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## Vitamin A and Pregnancy

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With the recent advent in popularity of multivitamins and megavitamins, it is becoming increasingly important to be aware of the possible teratogenic effects of high doses of vitamins during pregnancy. Vitamins are essential for maintaining good health, but consumption of large amounts of certain vitamins, particularly A and D, poses a teratogenic risk. Vitamin A is essential for the normal functioning of the retina and for growth and differentiation of epithelial tissue as well as necessary in embryonic development, reproduction and bone growth. However, vitamin A has been shown to produce teratogenic effects in animal studies when administered in high doses. The possible teratogenic risk associated with vitamin A has recently come under some debate concerning the amount that will begin to produce an increased frequency of congenital malformations in human offspring exposed during gestation. This RISK||NEWSLETTER will focus on the effect of large doses of vitamin A on pregnancy.

### RETINOID VERSUS BETA-CAROTENE

Vitamin A is a term encompassing two forms: a retinoid, a preformed vitamin A originating from animal tissue; and, beta-carotene, a provitamin A compound originating from plant tissue. Beta-carotene is a carotenoid occurring naturally in foods such as carrots, meats and dark green leafy vegetables. Beta-carotene is converted in the body to the retinol form of vitamin A. This conversion does decrease substantially when large amounts of beta-carotene are ingested (USP DI, 1994). Therefore, large amounts of beta-carotene should not lead to toxicity or teratogenicity because the conversion to the retinol form is actually decreased with increasing amounts of beta-carotene. The Teratology Society has concluded that beta-carotene is not a human teratogen (Teratology, 1987).

### ISOTRETINOIN (ACCUTANE)

Results of studies on a related compound, isotretinoin initially raised concerns about vitamin A dosages in pregnancy. Isotretinoin is a 13-cis-retinoic acid used to treat severe cystic acne. This chemical has vitamin A activity. It was shown to cause major malformations in 20% of fetuses exposed during early pregnancy (Lammer et al., 1985). These malformations involved four structures: the cranium and face; the heart; the thymus; and, the brain. Isotretinoin is thought to interfere with cranial crest cells, which contribute to the development of the ear and conotruncal areas of the heart. In this study mothers took daily doses of 0.5-1.5 mg/kg/day. The relative risk for brain, cardiac, or ear malformations in exposed fetuses was 25.6 times higher than the risk for unexposed fetuses (Lammer et al., 1985).

### VITAMIN A AND CONGENITAL ANOMALIES

Numerous animal studies involving vitamin A administration during pregnancy have reported

teratogenic effects. Pregnant rats fed 35,000 IU/day 2-16 of gestation had an increased frequency of encephaly, cleft lip and/or palate, brachygnathia and various eye defects (Cohlan, 1953). Subsequent reports on mice, guinea pigs, hamsters, and rabbits found these species to be similarly susceptible to hypervitaminosis A. The teratogenicity of vitamin A in animals lead to the assumption that vitamin A, not beta-carotene, is a human teratogen, even though much of the direct evidence for its teratogenicity comes from anecdotal reports of mothers consuming >25,000 IU/day during pregnancy.

One report stated urinary tract malformations were seen in an infant of a women taking 25,000 IU during the first three months of pregnancy and 50,000 IU during the fourth through ninth months of gestation (Bernhardt et al., 1974). An earlier report also described an infant born with gross urinary tract defects in which the mother had ingested 40,000 IU of vitamin A per day from the sixth through the tenth weeks of pregnancy (Pilotti et al., 1965). Central nervous system defects were present after ingestion of 150,000 IU per day during pregnancy (Stange et al., 1978). Between 1984-1986 there were ten case reports describing possible teratogenic effects of vitamin A on a pregnancy. These case reports were mainly reported by doctors to the FDA or by a state birth defect registry. Doses in these pregnancies ranged from 25,000 to 100,000 units/day before and throughout pregnancy. Those women taking 25,000 to 33,000 units/day had offspring with microcephaly, ear malformations, and transposition of great vessels. These three defects were not seen in combination in any of the infants (Rosa, 1986). Women taking doses of 40,000 units or more per day before and during pregnancy had infants with combinations of malformations. One infant had tiny ear canals, facial dysmorphy and high palate. Cleft lip and/or palate were consistently seen in all infants exposed to 40,000 IU/day or more (Rosa, 1986).

