

Teratogenic Risk of Hormonal Products for Contraception: A Review of the Literature

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A. Teratogenic Risk of Emergency Contraception (EC)

There is very limited information specifically on EC use during pregnancy since it is taken for the prevention of pregnancy, requires only two doses, and will not interrupt an existing pregnancy. A review of the literature on inadvertent use of oral contraceptives (OCs) during pregnancy provides the most information relevant to fetal exposure to sex hormones in early pregnancy. The doses of sex hormones in EC pills are about 2-5 times that that of OC pills containing the same hormones. There are many reported cases of women inadvertently taking OCs, either combination hormonal pills containing an estrogen and a progestin, or progestin-only pills (POPs), for up to several months while pregnant. The comprehensive reviews listed here provide strong evidence that exposure to sex hormones [both combination hormonal products and levonorgestrel-alone pills] in early pregnancy does not have a teratogenic effect. Much of the epidemiologic literature dates to the 70s and 80s when use of higher-dose oral contraceptives than currently prescribed was extensive, and reports of congenital anomalies were being analyzed as to general risk factors and maternal medications around the time of conception or during pregnancy.

Review articles:

The following are important review articles about teratogenic risk with sex hormone exposure around the time of conception and during the first trimester of pregnancy. These articles summarize the current state of science and primarily rely on clinical trials and prospective, cohort studies, which have less bias than case-control observational studies.

1. *Reproductive Toxicity Review*, last revised 2/01/01, from REPROTOX®, a reproductive toxicity database. "A large number of reports [13 are referenced] have failed to find an association between OC/progestin exposure just before or during pregnancy and congenital heart defects or other nongenital abnormalities. There have been reviews that detail the much larger collection of reports from which this sample was taken [5 are referenced]."

2. Raman-Wilms L, et al: Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol* 1995;85(1):141-9.
Out of 168 articles initially identified, 14 studies (7 cohort and 7 case-control) involving 65,567 women, met the criteria for meta-analysis. The authors concluded, "There was no association between first trimester exposure to sex hormones generally (or to OCs

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specifically) and external genital malformations. Thus, women exposed to sex hormones after conception may be assured there is no increased risk of fetal sexual malformation."

3. McCann MF and Potter LS: Progestin-only oral contraception: A comprehensive review. *Contraception* 1994;50(6)(S1):S9-195. "Conclusion: based on the findings of these studies, it is unlikely that fetal anomalies or developmental lags will occur because of accidental use of POPs [progestin-only pills] during pregnancy, nor is there any hypothesized biological mechanism for such an effect." (S52)

4. Simpson JL and Phillips OP: Spermicides, hormonal contraception and congenital malformations. *Adv Contracept* 1990;6:141-67.

This detailed review of the literature examined 18 major prospective studies evaluating the effects of progestin exposure during pregnancy, and determined that the doses received were not teratogenic.

5. Bracken MB: Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstet Gynecol* 1990;76:552-57.

Overall, the author analyzed data from 6,102 exposed and 83,167 unexposed women. He points out that it is improbable that a single source of bias would have influenced all the studies systematically. He concluded that the overall relative risk for all malformations from the 12 prospective cohort studies was the same for exposed and unexposed women. "This lack of association between OCs and birth defects in prospective studies agrees with the results of most of the better-designed case-control studies."

6. Population Council: Norplant Levonorgestrel implants: a summary of scientific data. *The Population Council* 1990, New York.

Clinical trials of NORPLANT® system found no evidence of teratogenicity of levonorgestrel administered by implants.

7. Wilson JC and Brent RL: Are female sex hormones teratogenic? *Am J Obstet Gynecol* 1981;141:567-80.

The four major teratogenic concerns associated with sex hormones are heart, limb, vertebral, and GI tract anomalies. The authors concluded that there is no association between oral contraceptives and birth defects based on several findings, including extensive surveillance data that did not show a corresponding rise in the incidence of the suspected birth defects as the use of OCs increased. They pointed out that because sex hormones act specifically on tissues with hormone receptors that are primarily on reproductive/genital tissues, the probability of receptor binding causing anomalies on non-genital tissue is low.

Animal Toxicology review:

Maier WE and Herman JR: Pharmacology and toxicology of ethinyl estradiol and norethindrone acetate in experimental animals. *Regulatory Toxicology and Pharmacology* 2001;34:53-61.

The authors concluded, "for over 30 years various combinations of synthetic estrogens and progestins have been used in OCs. Ethinyl estradiol (EE) and norethindrone (NA)

alone or in combination, possess low acute and chronic toxicity. These agents are not teratogenic when given in combination. Overall, the animal data demonstrates that long-term exposure to EE and NA formulations pose very little health risk to humans."