Effects of Drugs on the Male and Female Reproductive Systems

*EDWARD P. FODY, M.D.
and †ERNEST M. WALKER, M.D., Ph.D.

*Laboratory Service and †Clinical Laboratories
John L. McClellan Veterans Administration Medical Center
Little Rock, AR 72205

ABSTRACT

Infertility, permanent or temporary, resulting from drug-induced injury is an important clinical problem. Many common used drugs are potentially toxic to gonads. It is well-known that estrogens are toxic to the male genital system, but androgens may also produce infertility. Anovulation may also be a consequence of exposure to sex steroids. Cimetidine regularly produces hypospermia in men; phenytoin does so occasionally. Marijuana has been shown to be a gonadal toxin, while the effects of lysergic acid diethylamide (LSD) remain controversial. The most significant group of drugs that may injure the gonads is the cancer chemotherapeutic agents, of which the alkylating agents are the worst offenders. Prediction of infertility induced by these agents may be possible based on the duration of therapy and the patient's age and sex.

Introduction

Drug-induced gonadal injury is an important cause of infertility. Such injury is often unpredictable and, perhaps more significantly, may be reversible if the offending agent is discontinued.

Many different types of drugs may be toxic to the gonads. Protein and steroid hormones, analgesics, histamine antagonists, anesthetics, cardioactive drugs, and antimicrobials have all been implicated. Ethanol, heavy metals, and certain solvents are also toxic, but they will not be covered here.

The most clinically significant area of drug-induced gonadal toxicity involves the anti-neoplastic agents. These drugs regularly produce profound gonadal injury. Since increasing numbers of patients, especially young persons with hemic and lymphoid malignancies, are now experiencing prolonged survival after treatment with these agents, it is especially important to appreciate their role as gonadal toxins so that the patient's future reproductive potential may be assessed.

Physiology

In both male and female, the hypothalamus and adeno-hypophysis play major roles in control of gonadal function. Gonadotropin releasing hormone (GNRH - also called LHRH),42 a decapeptide, is secreted from the hypothalamus and travels via the intervening...
microvasculature to the adenohypophysis, where it causes the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These travel via the general circulation to the gonads, where they exert their principal effects.\(^1\) The release of GNRH into the hypophyseal portal veins is episodic, resulting in pulsatile secretion of LH and FSH.

In men, the secretion of GNRH is variable and subject to a number of influences of higher centers upon the hypothalamus. A negative feedback mechanism involving the effects of androgens and possibly other substances inhibits GNRH secretion.

Luteinizing hormone binds to specific membrane receptors on the Leydig cells of the testes. This binding causes the release of testosterone (and also estradiol) from the cell. Testosterone is not water-soluble; it is transported in the plasma primarily bound to albumin and testosterone-binding globulin. Testosterone has an inhibitory effect upon the secretion of GNRH by the hypothalamus and of LH and FSH by the adenohypophysis. This completes the negative feedback loop.

Follicle stimulating hormone, after release from the adenohypophysis, binds to membrane receptors of the Sertoli cells within the seminiferous tubules. This binding, like that of LH, causes an increase in intracellular cyclic AMP. FSH binding is necessary to allow the Sertoli cell to promote spermatogenesis. Androgens are also required. It has been suggested that the Sertoli cell secretes a substance known as inhibin in response to FSH stimulation. It is postulated that inhibin has a negative effect upon GnRH released from the hypothalamus and FSH released from the adenohypophysis.\(^23\)

In the female, the hypothalamic-adenohypophyseal axis operates similarly to the male. Gonadotropin releasing hormone is secreted from the hypothalamus at day 14 of the menstrual cycle. This causes a marked increase in the release of LH and FSH from the adenohypophysis.\(^32\)

Follicle stimulating hormone, as its name implies, is responsible for the growth of the ovarian follicle during the first half of the monthly cycle. Luteinizing hormone acts synergistically with FSH to accelerate follicular growth. Ovulation occurs in response to the midcycle peak of FSH and LH.

Thus FSH and LH cause the ovary to secrete both estrogen and progesterone. Estrogen has a negative feedback effect on the hypothalamus and adenohypophysis, reducing the secretions of GNRH and the gonadotropins, respectively. Progesterones and androgens may also exert a negative feedback effect, but this is less effective than that of estrogen.

