Chapter 4

Factors contributing to Infertility

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Chapter 4

Factors Contributing to Infertility

Current knowledge of the factors that contribute to infertility is limited. Classification of infertility due to any one condition is misleading, as contributing factors are often multiple and the boundaries between them are not clear. Those covered in this chapter do not always fit neatly into the categories in which they are discussed; for example, there may be a genetic component to endometriosis, yet the two are presented as separate factors contributing to infertility.

Another problem arises when examining reasons for infertility. Should the underlying condition, such as a sexually transmitted disease (STD), or the mechanism by which it leads to infertility, such as tubal damage, be called the contributing factor? For prevention, the underlying condition is the important factor, as the disease can potentially be avoided. For treatment, however, the mechanism is often more important; whatever damage it has caused must be repaired or circumvented for pregnancy to occur.

Sometimes the mechanism by which a given condition results in infertility is not clear; sometimes it is not clear what condition underlies a functional impairment. This chapter presents the current knowledge of factors contributing to infertility, whether they be an underlying condition, its mechanism of action, or both.

INFECTION

Sexually Transmitted Diseases

Sexually transmitted diseases are the third most common infectious diseases in the United States, after the common cold and influenza. They account for an estimated 20 percent of infertility in selected populations (29). Furthermore, they are usually difficult to diagnose, especially in women. STDS are most damaging to women and children (excluding acquired immunodeficiency syndrome, which is equally damaging to anyone who contracts it, regardless of age or sex), although they affect males as well. The three STDS that most affect fertility are gonorrhea, chlamydial infection, and mycoplasmal infection.

Gonorrhea is an infection caused by the bacteria ***Neisseria gonorrhoeae.*** More than 760)000 cases were reported in 1987 (33). In women, if the infection is not treated it can spread to the uterus and fallopian tubes, causing pelvic inflammatory disease (PID), which can lead to infertility. In men, bacteria can directly affect semen quality by inducing phagocytosis or stimulating production of antibodies (113). Also, untreated genital infection can cause infertility in men by creating inflammation or blockage in the upper reproductive tract. For example, untreated infection can spread to the epididymis, causing epididymitis. Epididymitis can impair fertility during the infection as well as cause scarring that can partially or completely block sperm transport. Reports from Nigeria and from the preantibiotic era indicate that various genital tract infection syndromes are associated with male infertility (2)8,126). However, followup fertility studies of men with documented inflammation of the urethra, epididymis, and/or testis or with accessory gland infection are not available, so knowledge of the actual effect of STDS on male fertility is scant.

Infection caused by ***Chlamuydia trachomatis*** is the most common STD in the United States today, infecting approximately 4 million people in 1985 (30,174). In women, chlamydial infection accounts for one-quarter to one-half of the PID cases seen each year (30). In men, chlamydial infections cause approximately half the reported cases of nongonococcal urethritis and also half the estimated Soo,ooo cases of acute epididymitis seen annually (3o). In both men and women, chlamydial infection is more difficult to detect than gonococcal infection, and thus may go untreated, resulting in more harm (149).

Considerable controversy surrounds another group of sexually transmitted organisms commonly found in the male and female reproduc-

tive tracts—mycoplasmas (24,76,82,149). Because mycoplasmal infections often coincide with other infections, it is difficult to determine whether the mycoplasmas themselves actually cause tissue damage (149).

Among sexually active women, a major cause of impaired fertility is damage to the fallopian tubes, and possibly the ovaries, caused by pelvic inflammatory disease (28). If untreated, the bacteria that cause gonorrhea, chlamydial infection, and other infections may ascend from the lower genital tract through the endometrium (causing endometritis) to the fallopian tubes (salpingitis), and possibly to the ovaries (oophoritis) and pelvic peritoneum (peritonitis). Reduced fertility due to PID probably stems primarily from physical damage to the fallopian tubes (28,49,175,185): Peritubal (around the tube) adhesions decrease tubal mobility, which is essential for passage of the ovulated egg. Blocked or deformed tubes can severely obstruct the movement of both ova and sperm that is necessary for fertilization. Bacterial products or byproducts of inflammation can also cause impaired function of the oviduct.

The majority of bacterial-based PID results from one or more sexually transmitted diseases; N. ***gonorrhoeae*** and C. ***trachomatis*** together account for more than two-thirds of the 1 million cases of PID seen each year (3). In 1982 approximately 14 percent of women between ages 15 and 44 reported being treated at least once for PID during their lifetime (5). According to two estimates, a woman with a gonococcal or chlamydial infection has a 10-percent risk of developing PID, and from 10 to 20 percent of the approximately 1 million women with PID each year will become infertile (140,174). The likelihood of infertility increases dramatically with increasing episodes of PID, from an estimated 11.4 percent after one episode to between 54.3 and 75 percent after three episodes (183,185). The likelihood of infertility also increases with the severity of the PID (17,185).

Although more common in developing countries than industrial ones, other genital tract infections can lead to PID. Infections after birth, cesarean sections, abortions, and many other obstetric or gynecologic procedures can cause tubal damage. Whether these infections actually lead to infertility is subject to some controversy (85,163).

Damaged or blocked tubes resulting from PID may lead to another complication, ectopic pregnancy. An ectopic pregnancy is one that occurs outside of the uterus, usually in a fallopian tube, because the fertilized egg cannot travel to the uterus through the damaged or blocked tube. PID is not the only cause of ectopic pregnancy; congenital tubal malformation and tubal ligation are other possible causes. The magnitude of PID's influence on the increasing incidence of ectopic pregnancy is controversial (7,36). From 1970 through 1983, the number of ectopic pregnancies in the United States quadrupled (31), possibly as a consequence of the increased occurrence of PID (102,176). Some estimates indicate that 30 to 60 percent of ectopic pregnancies are associated with evidence of PID (176,178). The frequency of tubal pregnancy increases sixfold to tenfold following a documented episode of PID (178,185). The likelihood of infertility in turn increases after an ectopic pregnancy (119).