IS THERE A DOSE-RESPONSE THRESHOLD?

Case reports and anecdotal studies suggest vitamin A intake of 25,000 IU or more during pregnancy increases the risk for congenital anomalies (Rosa et al., 1986). Rothman et al. (1995) undertook a study in order to clarify the issue of what dose of vitamin A begins to pose an increased risk for congenital anomalies. Between October 1984 and June 1987 22,748 pregnant women were identified of which 339 babies had birth defects; 121 of these infants had defects in sites arising from the cranial neural crest. The trend for the risk for musculoskeletal and urogenital tract defects was less apparent, and no discernible risk was observed for neural tube defects. Women who consumed more than 15,000 IU of preformed vitamin A from food and supplements had infants with defects associated with cranial-neural-crest tissue 3.5 times greater than women who consumed 5000 IU or less (95% CI, 1.7-7.3). The prevalence ratio of these defects for women who consumed more than 10,000 IU/day compared to women who consumed less than 5000 IU/day from supplement alone was 4.8 (95% CI, 2.2-10.5). Rothman et al. (1995) reported finding a threshold for supplemental vitamin A near 10,000 IU/day. The increased frequency of malformations was observed more frequently among infants born to women ingesting large amounts of vitamin A before the seventh week of gestation. The authors of this study concluded that approximately 1 in 57 infants would have malformations attributable to vitamin A supplements at doses above 10,000 IU/day.

The study by Rothman et al. (1995) is not without controversy over the results. Oakley and Erickson (1995) expressed concern about the need for more detailed data on the amount of vitamin A consumed by women who took 10,000 IU or more during pregnancy. The mean vitamin A intake in this group was 21,675 IU/day, which suggests some fetuses were exposed to more than 25,000 IU/day. Specific exposure information is necessary before it is recommended that the dose-response threshold curve described in the paper by Rothman et al. (1995) be utilized. In responding to this criticism the authors state, “the curve shows about a 5-fold increase in birth defects for women taking daily doses of retinol, and is fitted through individual data points.”

Several studies have assessed the risk to a pregnancy with maternal intake of 8000 IU or less of

preformed vitamin A during pregnancy. Khoury et al. (1996) examined data from a large population-based case control study of major birth defects conducted by the Center for Disease Control. Mothers of infants with serious birth defects were compared to mothers of infants without birth defects. No increased risk was observed among vitamin A and multivitamin users or among women who took both multivitamins and vitamin A supplements together (OR .54, 95% CI .22-1.33). These authors also reviewed numerous case studies in order to assess whether specific phenotypes were associated with vitamin A use. They compared case studies of babies with birth defects whose mothers used vitamin A supplements with babies with birth defects whose mothers reported not using any vitamin A supplements during pregnancy. No differences were observed between the two groups when looking at patterns and types of birth defects, presence of multiple congenital anomalies and recognizable phenotypes. They did not have information on the amount of vitamin A ingested, but most multivitamins and supplements during that time period contained 8000 IU of retinol. The authors state that "these data should provide reassurance that vitamin A supplements under 8000 IU do not increase the risk for birth defects (Khoury, 1996)".

Several studies have been reported revealing no increase in congenital anomalies after prenatal exposure to large amounts of vitamin A. These include 1203 infants exposed to 6000 IU daily during the first trimester of gestation (Dudas and Czeizel, 1992); and, a case control study of 11,293 children with minor and major malformations and maternal use of 10,000 IU or more of vitamin A per day (Martinez-Frias and Salvador, 1988, 1990).

SUMMARY

The recommended daily allowance for preformed vitamin A is 2700 IU/day or 8000 IU of beta-carotene. In 1987 the CDC, Teratology Society and Council for Responsible Nutrition independently published recommendations for use of vitamin A during pregnancy. These were made because teratogenicity appears to occur at some undetermined level above 8000 IU and pregnant women in the United States do not seem to benefit from additional vitamin A. They recommend limiting vitamin A in prenatal vitamins to 5000-8000 IU and vitamin A content of all multivitamins to 10,000 IU; therein suggesting women should not ingest more than 10,000 IU prior to consulting a physician.