

Of interest is the phenotype of an XX individual who is homozygous for the same mutation. This woman had secondary amenorrhea but no other obvious clinical manifestation of this mutation. This observation is instructive because it indicates that (1) a functional LHR is not necessary for pubertal ovarian function; (2) normal female puberty through menarche can be guided by FSH alone; (3) adrenal androgens alone are sufficient for normal sexual hair growth in the female (thus confirming other data); and (4) the heterozygous loss of 1 functional LHR is of no clinical or reproductive consequence. (The parents of the affected children were not studied but had 14 children.)

A mutation in the seventh transmembrane domain of the LHR in the child in family 2 prevents movement from the endoplasmic reticulum to the plasma membrane surface and thus binding of LH to its receptor. Since the affected subject with this defect had micropenis rather than ambiguous genitalia, presumably functional LHR was expressed on the fetal Leydig cell membrane in the first trimester of gestation, but not thereafter. (See GROWTH, Genetics & Hormones 1996;12[2]:24—2nd editor's comment.)

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Kremer H, et al. *Nature Genet* 1995;9:160-164.

Teratogen Update: Diethylstilbestrol

Diethylstilbestrol (DES) teratogenicity occurred over a period of about 3 decades when it was used to avert miscarriage. Female fetuses who had a significant exposure to DES and other synthetic estrogens (now collectively referred to as DES) are now known to be at risk for carcinogenic and teratogenic effects. DES-exposed daughters have an increased risk for developing clear cell adenocarcinomas of the vagina and cervix and structural abnormalities of the genital tract that predispose to vaginal adenosis and other vaginal epithelial changes. Some male fetuses exposed to DES have structural abnormalities of the genital tract, but as yet no increase in cancer has been reported. Fertility and sexual function in these men appear to be normal. Girls exposed in utero to DES also have a somewhat higher risk of breast cancer than women who were not exposed. There is no evidence that grandchildren of DES-exposed daughters and sons have any abnormalities. It would appear that the epidemic of clear cell adenocarcinoma is over. It is not entirely clear whether there may be problems in intrauterine DES-exposed individuals who now are over the age of 50. Carcinomas developed in only a small proportion of this population. It appears that the mechanism by which DES caused these problems has to do with interfering with the "natural regression" of certain tissues in embryonic and fetal life.

Mittendorf R. Teratogen update: carcinogenesis and teratogenesis associated with exposure to diethylstilbestrol (DES) in utero. *Teratology* 1995;51:435-445.

Wilcox AJ, et al. Fertility in men exposed prenatally to diethylstilbestrol. *N Engl J Med* 1995;332:1411-1416.

Editor's comment: These papers are helpful for reassuring at-risk individuals. The sad part of the whole DES story is that there was no beneficial effect in maintaining pregnancies and, consequently, a large number of children were exposed unnecessarily to DES. We must remind ourselves to be sure before prescribing a therapeutic agent that there is in fact a demonstrated therapeutic effect. We then must weigh the potential positive effect against the possible negative effects. Today we would like to think that clinical studies ensure that all therapies actually do what they are meant to do. However, possible long-term adverse effects are hard to predict, and a judicious approach to any therapy is obligatory under the Hippocratic oath to do no harm. Fortunately, future research funded by National Cancer Institute will permit monitoring of the DES-exposed population to determine whether any other abnormalities become apparent.

Those who wish to read a very complete and extensive review of the DES story are referred to Mittendorf's article. Wilcox's article is more limited in scope, as it is confined to findings in males; nevertheless, it is an important report.

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Teratogenicity of High Vitamin A Intake

In general, vitamins are thought to be essential for embryogenesis and necessary for health in the fetus, infant, child, and adult. However, fat-soluble vitamins have been recognized to cause toxicity and, potentially, teratogenicity when taken in large doses. Vitamin A is available in many forms as part of supplementary vitamin capsules. It also is present in the diet, coming from certain vegetables and animal sources, including dairy products, liver, and fortified foods. Currently,

the recommended daily allowance of vitamin A for women is 800 retinol equivalents, which corresponds to 2,700 IU. Vitamin A has been found to be teratogenic in humans, and recently there has been an epidemic of teratogenicity because of isotretinoid used to treat severe acne. The malformations that can be seen in retinoic acid embryopathy include craniofacial, cardiac, thymic, and central nervous system abnormalities (Table 1).