Douching may be related to both ectopic pregnancy and PID. One case-control study suggested that women who douche weekly have a significantly higher risk of ectopic pregnancy than women who never douche (37). It has also been proposed that douching may be a risk factor for PID (121).

Other Infectious Diseases

Past studies suggest that 30 percent of men with bilateral postpubertal mumps orchitis develop azoospermia (25). Approximately 2,982 men in the United States contracted mumps in 1985, with 725 of them being postpubertal cases (32). Mumps does not appear to be a major contributor to male infertility here, but rates of the disease have increased in recent years (27) and the number of cases doubled between 1986 and 1987 (33).

HORMONAL DISTURBANCE

Polycystic Ovarian Disease

Researchers disagree on the cause of the malfunction in the hormonal system that leads to poly - cystic ovarian disease, although many theories implicating the hypothalamus, the pituitary, the ovaries, and the adrenals have been suggested (87). However, the result of the disease-varies clogged with cysts and few or no ovulations each year-clearly undermines fertility (16,61).

Cervical Factors

The complex change of the cervical mucus of the female at the time of ovulation is under hormonal control. The changes assist the survival and transport of sperm. If the proper hormonal events do not occur, fertilization and pregnancy become much less likely, especially in the presence of other causes of impaired fertility such as a low sperm count in the male (53). Less commonly, insufficient mucus production due to physical destruction of endocervical tissue during surgery is also associated with evidence of decreased sperm transport (112). other possible causes of poor cervical mucus are secretory antibodies in the mucus, infection (cervicitis), and exposure to diethylstilbestrol (DES) (l). The effect of the change in the cervical mucus on fertility is highly controversial (71), and it is not considered a frequent factor leading to infertility.

Hyperprolactinemia: Physiologic and Pathogenic

In all mammals, including humans, lactation is a key link in the reproductive cycle (133). Ovulatory suppression prevails during nursing and serves as a primary means of birth spacing for humans (130,150). Continued suckling keeps levels of the hormone prolactin elevated to some degree (83), and elevated levels of prolactin suppress ovulation by affecting both hypothalamic-pituitary and ovarian processes (133). Lactation is not associated with any long-term fertility impairment.

However, hyperprolactinemia-the overproduction of the hormone prolactin—is identified as a factor contributing to infertility (115). It is associated with impaired fertility in the presence and absence of excessive milk production. Consistently hyperprolactinemic women are almost always infertile (115).

Hyperprolactinemia can also be associated with infertility in males, although it is rare in comparison with female cases. Hyperprolactinemia in men is associated with decreased levels of testosterone and markedly decreased spermatogenesis (13), but it is only significant when prolactin is markedly elevated and related to a tumor (100).

Causes of hyperprolactinemia are diverse and remain poorly understood. At least half the patients evaluated show evidence of pituitary tumor. Various medications, hypothyroidism, stress, exercise, excessive breast stimulation during lovemaking, and other causes of chest wall stimulation have been implicated in hyperprolactinemia.

Exercise

Considerable accumulated evidence indicates that regular, strenuous exercise alters menstrual function and temporarily impairs fertility in women. In males, gonadal steroid production may also be altered by rigorous training (104,186), but exercise does not appear to have an effect on male fertility. The frequency of amenorrhea (absence of menstruation) or oligomenorrhea (infrequent menstruation) among women participating in a variety of activities varies from 2 to 51 percent as opposed to 2 to 5 percent of more sedentary women (26). In a prospective study of women with previously normal menstrual cycles, fully 87 percent developed abnormality of these cycles when engaged in a strenuous exercise program (21).

Hormonal abnormalities described include disordered gonadotropin release and levels, decreased estrogen levels, corpus luteum inadequacies, and complete anovulation (48,131)137,145, 146). Abnormalities appear greatest when exercise is most intense or when training becomes more rigorous (103, I31), although a recent study did not find training intensity of olympic-caliber

marathon runners to be a key factor in loss of menses (63). Researchers suggest that even moderate exercise by recreational women runners (average 12.5 miles per week) reduces overall progesterone levels but does not delay luteal progesterone rises, which are suggestive of ovulation (48).

Mechanisms of menstrual irregularities associated with strenuous exercise regimens are not completely understood. It has been suggested that exercise results in changes in prolactins and endorphins, possibly affecting fertility (47)103). At this time, little information exists on the relationship between exercise-associated menstrual alterations and long-term infertility.

Poor Nutrition

In women, it is generally accepted that sexual maturation and continuation of cyclic ovulation depends on achieving and maintaining an adequate amount of body fat as a proportion of total body mass (59,60,166). Fatty tissue appears to directly influence reproductive maturation and function in both sexes by metabolizing both androgens and estrogens that, in turn, influence the central nervous system, hypothalamus, pituitary, and reproductive tract organs in complex ways (59,166). Too little and (much less commonly) too much adipose tissue have each been associated with impaired fertility.

According to estimates of one researcher, completion of pregnancy and lactation requires approximately 50,000 calories–roughly the amount of energy most normal women (26 to 28 percent body fat) possess in body fat (59). Because fat is the most labile and sustainable source of body energy, possession of adequate fat stores may serve as a physiologic precondition for conception and pregnancy. obesity is also associated with anovulation, endometrial hyperplasia, and subsequent hemorrhage (35).

Stress

Interactions with surroundings can cause bodily changes that impair fertility, yet the relationship between stress (stimuli or conditions that perturb homeostasis and require adaptation) and impaired fertility is extraordinarily difficult to prove in humans.

Input from the limbic system and other brain centers affects the hypothalamus, the pituitary gland, and the neurohormonal axis that orchestrates both the physical and behavioral aspects of reproduction. This complicated system provides ample opportunity for stress to interfere with the homeostasis of the individual. In recent decades, 40 to 50 percent of infertility was attributed to stress or emotional factors (143). Recent progress in neuroendocrinology and reproductive medicine has reduced this estimate to 5 percent or less (143). However, some would argue that a certain percentage of idiopathic infertility may be stress-related.

