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## Contraceptive Exposure and Pregnancy

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Eugene Pergament, MD, PhD; Amy Stein, MS; Tina Bartell

The focus of this issue of RISK//NEWSLETTER is the recent changes in the preparations of oral contraceptives and the implications of prenatal exposure to oral contraceptives. Teratogenicity of vaginal spermicides and depot preparations will also be reviewed.

### ORAL CONTRACEPTIVES

#### Preparations : Changes in Oral Contraception Content

Early studies reporting that the incidence of birth defects associated was increased with the use of oral contraceptives were conducted on preparations containing 150 µg of Mestranol and 9.35 mg of Norethynodrel (Thorogood et al, 1993). Since the middle 1970s, the dosages of estrogen and progestin have been progressively lowered (Djerassi, 1989). Although lower dose combination oral contraceptives seem to have fewer and milder side effects, studies have yet to be conducted comparing the long term adverse effects of the earlier and now obsolete oral contraceptives with the new dosages of combined oral contraceptives.

#### Estrogen

Most combination oral contraceptives contain ethinyl estradiol, although there are still two combination oral contraceptives that contain mestranol as their estrogen. Current oral contraceptives contain approximately 1/3-1/4 times less estrogen than in the past, with content ranges from 20 to 50 µg and an average of 35 µg per pill.

#### Progestins

Progestin dosage has declined three-fold compared to dosages in earlier preparations and may contain as little as 0.05 mg (Thorogood et. al., 1993).

#### New Progestins

Three new progestins were introduced in the 1990's: desogestrel, gestodene, and norgestimate. These new progestins are chemically related to levonorgestrel found in Norplant (Wyeth-Ayerst, Radnor, PA). Previous types and doses of progestins may have caused androgenicity in some women because of incidental affinity for the androgen receptor. Norgestimate in particular has been found to have a significant increase in selectivity for the progesterone receptor and a weak affinity for the androgen receptor (Phillips et al, 1992). Gestodene does not require further metabolism to be active and permits even greater reduction in the total steroid dose.

#### Teratogenicity

Before the introduction of low dose preparations, first trimester exposure to oral contraceptives was with birth defects (Thorogood et al, 1993). These birth defects involved the vertebrae, anus, heart, trachea, esophagus, kidney and limbs (VACTERL syndrome) (Nora et al, 1976). Most of these studies were retrospective and have been criticized for recall bias (Krickler et al, 1986). There have been a number of well-controlled, unbiased epidemiologic studies refuting the association of oral contraceptives and birth defects (Bracken et al, 1978; Oakley et al, 1973; Lammer et al, 1986). The data from these studies failed to find any increased risk of birth defects after exposure to oral contraceptives.

Studies evaluating the effects of progestin exposure during pregnancy found masculinization of female fetuses resulting in pseudohermaphroditism. One study estimated that 1% of exposed fetuses are masculinized (Schardein, 1980). Most cases of masculinization require that the exposure to progestins occur between the eighth to tenth week of development. Prenatal exposure to oral contraceptives has also been associated with male genital anomalies, specifically hypospadias. However, a recent study that evaluated the prenatal histories of over 2000 males with hypospadias did not find an association with the use of oral contraceptives (Kallen et al, 1991).

Currently, an increased risk of birth defects associated with oral contraceptives is less likely because current preparations have such low doses and the new synthetic progestins have an increased progesterone receptor specificity. Since the introduction of lower dose oral contraceptives and improved synthetic progestins, only a small series of prospective cohort and case controlled studies have looked at the possible risks associated with the use of oral contraceptives during pregnancy (Simpson et al, 1990; Wilson et al, 1981; Wiseman et al, 1984). These studies were unable to find any evidence of teratogenicity in association with oral contraceptives or progestins in appropriate doses. Time and further investigation of lower dose oral contraceptives is required, however, to substantiate these preliminary findings.

## VAGINAL SPERMICIDES

### Formulations

Vaginal spermicides are available as foams, creams, gels, films, suppositories, and sponges. The active ingredient in vaginal spermicides available to women in the United States is either nonoxynol-9 or octoxynol-9. Both of these agents have been approved by the FDA. The formulations of each spermicide differ in the amount of active ingredient, speed of distribution, and degree of surface coverage.

### Teratogenicity

Several studies have suggested that the use of vaginal spermicides may be associated with an increased risk of chromosomal or fetal abnormalities (Strobino et al, 1980; Rothman, 1982; Jick et al, 1981; Polednak et al, 1982; Huggins et al, 1982). However, later studies using meta-analysis have found evidence to support the teratogenicity of spermicides in regard to adverse fetal outcomes including chromosomal aberrations, malformations, neoplasms, and undescended testes (Einarson et al, 1990).

## DEPOT PREPARATIONS

### Norplant

Norplant administers constant low levels of levonorgestrel. Each of the six rubber capsules contain 36 mg of levonorgestrel. Delivery within the first year ranges between 50 to 80  $\mu$ g of levonorgestrel. This dose is similar to that provided by one levonorgestrel-only contraceptive pill. After the first year, drug release is relatively constant, the daily dose varies between 30-35  $\mu$ g over the next 4-5 years.

### Teratogenicity

The teratogenicity of Norplant has not been studied but its theoretical risks are probably similar to other progestins. No adverse effects have been reported in infants conceived during Norplant use (Liskin et al., 1987).

#### Depo-Provera

Depo-provera (DMPA) is a medroxyprogesterone acetate that is similar to natural progesterone. It was accepted by the Federal Drug Administration in 1992 after investigating its association with an increased incidence of both benign and malignant breast tumors in beagle dogs and endometrial cancer in Rhesus monkeys (Drug Evaluations Annual, 1993).

#### Teratogenicity

DMPA has been used for over two decades in countries other than the United States. There have been no reports of teratogenicity (Drug Evaluations Annual, 1993). A study of 987 teenage children exposed to DMPA in utero revealed no impairment of intellectual development (Jaffe et al, 1988). The pregnancy outcomes of women unsuccessfully treated with large doses of DMPA for threatened abortion or recurrent fetal losses showed no significant increase in congenital abnormalities (Yovich et al, 1988). DMPA in large doses has been found to be teratogenic in rabbits, an effect that could be related to the glucocorticoid properties of DMPA (Drug Evaluations Annual, 1993).

#### SUMMARY

Current studies on the teratogenicity of combined birth control pills inadvertently used during pregnancy indicate that prenatal exposure does not increase the risk of congenital anomalies or adverse outcome. Previous reports reflect the use of higher dose preparations of oral contraceptives and claims of teratogenicity, after thorough investigation, have not been substantiated.

Vaginal spermicides have also been studied extensively and are not considered to be teratogenic when used just before or during pregnancy.

Depot preparations have not been studied for their possible teratogenic effect. While the risk is most likely the same as that for any other progestin, further investigation is required before the risk of congenital malformations or of any other adverse outcome can be determined.