

EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF PROGESTERONE

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Progesterone Pharmacokinetics

- Low oral bioavailability
 - Vaginal, nasal, dermal bioavailability
 - Micronized progesterone orally bioavailable
- Short half life (5 min in serum)
- Metabolized in liver
- Activates progesterone receptors

Progesterone Exposure

- Contraception (IUD)
- IVF pregnancy support
- Gynecological disorders
- Hormone replacement therapy
- Supplement/cosmetic
- Livestock growth promoter
- Environmental contaminant

Male Reproductive Effects

- Humans
 - 1958, 8-9 prison volunteers, 50 mg/d i.m., 10 weeks
 - Azoospermia
 - Reduced libido and testicular size
 - Fewer mature sperm in seminiferous tubules
 - 2003, 10 young men, 50 mg/d i.m., 7 days
 - Reduced LH, FSH, testosterone, GNRH response
- Animals
 - Spermatogenesis, monkeys, rabbits, rats
 - Altered sexual development, rats

Female Reproductive Effects

- Humans
 - 1956, 32 women, 300 mg oral
 - Suppressed ovulation
 - 1982, 80 women, progesterone IUD
 - Lower postpartum menstruation
 - Greater milk production, altered composition
- Animals
 - Reduced fertility, several species
 - Altered sexual development
 - Parturition and maternal behavior

Developmental Toxicity-Human

- Malformation
 - Six studies including progesterone- treated women
 - No statistically confirmed associations
- Pregnancy outcome
 - Three prospective random studies
 - No statistically confirmed effects
- Female virilization
 - Confirmed for several progestagens
 - Only case reports for progesterone
- Male hypospadias
 - Progestagen case-control studies
 - Two progesterone studies; no control groups

Developmental Toxicity-Animals

- Pregnancy outcome
 - Rats, intrauterine death and growth retardation
 - Rats, rabbits, altered sex ratio of newborns
 - No increase in malformations
- Altered sexual development
 - Two studies in mice
 - Impaired adult mating in males
 - Enhanced postpartum aggression in females

Developmental Toxicity-Animals

- Female virilization/anogenital distance
 - Nor-testosterone effects confirmed in animals
 - 2/10 progesterone studies found anogenital distance effects
- Male hypospadias/anogenital distance
 - Six studies
 - Increases, decreases, no effects on anogenital distance

Summary of DART Effects Reported for Progesterone

Developmental

- Intrauterine death and reduced fetal weight
- Altered male and female sexual development

Male Reproductive

- Suppressed spermatogenesis
- Reduced fertility, altered sexual development

Female Reproductive

- Suppressed ovulation
- Reduced fertility, altered sexual development