Critical reviews of the large volume of information regarding stress and fertility in different lifestyles are available (38,39,1 11,189,190). In humans, evidence suggests that mild to severe emotional stress alters sexual behavior, interferes with ovulation, depresses testosterone, and perhaps interferes with spermatogenesis (111,143). In women, anorexia nervosa can cause amenorrhea, apparently independently of weight loss (69). Anecdotal accounts indicate that anxiety can play a role in infertility; for example, 10 percent of patients become pregnant after having made an appointment for or having had their first professional visit for infertility (46).

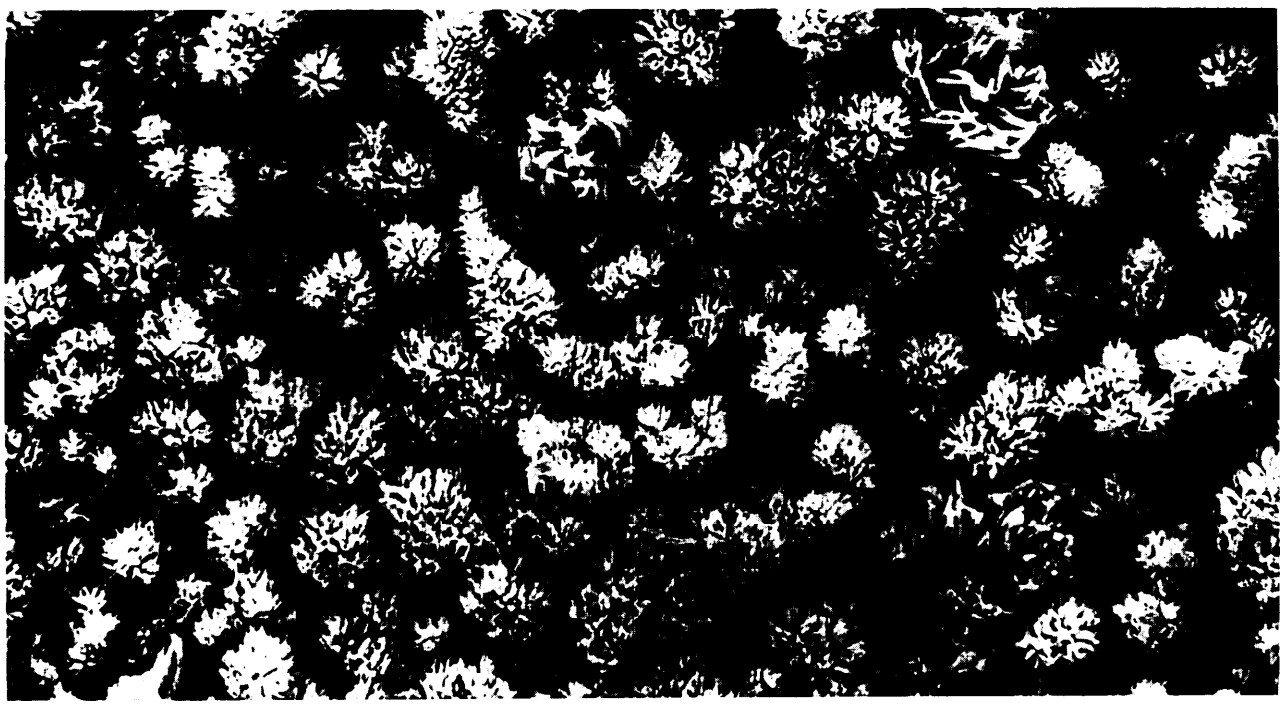
Neurotransmitters play central roles in adapting to stress. Furthermore, neurotransmitter roles are not limited to effects on the central, peripheral, or autonomic nervous system functions, but are also directly involved in reproductive tract physiology (65). Understanding of increasingly unified and shared concepts of organ system physiology is growing rapidly. Yet, despite this information, great difficulties persist in accurately attributing individual cases of human infertility to stress, whether primarily physical or psychological.

ENDOMETRIOSIS

Endometriosis is characterized by the presence of cells of the uterine lining outside of the uterus. The ovaries, fallopian tubes, pelvic peritoneum, and visceral peritoneum are the most common locations of endometrial implants, but other sites, such as pleura, lung, and lymph nodes, have also been reported (54). Endometriosis afflicts approximately 7 to 17 percent (studies range from 4 to 50 percent) of menstruating women (120).

When symptomatic, the process is classically characterized by painful menstruation, painful ovulation, painful intercourse, and infertility. Expression of each symptom varies and correlates poorly with the physical extent of endometriosis. One estimate states that 30 to 40 percent of women with endometriosis are subfecund (93). Evidence of endometriosis is frequently found in women with otherwise unexplained impaired fertility. There is some indication that pregnancy might ameliorate the effects of endometriosis; however, this claim is controversial (23).

Suggestions on how endometriosis might impair fertility are multiple and not mutually exclusive; they include interference with ovulation, ovum transport, or implantation, or induction of early spontaneous abortion (66,8 I). Clinical and laboratory animal evidence supports each of these mechanisms. These processes may be mediated in turn by physical scarring; by increased destruction of male or female gametes; by growing numbers of activated peritoneal or tubal macrophages (cells that ingest other cells); by altered tubal, ovulatory, or corpus Iuteum function because of altered prostaglandin secretion; or by autoimmune phenomena (66,67). Overall, the precise mechanisms contributing to infertility in conjunction with endometriosis when organic and structural abnormalities are absent remain poorly understood.



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The development of endometriosis is also not completely understood. With rare exception, it is only ovulating and menstruating women who develop the condition. Some women, however, may beat greater risk. Genetic predisposition for initiation and propagation of endometriosis has been documented (132,152).

