

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).

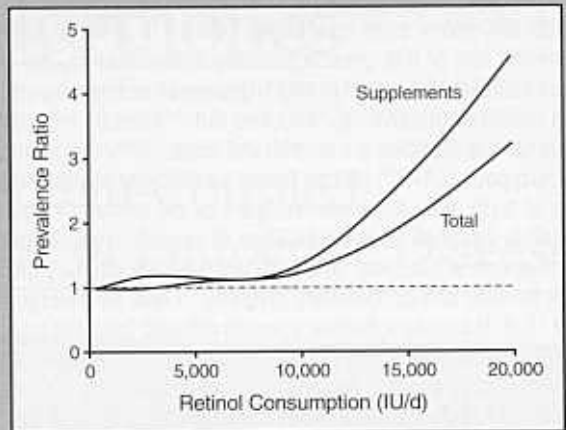
Table 1  
Birth Defects According to Category With Retinoic Acid Embryopathy

Type of Defect	No.
Cranial neural crest	
Craniofacial, central nervous system (except neural tube), and thymic	69
Heart	52
Total	121
Neural tube	48
Musculoskeletal and Urogenital	
Musculoskeletal	58
Urogenital	42
Total	100
Other	
Gastrointestinal	24
Nongastrointestinal	46
Total	70
<b>Total</b>	<b>339</b>

Rothman et al have interviewed 22,748 women concerning their diet and illnesses during the first trimester of pregnancy. All sources of retinol intake were tabulated and an association was made with various types of birth defects. There is a major concern regarding supplementary vitamin A but not the beta carotene of the dietary form of vitamin A. A relationship was found between high vitamin A consumption during early pregnancy and the occurrence of a variety of birth defects. The data appeared to indicate a teratogenic effect of vitamin A intake not far above the currently recommended dose. Consuming more than 10,000 IU per day was found to be associated with an increased incidence of birth defects when the high levels of vitamin A were taken before the seventh week of gestation (Figure 1). It was estimated that 1.4% of the women in the study averaged more than 10,000 IU of vitamin A per day.

Table 1 and Figure 1 reprinted by permission of *The New England Journal of Medicine*; Rothman K J, et al. *N Engl J Med* 1995;333: 1369-1373.

Figure 1  
Retinol Consumption (IU/d)



Estimated prevalence ratio for birth defects related to the cranial neural crest, according to retinol intake during the first trimester of pregnancy.

**Editor's comment:** This finding is of great concern because the general public thinks that vitamins are benign and if "a little is good, a lot is better." The study points out there is a fine line between enough and too much. Of particular concern are the additive effects of multivitamins, prenatal vitamins, and fortified foods. Care should be taken by pregnant women or women who wish to become pregnant to limit vitamin A supplementation. In view of the fact that we wish pregnant women to be sure to take sufficient folic acid prior to becoming pregnant and in early pregnancy, the situation can be confusing. It is quite clear that vitamin A can be teratogenic and can be related to other problems besides the classic picture of retinoic acid embryopathy.

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## Growth and Physical Outcome of Children Conceived by in Vitro Fertilization

The authors report the status at 2 years of age of 289 Australian children from Victoria who were conceived by in vitro fertilization (IVF). The birth weights of singleton IVF and naturally conceived control infants were similar (IVF: 3,196 g; control: 3,294 g), while the birth weights and gestational ages of IVF twins were slightly greater than those of control twins (IVF: 2,297 g, 35.0 weeks; control: 2,053 g, 33.7 weeks). At 2 years of age, the weight and head circumference percentiles of the entire group of IVF and control children were similar (IVF: 56.3 g; 63.4 cm, respectively; control: 56.2 g; 65.7 cm, respectively). Length percentile of the IVF children was significantly ( $P=0.004$ ) greater than that of the control children (57.7 cm versus 49.9 cm), the reason for which was not apparent. There was no significant difference between

IVF and naturally conceived children with respect to: congenital malformations, subsequent hospitalizations and operations, or neurologic status. The investigators concluded that IVF had no adverse effect on growth, general health, and development at 2 years of age.

Saunders K, et al. *Pediatrics* 1996;97:688-692.

**Editor's comment:** More than 34,000 children have been delivered by assisted reproductive techniques. It is encouraging to note that these interventional methods have produced predominantly normal offspring.

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