DES Action VOICE

A FOCUS ON DIETHYLSTILBESTROL

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DES Granddaughters Show Delayed Menstruation Regularity In New Study

Infertility Problems Also Hinted

"Menstrual and reproductive characteristics of women whose mothers were exposed in utero to diethylstilbestrol (DES)," Linda Titus-Ernstoff, et al, *International Journal of Epidemiology*, June 2006.

Reviewed by Fran Howell

DES Granddaughters participating in a recent study reported starting menstruation at about the same age as unexposed women (mean age 12.6-years for both groups), but it took longer for DES Granddaughters to achieve regular menstrual periods (meaning a period is predictable within 5 days).

Health questionnaires for this self-reported study were filled out by 793 individuals, including 463 DES Granddaughters and 330 unexposed females. They are all offspring of women being followed as part of the long-running National Cancer Institute DES Follow-up Study.

Researcher Linda Titus-Ernstoff, Ph.D., found that on average DES Granddaughters attained menstrual regularity at 16.2 years of age, which is slightly later than the unexposed women at 15.8 years.

Titus-Ernstoff is a professor in the Department of Community and Family Medicine and is associate director of the Hood Center for Children and Families at Dartmouth Medical School. She is a Principal Investigator with the NCI DES Follow-up Study and leads the granddaughters study.

According to Titus-Ernstoff, "daughters of the exposed women were more likely to report periods that were usually irregular and at least one episode of amenorrhoea (defined as more than six weeks without a menstrual period during the previous 12 months)."

The study factored in such variables as menstrual and reproductive histories, the number of doctor visits

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Noted Scientist Shares His Thoughts On DES Grandchild Research

"Commentary: Prenatal exposure to diethylstilbestrol (DES): a continuing story," by John A. McLachlan, *International Journal of Epidemiology*, June 2006.

Reviewed by Fran Howell

Researcher John McLachlan, Ph.D., Director of the Center for Bioenvironmental Research, Tulane University, is highly regarded in the DES community.

So his commentary, following Linda Titus-Ernstoff's DES Granddaughter article in the *International Journal of Epidemiology*, is worth noting.

In this article he describes the long scientific search to learn why an estrogen, such as DES, can be given to a mother and then have it cause problems in her offspring. "The DES-exposed population of men and women became the model through which understanding of delayed effects of gestational exposures to hormones or other compounds could be gained," McLachlan says.

After much study he says scientists in laboratories, including his own, have ruled out mutagenicity, or the ability to change the base structure of DNA, as the primary

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and hormone use. Not many participants reported using oral contraceptives for other than birth control, but of those who did, DES Granddaughters generally used them longer than the daughters of unexposed women (16.1 months vs. 3.6 months). Stated reasons were for regulation of periods and reduction of menstrual cramps.

Possible Infertility Issues

The study suggests that infertility may be more frequent in DES Granddaughters and DES exposure may exacerbate age-related infertility for them.

Titus-Ernstoff cautions, however, that the study is small and most participants were too young to have attempted starting a family. About 5.4 percent of the DES Granddaughters and 5.2 percent of the unexposed young women in the study reported dealing with infertility, which is defined as difficulty getting pregnant for 12 months or more. After adjustment for age and cohort, the data suggested that DES Granddaughters might be at increased risk for infertility. Interestingly, what the researchers noted is that problems with infertility seemed to increase with age, primarily for DES Granddaughters over age 30. But again, the numbers were very small, and most women hadn't yet tried to start a family.

Among those who had given birth, Titus-Ernstoff says, "daughters of the exposed were slightly less likely to report a live birth, but the relationship was compatible with chance. On average and adjusted for age and cohort, the exposed women had fewer live births than the unexposed." She also found the mean birth weight of babies born to DES Granddaughters was lower than in the unexposed group.

Titus-Ernstoff stresses that this research is preliminary and further follow-up is needed as more DES Granddaughters enter their reproductive years. DESVOICE

Scientist Shares Thoughts *from page 1*

method for DES' effects through generations.

Instead, McLachlan explains that scientists now believe DES causes problems to occur during cell differentiation and formation of organs. He suspects DES changes the normal patterns of gene expression. "In the very simplest terms, skin expresses skin genes, while bones express bone genes; just as importantly, bone-specific genes are turned off in skin and vice versa."

But sometimes something causes the process to go awry, turning off genes that should remain active and turning on others that shouldn't be, all the while leaving the gene code, or DNA, intact. This field of study is called epigenetics. Endocrine disruptors, like DES, have been implicated in improper gene functioning.

McLachlan says work from his laboratory and others, "raises the possibility that early exposure to DES may cause persistent epigenetic changes in some genes and not others such that the fate of tissues or organs is altered." He adds that, "the epigenetic change can actually persist through generations of cells in one organism or, if the change occurs in the germ cell line (egg cells in females and sperm cells in males), could even persist into the next generation of an organism."

The study done by Titus-Ernstoff and her colleagues shows young women, who were not themselves exposed to DES, may have altered reproductive tract function because their mothers are DES Daughters. McLachlan finds it extremely interesting. "This is a remarkable finding, if replicated, since it would mean that in humans, maternal ingestion of DES during pregnancy can not only alter the reproductive capacity of the woman exposed directly while a fetus, but that the alteration may be passed on to another generation (the so-called DES granddaughter effect). The effect described in the current paper, later attainment of menstrual regularization and more irregular periods, is small, but biologically consistent for an oestrogenic effect."

According to McLachlan, this is preliminary evidence that DES can alter the way genes work in certain cells so that the changes, not to DNA but to the way genes function by turning on and off, can extend into future generations. "More than half a century of DES experience has shown us that numerous defects can be encoded in the genome of the exposed fetus to be expressed later in life. This paper (by Titus-Ernstoff) and the supporting animal research data suggest that these encoded or imprinted defects may, in some cases, persist into the next generation. This is a small study with many questions, but the questions are profound enough that they merit an enhanced and continued follow-up of DES-exposed offspring and their offspring."

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Finally, McLachlan gives a nod to Arthur Herbst, M.D., who first alerted us to the fact that DES given to pregnant women could cause cancer in their daughters. "It is notable," says McLachlan, that 35 years later, Herbst may be "illuminating the first example of transgenerational effects of DES in humans as one of the authors of the current Titus-Ernstoff paper." DESVOICE