In general, theories on the development of endometriosis suggest that viable endometrial cells or tissue are transported directly and grow in a different location, that endometrial tissue arises in situ from local tissues, or that a combination of these processes holds. The first explanation has the most support. Many observers have noted "bits" of endometriosis within pelvic or other lymphatic areas "downstream" from the uterus. Vascular spread, primarily to the lung, is also possible and could account for rare cases where endometriosis is noted in diverse locations of the body.

Pelvic endometriosis is common and has been linked to retrograde menstruation (menstrual flow backwards through the uterine tubes) (138). Past or anecdotal evidence has suggested that intra-abdominal spillage of menstrual fluid during menses occurs in roughly one-third of ovulating women. Blood has been detected in peritoneal fluid of 90 percent of 52 women with unobstructed fallopian tubes undergoing laparoscopy in the perimenstrual period (67). A larger study in which elective laparoscopic sterilization was performed during menstruation showed that retrograde menstruation occurs in up to 78 percent of ovulating women (57 of 75 women, ages 26 to 48) (101).

VARICOCELE

A controversial contributor to male infertility is the testicular varicocele, or varicose vein of the testis. A varicocele is an abnormal dilation and twisting of the veins carrying blood from the testes back to the heart. Varicoceles most often occur in the left testis, most likely due to a difference in anatomy between the veins leaving the two testes (16).

Exactly how varicoceles lead to infertility is unclear; some suggestions are based on the possibility that the pooled blood overheats the testes, either killing the sperm or speeding up the sperm production process too much.

There is considerable controversy over the contribution of varicoceles to infertility. The estimated incidence of clinically evident varicoceles in the general male population varies from 8 to 23 percent. A recent study reported that a majority of a group of fertile males had either palpable or subclinical varicoceles (97). Whatever the incidence or contributory role, many experts believe that varicocele correction leads to improved fertility (97).

EXTERNAL FACTORS

Contraception

Contraception—intentional, temporary infertility—is sometimes linked to unintentional, long-term infertility. Contraceptives are extensively used, especially by young individuals whose reproductive years generally lie ahead of them. For this reason, the association of contraceptive use and fertility has been explored in detail.

overall, types of contraception used vary with age, marital status, reproductive history, and race (9). In 1982, surgical sterilization was the most widely used method of contraception (18 percent). Next in popularity were birth control pills (16 percent), condoms (7 percent), diaphragms (5 percent), and intrauterine devices (IUDS) (4 percent) (9). About 2 percent of women used some form of periodic abstinence. Withdrawal, douche, foam, and suppositories were used by similarly small percentages of women.

Sterilization

Surgical sterilization is the most common form of birth control used in older age groups (9). In 1982, approximately 39 percent of currently married couples of reproductive age had been surgically sterilized for contraceptive reasons (116). Some of these couples may desire a reversal of the procedure, with a smaller percent actually obtaining the reversal (20).

For reversal of contraceptive sterilization in women, several factors are important in determining whether fertility can be restored: the surgical method initially used, tubal site, length of tube remaining, and surgical skill in restoration (180). Factors that are most important in male sterilization reversal are time elapsed since sterilization, surgical technique originally used (180), age at reversal (135), and skill of the surgeon.

Oral Contraceptives

Two studies of women with and without children who discontinued oral contraceptives in order to become pregnant demonstrate similar findings from vastly different parts of the world (124,170). Both studies found a small but significant initial impairment of fertility in women who discontinued pill use compared with women who discontinued other contraceptive methods. The magnitude of this relative decrease diminished rapidly with time and was probably due to transient pill-associated amenorrhea and anovulation. other data from smaller studies confirm these findings (57). These modest fertility differentials primarily concern older women or couples with previously impaired fertility (155).

Estimates of the incidence of postpill amenorrhea range from 0.2 to 2.7 percent. Disagreement persists as to whether this syndrome is specific to pill use, is coincidental, or is related to the use of birth control pills to suppress anovulatory menstrual bleeding originally. Postpill amenorrhea in which no concomitant factors (e.g., weight loss, prior oligomenorrhea, hyperprolactinemia, or polycystic ovarian disease) (70,73) are found diminishes with time and responds quickly to ovulation induction (84).

Progesterone-only "minipills)" which act primarily by inducing local genital tract alterations rather than inhibiting ovulation, are even less likely to impair fertility than combination pills (98). Data from several small studies suggest there is little or no ovulatory suppression after discontinuing minipills (57).

There is some evidence that oral contraceptive use may actually protect against tubal infertility (117). However, a recent study indicated no change in a woman's risk of tubal infertility with past use of oral contraceptives overall (41). The same study indicated that the association between tubal infertility and oral contraceptive use may vary with the amount of estrogen and type of progestin in the oral contraceptive used, with users of estrogen-dominant pills slightly more at risk for tubal infertility. Finally, oral contraceptive use may provide some protection against uterine and ovarian cancer and may decrease the frequency of ectopic pregnancy (86).

Injectable Contraceptives

Much concern exists about the delay in the return of fertility following the use of various injectable hormonal contraceptives (56). However, no evidence suggests that injectable permanently impair fertility. On average, the delay in return to fertility following discontinuation of use results from the time required to clear the drug from the body (47). One such hormonal contraceptive, Depo Provera, results in a median delay in conception of 5.5 to 7 months after the term of complete contraceptive protection ends (56). This is 1 to 4 months longer than the median conception time following intrauterine device discontinuation (56,57,125). A number of other injectable contraceptive formulations are less well studied but none of them appear to decrease fertility after the medication is metabolized (56)57).

Intrauterine Devices

Based on recent, well-controlled studies, IUD use is thought to increase a woman's risk for tubal infertility (42)44). Women who did not have any prior births and who had ever used an IUD were about twice as likely to suffer from tubal infertility subsequently as women who had never used

an IUD. However, the risk varied by type of IUD used, with the greatest risk being evident for the Dalkon shield and the lowest risk apparent for copper-containing devices. In one study (42), IUD users who reported having only one sexual partner were not found to be at increased risk.