A positive feedback effect of estrogen upon the adenohypophysis also exists and is stronger, on a mole per mole basis, for LH than for FSH. Progesterone also exerts a positive feedback.

### Methods of Evaluation of Drug Effects on the Gonads and Fertility

Drug effects on the gonads and fertility may be evaluated by studies of animals or humans.

Animal studies are usually carried out according to the following protocol. The experimental species, often a mouse, rat, or rabbit, is given the drug or chemical of interest over a period of time. Often rather large doses are used. Exposure to fecund controls of the opposite sex may sometimes be allowed to study reproductive ability. After a predetermined interval, sacrifice occurs, and the gonads are examined histologically.

Animal experiments have several obvious advantages. Experimental variables can be controlled, large doses may be administered, and the entire gonad may be examined at any desired interval.
The principle disadvantage is that extrapolation of data from animal to man is often not valid.

In men, assessment of reproductive function is simplified by the fact that germ cells (spermatozoa) may be collected and studied. Thus, seminal fluid analysis provides the basis for fertility studies. If hypospermia or azoospermia is found, additional tests, such as testicular biopsy or hormonal studies, may be performed.

In women, evaluation of reproductive function is more difficult, since germ cells are not readily accessible. A woman is assumed to be infertile if she desires to be pregnant and is not successful after two years. Infertility of her male partner must be excluded, as must mechanical factors, such as obstruction of the fallopian tubes, if gonadal factors are to be implicated. Amenorrhea or decreased levels of gonadotropins or estrogens in the blood or urine strongly suggest that a woman is subfertile. Demonstration that such changes occur after exposure to a drug or chemical and, even more importantly, disappear following withdrawal of the offending agent, often is used to implicate the particular substance as a gonadal toxin.

However, in all human studies, confounding variables exist. For example, a patient with a suspected drug-induced gonadal lesion may be receiving other drugs as well, or may be incidentally exposed to other gonadal toxins such as ethanol, heavy metals, radiation or industrial chemicals. Therefore, implication of a particular agent as a gonadal toxin is almost always based on population studies.

**Sex Steroids**

Estrogens have a pan-toxic effect on the male genitalia. They are inhibitors of gonadotropin release and have a direct toxic effect on the testes. The histology of the testis following estrogen administration is similar to that seen after hypophysectomy.26 Azoospermia, gynecomastia, and loss of libido also occur.13

Progesterone has much less effect on the testis than estrogens, perhaps in part because it can serve as a substrate for testosterone synthesis.30 Its effect on testicular function and histology is highly variable.13

The action of androgens is more subtle. Testosterone is normally produced by the Leydig cells under the influence of LH. Testosterone, accompanied by FSH, is necessary for spermatogenesis to occur in the seminiferous tubules. Supraphysiologic doses of testosterone result in accentuated feedback inhibition upon the hypothalamus and adenohypophysis, suppressing the release of FSH and LH. The loss of LH matters little, since its primary purpose is to stimulate testosterone production by Leydig cells. However, FSH is required for spermatogenesis. Therefore, men receiving large doses of androgens may develop oligospermia.1

In women, estrogens and progesterones are not directly toxic to the ovaries. However, administration of these agents may cause anovulation by suppression of gonadotropin secretion through negative feedback.

Experimental evidence exists that prolactin is essential for normal gonadal function in males. Barthe has demonstrated that treatment with prolactin normalizes reproductive function in a strain of mouse with a congenital deficiency of the hormone.3 Prolactin probably acts by potentiating the effects of LH on Leydig cells,1 which have been shown to have prolactin receptors.2,11

In female rodents, prolactin is known to be important as a leukotrophic agent, but its role in women is unsettled. Prolactin levels vary little with the menstrual cycle.32

Hyperprolactinemia causes impotence
in men and amenorrhea and galactorrhea in women. Although most often hyperprolactinemia results from a pituitary tumor, a number of drug effects exist. A reciprocal relationship exists between prolactin and LH, i.e., drugs that elevate one tend to depress the other. Chlorpromazine, opiates, and opiate antagonists have been reported to cause hyperprolactinemia by interfering with LH secretion.

