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DIETHYLSTILBESTROL (DES) AND ITS RELATIONSHIP TO REPRODUCTIVE FAILURE

It is well recognized that prenatal exposure to diethylstilbestrol (DES) sometimes results in reproductive failure. Tubal (ectopic) pregnancies, miscarriages, premature labor, and both male and female infertility are all relatively prevalent in the offspring of women exposed to DES during the first half of pregnancy. It is important to recognize however, that only about 30% of women prenatally exposed to DES experience these problems. The reason for this has to do with the stage of the pregnancy at which the exposure occurred (i.e. what organs were in development at the time of the exposure), as well as the dose which the developing fetus was exposed to (greater exposure equates to greater deleterious effects).

Diethylstilbestrol is a synthetic hormone with profound estrogen-like properties. However, its chemical structure bears no similarity whatsoever to that of natural estrogen. Natural estrogen is a lipid (fatty) substance with a "steroid structure" while DES is a non-lipid chemical containing a "stilbene nucleus." DES is very similar in structure to the fertility agent, Clomiphene Citrate (Serophene, Clomid).

In order for a natural hormone such as estrogen to exert a biological effect, it must first attach to the cell surface at specialized sites called receptors. These receptors are uniquely specific for each hormone. DES paradoxically has great affinity for estrogen receptors and is even capable of displacing estrogen from its own receptor sites. It is not surprising that the development of reproductive structures such as the upper vagina, cervix, uterus, fallopian tubes and sperm ducts in the male, all of which are dependent upon maternal estrogen for their development, are adversely influenced by exposure to DES. The structures referred to above share a common embryologic origin. They are all derived from the Müllerian system, which undergoes maximal development during the third and fourth months of pregnancy. Accordingly, exposure to DES during this critical period often adversely affects development of the upper vagina, cervix, uterus, fallopian tubes and male sperm ducts. This could explain why the severity of reproductive abnormalities caused by prenatal DES exposure varies dependent upon the exact time and duration of exposure during the first half of pregnancy. For example, it is highly unlikely that the offspring of women who ingested DES for a brief period of time during early pregnancy would have severe developmental abnormalities of the reproductive tract, while the offspring of women who

were exposed to DES for an extended period of time extending through the third and fourth months of pregnancy would be very likely to be affected.

DES was prescribed in the late 1950's and early 1960's for the purpose of preventing miscarriages. Some women with a history of previous miscarriages were automatically prescribed DES in the hope of preventing spontaneous abortion from occurring in the current pregnancy. In a number of such cases (the minority), the administration of DES was continued beyond the second and third month of pregnancy (i.e., the critical period of Müllerian development). The offspring of these women were highly likely to develop serious DES-related complications. Fortunately, in the majority of cases, DES was only prescribed for a brief period of time during the second month of pregnancy while the woman was experiencing vaginal bleeding (a threatened miscarriage) and was discontinued when bleeding stopped. These women usually did not ingest DES during the critical phase of Müllerian development and accordingly the reproductive function of their offspring was left unaffected. This probably explains why most DES exposed individuals do not experience reproductive failure.

Women who experience reproductive failure due to DES exposure often exhibit characteristic abnormalities of their reproductive tracts. These include structural deformities of the upper vagina and cervix, as well as the presence of glandular tissue (normally absent in the vagina and outer cervix) referred to as vaginal adenosis. The cervical canal, which connects the vagina to the uterine cavity, is often long and distorted in DES affected women whose uterine cavities are often disproportionately short and distorted. Moreover, the walls of the DES-uterus tend to be more fibrous. Perhaps this results in reduced stretchability of the DES-uterus and is responsible for the high incidence of premature births.

The abnormal uterine cavity associated with DES exposure can be readily demonstrated through the performance of a hysterosalpingogram (x-ray dye test) which often reveals a T- or butterfly-shape rather than a normal rounded pear-shaped appearance. The fallopian tubes of the DES daughter are also often deformed. They tend to be shorter than normal and have an abnormal inner structure. The typical longitudinal folds of the inner lining of the normal fallopian tube are often absent, irregular, or distorted, a possible explanation for the high ectopic (tubular) pregnancy rate associated with DES anomalies.

It is important to emphasize that the ovaries are not of Müllerian origin and are accordingly unaffected by prenatal DES exposure. DES daughters usually ovulate normally, have normal blood hormone levels and perfectly normal temperature charts. It is probably for this reason that the cause of reproductive failure sometimes goes undetected in such cases.

The above mentioned structural abnormalities explain most of the serious reproductive complications that occur in women who were exposed to DES prenatally. However, these anomalies do not completely explain the relatively high incidence of early and recurrent spontaneous miscarriages that so commonly occur in association with DES uterine anomalies. Recent research has demonstrated that prenatal DES exposure at the critical period of Müllerian development might permanently alter the structure and function of estrogen receptors, rendering them permanently incapable of responding appropriately to natural estrogen in later life. This could explain why the uterine lining (endometrium) and cervical lining

of DES daughters often fail to respond appropriately to estrogen. Research has confirmed that women with obvious Müllerian anomalies secondary to prenatal DES exposure commonly present with cervical mucus insufficiency and a thin endometrial lining in spite of normal blood estrogen concentrations around the time of ovulation. The poor quality cervical mucus and thin uterine linings might explain the high incidence of infertility associated with DES anomalies. The thin uterine lining is likely responsible for the relatively high incidence of early miscarriages. Perhaps the poor thickness and quality of the uterine lining compromises healthy implantation and placentation that is essential for early fetal development and growth.

And so it is that the "ill-conceived" administration of DES to women more than 25 years ago, without clear evidence of potential benefit, resulted in serious reproductive consequences to their offspring. Hopefully the medical profession has learned an important lesson from this tragedy, one that calls upon the medical profession to resist the temptation of administering medications to patients simply on anecdotal grounds. Concrete evidence of benefit is important before recommending the administration of untried therapeutic regimens.

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