Earlier studies that followed up large populations of women who stopped using an IUD and measured the length of time until conception found that cumulative conception rates for IUD users and nonusers were similar (161,169,172). In most of these studies, however, the women were married and had had a prior pregnancy. Also, many of the studies included only women who had used an IUD successfully; women who had experienced medical complications associated with IUD use were excluded from the analyses. Both these factors would have the effect of masking an increased risk for infertility (117).

Some IUDS have been associated with an increased risk for PID (92,184) and this is thought to be the reason for their association with tubal infertility. IUDS were largely withdrawn from the market in the 1980s because of their potential association with tubal infection. only one, the Progestasert" system (ALZA Corp., Palo Alto, CA) is available in the United States. A copper-containing IUD developed by researchers at the Population Council and approved by the U.S. Food and Drug Administration in 1984 is slated for marketing by GynoPharma Inc. of Somerville, NJ, in 1988 (154). This IUD, the T-380A, has been used in other countries since 1982.

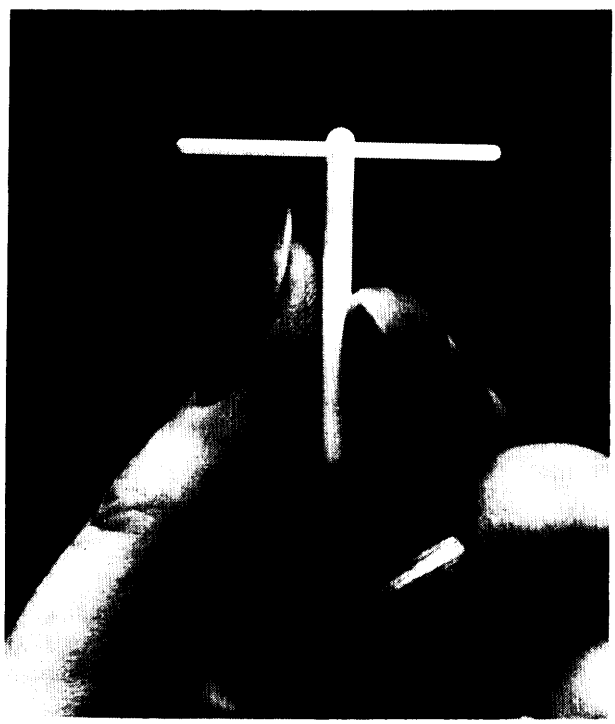


Photo credit: ALZA Corp., Palo Alto, CA

Progestasert" intrauterine progesterone contraceptive system.

Other Contraceptives

Use of most other effective forms of contraception is not linked to any specific fertility impairment beyond that associated with aging. However, a recent study found that a greater proportion of infertile women with abnormalities of the cervical mucus had previously used a diaphragm than had fertile women (43). Effects on subsequent fertility caused by use of newer agents, such as the progesterone antagonist RU486, remain unstudied (40). Barrier methods have been shown to offer protection against STDS (41).

Abortion

Approximately 90 million births occur worldwide each year (40) and some 33 million to 60 million abortions (both legal and illegal) (64). In the United States, approximately 3.7 million births and 1.6 million legal abortions are recorded annually (77).

The impact of induced abortion on subsequent fertility has been extensively reviewed (45,79,80). With the exception of an early study from Greece (162), where abortion is illegal and therefore is primarily carried out in unsanitary conditions, these studies indicate there is no increased risk for infertility following legal induced abortion. Indeed, two studies report significantly shortened interpregnancy intervals following abortion (78,158). These findings are most probably explained, however, by enhanced fertility in women with unplanned pregnancies rather than any enhanced fertility due to the abortion itself.

Environment and Drugs

Currently no reliable estimates can be made of reproductive risk from environmental factors. Until recently, little attention was paid to environmental and drug-induced infertility and subfecundity. However, four health hazards–ionizing radiation, lead, ethylene oxide, and dibromochloropropane—are regulated in part because of their effects on the reproductive system. Possible environmental hazards include chemical agents; physical agents such as altitude, temperature, and radiation; and personal habits such as smoking, alcohol consumption, use of drugs (both therapeutic and nontherapeutic), and eating patterns (164).

Industrial exposures that may interfere with fertility are presented in table 4-1. Because possibly toxic agents vary in importance and in how much is known about them, only a few substances are selectively discussed here. Many more agents are known to be associated with poor reproductive outcomes (e.g., teratogenicity, growth retardation) than with infertility (12), but this may be because the connection between toxic exposures and infertility has not been studied as carefully as other reproductive outcomes (117).

Glycol ethers, a chemical species found in a wide variety of products, including paints, stains, varnishes, and solvents, are the best studied of reproductive toxicants (72). This important and widely used class of solvents is embryotoxic and teratogenic (causing defects in formation) in male and female animals, and it produces testicular atrophy and infertility in male animals; studies have confirmed that glycol ethers can cause oligosper - mia, azoospermia, and decreased sperm count per ejaculate in human males as well (165,181).

In utero exposure to DES is associated with abnormal reproductive development in males and females when they mature. Development of vagi-

Table 4-1 .—Industrial Exposures That May Affect Reproductive Health

Metals	Chemicals	Undefined industrial exposures
Antimony	Agricultural chemicals:	Agricultural work
Arsenic	Carbaryl	Laboratory work
Boron	Dibromochlorpropane (DBCP)	Oil, chemical, and atomic work
Cadmium	DDT	Pulp and paper work
Chromium compounds	Kepone (Chlordecone)	Textile work
Lead	2,4,5-T Dioxin (TCDD) and Agent Orange	
Manganese	2,4-D	
Mercury	Anesthetic agents	
	Epichlorohydrin	
	Ethylene dibromide (EDB)	
	Ethylene oxide (EtO)	
	Formaldehyde	
	Organic solvents:	
	Carbon disulfide	
	Dinitrotoluene and toluene diamine	
	Styrene	
	Benzene	
	Carbon tetrachloride	
	Trichiorethylene	
	Polyhalogenated biphenyls:	
	Polybrominated biphenyls (PBB)	
	Polychlorinated biphenyls (PCB)	
	Chemicals in rubber manufacturing:	
	1,3-Butadiene	
	Chloroprene	
	Ethylene thiourea	
	Vinyl chloride	
	Hormones	