Gossypol

Gossypol is a yellowish phenolic compound derived from cotton plants. It is a promising male antifertility agent. The mechanism by which gossypol acts has not been fully elucidated. Its effect on the structure of Leydig cells is variable, although it does suppress Leydig cell testosterone synthesis.

Many investigators have studied the effect of gossypol treatment on blood hormone levels (testosterone, FSH, and LH) in experimental animals and man. The results have been inconsistent. Gossypol does regularly suppress sperm counts in men. Azoospermia results if therapy is continued and is reversible if the drug is stopped. Side effects have generally limited the clinical utilization of gossypol.

Cimetidine

Cimetidine is one of the most commonly prescribed drugs in the United States. Although its primary pharmacologic function is as a histamine H2 receptor antagonist, cimetidine also is an androgen antagonist at Leydig cell binding sites.

Hypospermia regularly has been documented in groups of men receiving cimetidine therapy. Testosterone levels were also reduced. Cimetidine apparently blunted the peak response to gonadotropin secretion, since overall basal gonadotropin levels did not decrease. Decreased prostate and seminal vesicle weights have been reported in experimental animals treated with cimetidine.

Anticonvulsants

Chronic phenytoin therapy has been associated with decreased FSH levels and hypospermia. Testosterone levels were unaltered. Animal experiments suggested that the metabolism of sex steroids is increased by phenytoin.

Other anticonvulsants have not been proven to be toxic to the gonads. Several, including phenobarbital, phenytoin, and valproate, have been shown to be teratogenic in human or animal studies.

Drugs of Abuse

Infertility, impotence, and sperm abnormalities have been described in a group of previously fertile men receiving methadone. Heroin users remained fertile.

Two studies have described the gonadal effects of chronic marijuana use in men. Both describe hypospermia and sperm structural abnormalities. These may be reversible if marijuana use is discontinued. There have been no reports of abnormal offspring of male users. A single study of chronic female marijuana smokers demonstrated irregular menstrual cycles, anovulation, and decreased prolactin levels. There have been no long-term studies of fertility rates, libido, or sexual function among chronic marijuana users.

A number of studies have looked at the toxic effects of lysergic acid diethylamide (LSD). These studies have been examined for the effect of LSD on chromosomes, usually in the peripheral blood. Different results have been reported; some studies have described chromosomal gaps and breakage as a result of
LSD exposure, while others have found no such changes. Studies of the teratogenicity of LSD in animals have shown inconsistent results. A study of pregnancies in women who had taken LSD did not reveal an increase in abortions or birth defects compared to controls. 9,10,14,19,20,21,25,28

**Insecticides**

Organophosphate and carbamate insecticides are generally not toxic to the gonads. Chlorinated hydrocarbons, however, have been shown to affect the testes in an adverse manner.

Dibromodichloropropane (DBCP), in one study, was shown to cause azoospermia, with loss of germ cells on testicular biopsies, in men chronically exposed for more than ten years. Men with two to ten years exposure to DBCP showed variable degrees of oligospermia and hypospermatogenesis. Those with less than two years exposure showed no changes.5,35 Polychlorinated biphenyl (PCB) and dimethyl-2-dichlororinyl phosphate (DDVP) have been shown to produce marked testicular toxicity in animals.12,22

The prototype halogenated organic insecticide, DDT, may have an estrogenic effect, but no gonadal toxicity has been reported.

**Cytotoxic Agents**

With the recent advances that have been made in the chemotherapy of cancer, the effects that these compounds may have on the gonads has become of great concern. Many of the malignancies, such as acute lymphoblastic leukemia, Hodgkin’s disease, Wilms’ tumor and neuroblastoma, that are treated with aggressive chemotherapy regimens occur primarily in young people. Prolonged remissions and cures of these conditions are now considered possible, and preservation of reproductive function is obviously of great concern.

Alkylating agents (chlorambucil, cyclophosphamide, nitrogen mustard, etc.) bind to deoxyribonucleic acid (DNA). Rapidly dividing cells, such as germinal epithelium, are especially sensitive to their effects.8,35

Antimetabolites such as methotrexate and 5-fluorouracil appear to have less gonadal toxicity.

The vinca alkaloids, vincristine and vinblastine, and antibiotics such as bleomycin and adriamycin have little direct gonadal toxicity.

