoticed had there not been an extraordinarily strong association of diethylstilbestrol with a rare vaginal tumor.² This fact called attention to the broader consequences of prenatal exposure to diethylstilbestrol, particularly its potential effects on the reproductive systems of both sexes.

Studies in Animals

Much of our understanding of the effects of prenatal exposure to diethylstilbestrol has come from studies of

rodents. Mice are exquisitely sensitive to the prenatal effects of diethylstilbestrol; female mice are rendered virtually sterile at weight-adjusted concentrations of diethylstilbestrol only 5 percent of the average dose received by women in the University of Chicago clinical trial.⁶

Diethylstilbestrol also impairs fertility in male mice. However, the effect of diethylstilbestrol in males does not follow the steady dose-response pattern seen in females; instead, the effect is found only above a relatively high threshold level of diethylstilbestrol.⁶ Impaired fertility appears to be secondary to retained testes and other gross anatomical disruptions of the male reproductive system.⁶

Genital Malformations

Diethylstilbestrol-related malformations of the reproductive tract have been reported in both men and women.^{8,15} Men exposed prenatally to diethylstilbestrol reported more malformations of the genitalia than unexposed men in our study, as would be expected from the results of their clinical examinations in the 1970s.^{8,12}

Previous studies of the Chicago cohort did not consider the influence of the timing of exposure on malformations in males. Our data suggest that the risk of genital malformation is higher among men who were exposed relatively early in gestation. Adult men are presumably unaware of the week of gestation during which their mothers' treatment began, so reporting bias is unlikely to account for this association. The higher risk of malformation with exposure to diethylstilbestrol in the first 10 weeks and 6 days after the last menstrual period is consistent with the timing of embryogenesis. The external genitalia have passed their period of highest susceptibility to teratogens by the end of the 9th week of embryonic life (a date corresponding approximately to 11 weeks after the last menstrual period).¹⁶

Fertility

Effects of prenatal exposure to diethylstilbestrol on women's fertility have been reported, although not consistently. In the Chicago cohort, primary infertility was more than twice as common among the daughters of women given diethylstilbestrol during pregnancy as among the unexposed daughters.³ No excess infertility was reported in another group of women exposed in utero for whom doses were not as well documented; many may have been exposed to lower doses or had their initial exposure later in gestation.¹⁷

The existence of diethylstilbestrol-induced infertility among the sons of women treated with this drug during pregnancy has been widely conjectured.¹⁸⁻²⁰ Such an effect is not implausible, given the infertility seen in studies of rodents⁷ and the excess rate of minor genitourinary malformations and changes in sperm reported among diethylstilbestrol-exposed men.¹² An apparent

decrease in penetration of zona-free hamster eggs by sperm from men exposed prenatally to diethylstilbestrol was reported in 1981,¹⁰ but in a larger study the same authors were unable to confirm this finding.²¹ In 1984, investigators from the Mayo Clinic reported that they found no effects of diethylstilbestrol on male fertility.²² The data were inconclusive, however, since the ages of the men were not reported, data on fertility were scant, and the dose of diethylstilbestrol given to the mothers of the men in the study was a small fraction of that received by the mothers in the Chicago cohort (mean cumulative dose, 1430 mg). Other studies have suggested that exposed men have infertility problems, but their results have been based on preliminary data on young men or on small samples.^{8,9}

In our survey of nearly 500 exposed and unexposed men, we found no evidence that diethylstilbestrol impairs male fertility. The men exposed to diethylstilbestrol in utero reported a general concern about their fertility, which is understandable given their knowledge of their own exposure to the drug. However, specific fertility-related difficulties were no more common (and sometimes less common) among the diethylstilbestrol-exposed men than among the unexposed men. Among the subgroups of men for whom we were able to measure the length of time to conception in a female partner, fecundability was apparently unaffected either by exposure of the male partner to diethylstilbestrol or by the presence of male genital malformations.

It has been speculated that prenatal exposure to diethylstilbestrol alters sexual orientation,²³ which could affect measures of fertility. In the present study, the overall percentage of men who reported ever having a male sex partner in adulthood was 3 percent, which is consistent with the results of a recent U.S. survey of male sexual behavior.²⁴ Diethylstilbestrol-exposed men and unexposed men were no different in this regard.

The chief strengths of this study derive from its origins in a clinical trial. Diethylstilbestrol treatment (or receipt of placebo) was documented for every mother in the original study, and the randomized, double-blind, placebo-controlled design provided a suitable comparison group in the sons of the women given placebo. Also, the men exposed to diethylstilbestrol whom we surveyed were old enough to have completed a substantial portion of their reproductive lives and thus were able to provide relatively complete data on their fertility.

The chief weakness of the study lies in its incomplete follow-up data. Of the male children of women in the study, 18 percent of both the exposed group and the unexposed group had died by 1992 or were never located after birth. The percentage of men who died or were lost to follow-up after the clinical examinations in the mid-1970s was 18 percent for the exposed group and 20 percent for the unexposed group. Missing data may

have distorted the results if the characteristics of the missing men differed from those of the men we studied in terms of exposure to diethylstilbestrol. We have little information about the missing men and so cannot evaluate this issue directly.

Indirectly, we can infer that the effects of this source of bias may be limited, for several reasons. First, the percentage of men lost to follow-up was similar for the exposed and unexposed groups. Second, a comparison of the background characteristics of the exposed and unexposed men in the study provided no evidence that differential selection distorted the composition of the two groups. Moreover, the usual epidemiologic concern is that persons with a health problem may be more likely to volunteer for a study if they know they have been exposed than if they are unexposed. The possibility of response bias would have to be considered if there had been an association of infertility with diethylstilbestrol. With no observed differences in fertility between the exposed and unexposed men, response bias is unlikely.

We found no evidence that diethylstilbestrol has impaired the fertility of men prenatally exposed to the drug. The apparent inconsistency between this result and the results of earlier studies bears closer inspection. Differences in semen measures do not necessarily mean differences in fertility. There could be subtle abnormalities of testicular function caused by diethylstilbestrol that have no effect on a man's fertility. The minor anomalies of the genital tract reported by these men are apparently compatible with full fertility. Moreover, studies of rodents suggest that diethylstilbestrol impairs male fertility but that the effect on male fertility is not as strong as that on female fertility.⁶ Thus, it is plausible that diethylstilbestrol could affect the fertility of the daughters of the women in the Chicago cohort but not that of the sons. Finally, since the analysis of the length of time to conception was applied only to the most recent pregnancies in the men's female partners, we cannot rule out the possibility that small decrements in fertility could have been present among the exposed men at younger ages, which then resolved with time. Such resolution over time has been suggested for certain diethylstilbestrol-related abnormalities of the female vaginal canal²⁵ and has been reported for abnormalities of the male reproductive tract in a small study of monkeys.²⁶ Still, the men's similar ages at the births of their first children would tend not to support differences in fertility even at younger ages.

The mothers in the Chicago study received a standard dose of diethylstilbestrol, but one that is higher than that used by many clinicians.^{11,27} The absence of detectable effects on fertility in men exposed prenatally to these high doses should reassure all sons of women treated with diethylstilbestrol. However, our data do not address any health effects of diethylstilbestrol that might emerge at older ages.

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