SOURCE: U.S. Congress, Office of Technology Assessment, *Reproductive Health Hazards in the Workplace*, **OTA-BA-266 (Washington, DC: U.S. Government Printing Office, 1985); D.D Baird and A.J. Wilcox, "Effects of Occupational Exposures on the Fertility of Couples, "** *Occupational Medicine: State of the Art Reviews* 1:361-374, *1986*

nal cancer in daughters of DES users, although rare, is significantly more common than among nonexposed women, and exposed women are known to have a higher proportion of reproductive tract anomalies resulting in infertility (117). Reports suggest that males exposed to DES commonly have abnormal spermatozoa and potentially diminished fertility (156).

The effects of physical agents on fertility are outlined in table 4-2.

Certain medications and substances used for self-intoxication can also interfere with fertility. Most prominent among these agents are cigarette smoking (discussed in next section) and chronic and acute alcohol consumption. Chronic alcohol abuse is consistently associated with abnormalities of spermatogenesis and presumed subfecun - dity in males. Although alcohol consumption impairs fertility in laboratory animals through a variety of mechanisms, human infertility from "moderate" nonhabitual alcohol consumption is not apparent (123).

Table 4-2.—Summary of Effects of Physical Forces on Fertility

Condition	Comment
Atmospheric pressure	
Low (high altitude)	Lower human birth rate
High (scuba diving)	No data
Electric and magnetic fields (many sources)	Possible increase in congenital malformations
Gravity and acceleration	No adverse effects noted
Hyperthermia	Reversible damage to spermatogenesis
Hypothermia	No adverse effects noted
Ionizing radiation	Dose-dependent effects at high but nonlethal doses; reduce to "as low as reasonably achievable"
Noise	Conflicting results
Optical radiation (UV, visible, infrared, laser)	No adverse effect noted Subjective complaints with video displays
Radio-microwave radiation	No adverse effects in absence of measurable heating
Ultrasound	Not adequately studied
Vibration	Little data

SOURCE: American Medical Association Council on Scientific Affairs, "Effects of Physical Forces on the Reproductive Cycle," *Journal of the American Medical Association* 251:247-250, 19S4; H.B. Holmes, *Risks of Infertility Diagnosis and Treatment*, prepared for the Office of Technology Assessment, U.S. Congress, Washington, DC, August 19S7; S. Nordstrom, E. Birke, and L. Gustavsson, "Reproductive Hazards Among Workers at High Voltage Substations," *Bioelectromagnetics* 4:91-101, 19s3.

Marijuana use has also been implicated in reproductive impairment, although studies present conflicting results. Decreased hormone levels in men and women, ovulatory disorders in women, and decreased sperm counts in men have been associated with infertility in some studies. The development of tolerance to the drug may account for some of the conflicting data (153).

Smoking

Experimental evidence in animals indicates that cigarette smoking has adverse effects on reproduction. In humans, evidence suggests that smoking has a deleterious effect on menstrual cyclicity, oocyte production, and tubal function (136).

Variously designed epidemiological studies from different countries confirm an association between smoking and infertility and menstrual abnormalities in women (11,74,123,160). Other studies have noted the adverse effects of smoking on tubal function (157). A recent study noted significant association between cigarette smoking and primary infertility resulting from cervical factors and tubal disease (128). No association between smoking and ovulatory factors was found in this study. Finally, smoking can shorten the reproductive lifespan by decreasing the age of menopause in a dose-related way (89).

In males, some studies have found that smoking or nicotine consumption is associated with decreased sperm motility and count, altered sperm morphology, and altered hormonal levels (179, 182). Experimental findings suggest that these alterations are caused by changes in hypothalamic pituitary axis function and possibly by impaired motility of cilia in the genital tract (110). One study found that smokers with testicular varicoceles had a tenfold increase in incidence of oligospermia over nonsmokers with varicoceles, and a fivefold increase in incidence of oligospermia over smokers without varicoceles (94). Other studies have found no significant effect of cigarette smoke on sperm density, motility, or morphology (171).

Congress has recognized the harmful effects of smoking on the reproductive system. In 1985, new warning statements were required (Public Law 98-474) on the packages and advertising of all cigarette brands sold in the United States (177). Two of these statements call specific attention to the reproductive hazards caused by smoking:

SURGEON GENERAL'S WARNING: Smoking by Pregnant Women May Result in Fetal Injury, Premature Birth, and Low Birth Weight.
SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, and May Complicate Pregnancy.

Spinal Cord Injury

The outlook for fertility in paraplegic men after spinal cord injury is poor; the outlook for paraplegic women is often better. Paralyzed men often (but not always) suffer from impotence because of neurological deficits in the spinal cord. Problems resulting from spinal cord injury include inability to achieve an adequate erection, inability to ejaculate normally, infection resulting from prolonged or intermittent catheterization, and decreased sperm quality. This topic is discussed in detail in chapter 10.