One of the problems in assessing the effects of anticancer drugs in humans is that the drugs are almost always used in combination. This makes assessment of the toxicity of a single agent quite difficult.

There is little doubt that significant testicular injury can occur in males being treated with alkylating agents. It appears that the prepubertal testis is more resistant to such damage than the postpubertal one.

Ten of 63 boys treated with cyclophosphamide developed gonadal toxicity. By contrast, 10 of 15 postpubertal boys treated with the same drug showed evidence of gonadal injury.8

Sherins et al demonstrated that mechlorethamine hydrochloride (MOPP) therapy for Hodgkin’s disease was significantly more toxic to the prepubertal than the postpubertal testis.34

Maguire et al performed testicular

### TABLE 1

<table>
<thead>
<tr>
<th>Duration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 30 days</td>
<td>normal testes</td>
</tr>
<tr>
<td>Five days to 40 months</td>
<td>maturation arrest</td>
</tr>
<tr>
<td>Seventeen days to 84 months</td>
<td>hypospermatogenesis</td>
</tr>
<tr>
<td>Three to 63 months</td>
<td>Sertoli cells only</td>
</tr>
</tbody>
</table>

biopsies on 29 adult males with acute leukemia who received cytotoxic chemotherapy. The results are summarized in table I.27

Hensle et al, in a study of testicular biopsies of young men receiving cytotoxic therapy for acute lymphoblastic leukemia, found that all patients had some histologic abnormality. The results are shown in table II.17

Recovery of reproductive function in men is highly variable and depends in part on duration of therapy. Maguire et al found that irreversible injury occurred after 3 to 84 months of therapy for acute leukemia. Azoospermia is a bad prognostic sign as it is usually permanent.

The assessment of infertility in women uses different systematic criteria and methods. Failure to re-establish a normal menstrual cycle is almost always indicative of loss of reproductive potential. Direct assessment of germ cells, however, as is done with sperm analysis in men, is usually not possible.

In men, the critical period for increased gonadal sensitivity appears to be puberty. After this time, age is not a determinant of toxicity. Older women, however, have been shown clearly to be at increased risk for ovarian toxicity as compared to younger counterparts. The critical age is not known; however, 85 percent of women over 25 treated with MOPP for Hodgkin’s disease developed permanent ovarian failure.8 The alkylating agents appear to be the worst offenders, and the dose of cyclophosphamide needed to produce irreversible ovarian failure ranges from 12 to 27 g in women less than 29 years to three g or less in one third of women over 30. Toxicity appears to be enhanced when multiple chemotherapeutic agents are used.37,39

The current state of knowledge concerning the effects of cytotoxic chemotherapy in men and women is summarized in table III.

Conclusion

Toxicity to the gonads is a common effect of certain commonly used drugs. For most of these, the toxicity is reversible with cessation of therapy. The most toxic drugs are those used in cancer chemotherapy, especially the alkylating agents. Injury produced by these drugs is often irreversible.

References


### Table II

**Effects of Cytotoxic Chemotherapy on Males (Testes)**

1. Interstitial fibrosis (70 percent)
2. BM thickening (50 percent)
3. Hypospermatogenesis (80 percent)

No relationship to age.

Almost all patients treated for acute lymphoblastic leukemia have abnormal biopsies following therapy.

### Table III

**Conclusion Regarding Gonadotoxicity of Cytotoxic Agents**

1. Alkylating agents are principal offenders.
2. Drugs act synergistically.
3. Other agents (e.g., vincristine, bleomycin) may be cytotoxic for gonads.
4. Combination chemotherapy makes it difficult to implicate single agents.
5. Likelihood of permanent gonadal injury is related to dose and duration of therapy.
6. Whether or not the prepubertal gonad is less sensitive to cytotoxicity than the postpubertal remains controversial.
7. In adult males, age is unrelated to toxicity.
8. In adult females, age is an important determinant of toxicity.
9. In both males and females, germinal epithelium is the principle target of cytotoxic drugs. Leydig cell damage may also be important.
10. Treatment with estrogen and progesterone may reduce toxicity in females.
EFFECTS OF DRUGS ON REPRODUCTIVE SYSTEMS