GENETIC AND CHROMOSOMAL ABNORMALITIES

Genetic and chromosomal abnormalities can affect fertility in several ways. Most significantly, abnormalities in human embryos can lead to early fetal loss, and genetic diseases (e.g., cystic fibrosis) that are not serious enough to cause embryonic death can impair reproductive function in adults. Many of the factors contributing to infertility mentioned elsewhere in this chapter may have genetic components,

Substantial pregnancy loss occurs between implantation and the time pregnancy is usually recognized (173), some portion of which may be caused by chromosomal abnormalities of early embryos. Abnormalities can affect the chromosomal health of a human embryo in five ways:

- The sperm can have a chromosomal abnormality. One study found that approximately 9 percent of human sperm are abnormal (107).
- The oocyte can be abnormal. A study of infertile women undergoing clomiphene stimulation found that nearly 50 percent of the oocytes recovered were abnormal (188). Chromosomal abnormalities of human oocytes are known to increase as a woman ages. (The women described in this study maybe representative of all women of their age group (mean age 30.8), but they are probably not representative of women of all ages.)
- The early embryo can fail to divide (35).
- The early embryo can drop or fail to incorporate one or more chromosomes, resulting in an incomplete set of chromosomes (141).
- There can be double sperm penetration, leading to triploidy (141).

Chromosomal abnormalities of human embryos are thus a sum of these problems. Limited data suggest that from 23 to 50 percent of human embryos may have chromosomal abnormalities (4,129,167).

Chromosomal abnormalities that do not cause early fetal loss can also impair the reproductive functioning of an adult. The spectrum of chromosomal abnormalities associated with infertility is more complex than originally supposed (151). Mutations or deletions of sex-determining chromosomal regions have been linked with infertility (95). Women with XO, XY, and other abnormalities are subfecund or sterile. A region of the long arm of the X chromosome appears essential for normal ovarian function; deletion of this region is associated with premature ovarian failure (51,96). Furthermore, the genetic makeup of an individual may predispose that person toward certain diseases, such as cancer or endometriosis.

A number of Mendelian traits, most of which are extremely rare, are associated with infertility (151). In Caucasians, the most common of these is cystic fibrosis, with an incidence of 1 in 1,600 to 1 in 2,000 individuals (142). With contemporary multisystem supportive care, half of all cystic fibrosis patients survive to age 19. This trend is expected to continue, allowing many more patients

to survive into reproductive age groups. Puberty is commonly delayed in cystic fibrosis patients and the degree of delay correlates primarily with severity of illness and height-weight ratios (142). In males with cystic fibrosis, abnormalities of the vas deferens are common (100). Although pulmonary disease of any origin can restrict sexual performance, most couples in which one partner has cystic fibrosis can have sexual relationships (99). In earlier decades, most affected individuals died before reaching reproductive potential.

CANCER

Cancer can affect fertility in three ways. As with many diseases, the very presence of cancer in the body is known to affect semen quality (122) and is likely to affect the female reproductive process as well. The tumor itself can affect fertility if there is direct gonadal involvement. Finally, treatment of cancer—surgery and therapy (radiation and chemotherapy)-can also reduce fertility (see table 4-3).

Obviously, fertility will be impaired if there is direct damage of female or male genital tract structures required for procreation. Cervical, uterine or endometrial, ovarian, and testicular neoplasia are not uncommon. (Neoplasia refers to the progressive multiplication of cells under conditions that cause the cessation of multiplication of normal cells.) Cancer of the cervix, of the uterus, and to a lesser extent ovarian cancer are associated with certain risk factors involving lifestyle, possible carcinogenic exposures, and inherited predispositions (14). Infertility caused by hormone deficiency can be a risk factor for uterine cancer (134). Cervical and, to a lesser extent, vaginal and vulvar cancer have been associated with increased numbers of sexual partners and the increased occurrence of sexually transmitted disease. Development of endometrial cancer is associated with a history of sustained high-fat diet and prolonged periods of anovulation or relative infertility. For testicular cancer, undescended testes, prior history of mumps orchitis, an inguinal hernia in childhood, and previous testicular cancer in the other testis have been identified as risk factors, but in the majority of cases no predisposing factors are evident (19).

Table 4-3.—Reproductive Consequences of Cancer and Cancer Therapy

Cancer or therapy	Consequences
Tumor	Direct gonadal involvement
Surgery	Removal of gonad
	Neurogenic dysfunction Failure of emission Retrograde ejaculation Loss of orgasm
Therapy	Germ cell depletion Clinical hypogonadism Mutagenic changes in germ cell Teratogenic effects on fetus Seminal transmission of drug

SOURCE: R.J. Sherins, "Reproductive Hazards of Radiotherapy and Chemotherapy in Adult Males, " paper presented at the International Conference on Reproduction and Human Cancer, Bethesda, MD, May 12, 1987.

Therapeutic removal of genital tract structures will obviously lead to infertility if not sterility. Surgical procedures involving areas such as the prostate may also result in infertility; prostate surgery often leads to impotence in males. Modification of surgical procedures has drastically reduced the problems associated with male cancer surgery (147), but a recent study found a 20-percent fertility deficit in men treated with surgery for childhood cancer. Women treated with surgery in childhood or adolescence had almost no fertility deficit (24).

Transient or permanent gonadal damage and dysfunction may also occur during cancer therapy with radiation and chemotherapy. The National Cancer Institute has developed a device to prevent testicular damage in male patients undergoing radiation therapy (see figure 4-l). Research suggests that the impacts of various treatments vary by age, sex, type of cancer, type of drug, total drug or radiation dose, duration of treatment, use of single v. multiple agents or combined modalities, and length of time since cessation of treatment (91)144,148).

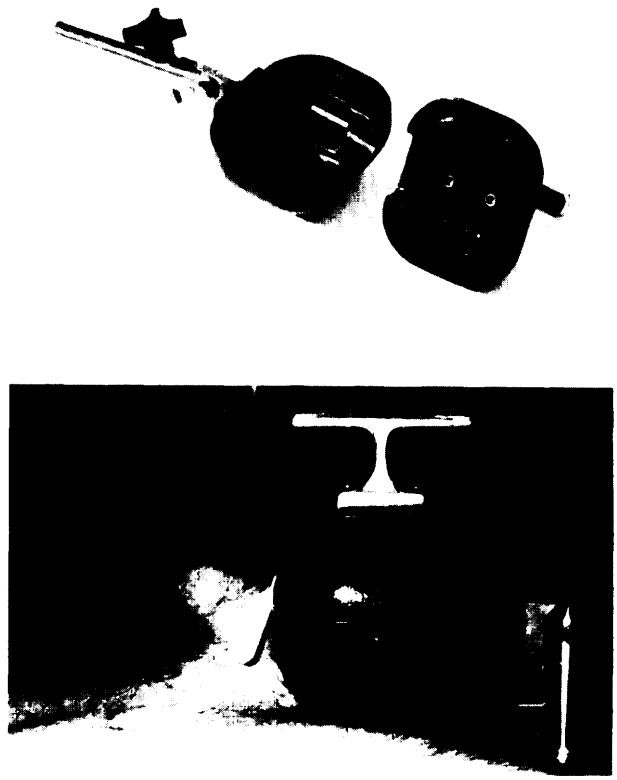
Germ cells have a normal mutation rate of approximately 12.5 percent (50). Cancer therapy

causes an increase in the mutation rate, which decreases quickly with cessation of treatment but remains higher than normal for about 10 years. In men, nearly all cytotoxic agents used in cancer therapy produce at least a temporary reduction in sperm counts. However, even after 2 to 3 years of total azoospermia, sperm production can gradually return to normal levels (114). One study reports that for all forms of therapy combined, the fertility of male cancer survivors is decreased significantly while the fertility of female cancer survivors is not. Radiation therapy is the exception; it affected men and women similarly (24). Newer regimens for treatment of testicular cancer affect spermatogenesis less than earlier ones, since they use less toxic drugs and do not last as long (18).

Various effects of cytotoxic drugs and radiation on the ovary have been described. These include ovarian fibrosis, follicular destruction, reduced estradiol levels (estradiol is a form of estrogen), increased follicle-stimulating and luteinizing hormone levels, amenorrhea, and premature menopause (probably the most frequent effect) (10). ovarian failure in these circumstances is age-related, with older women being predisposed to sterility at lower dose regimens (144).

Overall, Hodgkin's disease and male genital cancer appear to cause the greatest decrease in fertility (24,1 12). Precise information on thresholds of gonadal vulnerability and ability to recover depends on the drug, dosage, or amount of radiation used. The influence of pubertal status remains controversial (91,144).

Figure 4.1 .—Testicular Shield



The National Cancer Institute has developed a shield designed to protect the testes from scatter radiation during cancer therapy. The shield is recommended for patients receiving radiation treatment to the lower abdomen, pelvis, and thigh. It is constructed of lead and coated with plastic.

SOURCE: T.J. Kinsella, Deputy Chief, Radiation Oncology Branch, Clinlcal Oncology Program, Division of Cancer Treatment, National Cancer Institute, personal communication, June 25, 1987

IATROGENIC FACTORS

Iatrogenic factors contributing to infertility are those produced inadvertently by physicians or by treatment by them. Procedures listed in table 4-4 can lead to infertility, especially when not performed properly. The most common of these is tubal occlusion resulting from contraceptive sterilization. Obviously the intent of tubal sterilization is tubal occlusion, but for the small percentage of women who want the sterilization reversed, a poorly done procedure can mean later undesired infertility.

Surgical procedures can impair a woman's fertility primarily by producing fallopian tube or ovarian adhesions (as well as by causing infection, as discussed previously). Much information links appendicitis, appendectomy, overuse of dilation and curettage (the procedure used to remove remaining placental material after pregnancy or spontaneous abortion), and other pelvic operations with tubal-based infertility (35,1 18,163).

Table 4-4.–Iatrogenic Causes of Infertility

Procedure	Finding
Tubal sterilization	Tubal occlusion
Vasectomy	Blockage of vas deferens
Misdiagnosed incomplete abortion	Tubal occlusion or adhesions
Ovarian wedge resection .,	Tube-ovarian adhesions
Ovarian cystectomy	Tube-ovarian adhesions
IUD insertion or retained IUD	Tubal occlusion or adhesions
Appendectomy	Tube-ovarian adhesions
Uterine suspension	Partial tubal obstruction
Cesarean section	Tube-ovarian adhesions
Hysterosalpingogram	Tubal occlusion
In utero exposure to DES	Hypoplastic uterus Poor cervical mucus Increased susceptibility to adhesions following trauma such as D&C
Infant hernia repair	Blockage of vas deferens
Dilation and curettage	Scarring and Asherman's syndrome

SOURCE: Adapted from W.R. Keye, "Avoiding Iatrogenic Infertility," *Contemporary Obstetrics/Gynecology* 19:185, *1982.*

MISCELLANEOUS FACTORS

Sexual dysfunction may contribute to infertility in as many as 5 percent of infertile couples (139). In the male, these conditions usually fall into one of three categories; impotence, which can have psychological or organic causes; premature ejaculation, which, if severe, causes failure of sperm transmission to the female reproductive tract; and retrograde ejaculation, where semen is propelled into the bladder rather than out through the penis. Sexual dysfunction in the female can also affect reproduction, although negative consequences of these disorders on fertility are not as common.

It is possible that immunological factors maybe associated with otherwise unexplained infertility (106,109). Three such potential factors are antibodies to sperm (from the male or the female), cellular immunity to sperm, and antibodies to the oocyte zona pellucida (105). A number of studies in humans have demonstrated impairment of fertility with sperm antibodies. Since normally fertile men and women frequently possess such antibodies, it has been suggested that they play a role in destroying aging sperm (41), Development of such antibodies is not understood. It is presumed that women develop antibodies to sperm or seminal plasma antigens during intercourse. Details of the specific stimuli and time course in developing such antibodies remain unstudied. The roles of cellular immunity and antibodies to the zona pellucida in infertility are not as well established. Despite enthusiasm for greater recogni-

tion of immunologic infertility, controversy surrounding the subject makes it an unsettled area (55,108).

Macrophages can occur in elevated numbers during menstruation, possibly due to the release of chemotactic or irritating substances from retrograde menstruation or infection (68). Macrophages are thought to destroy male and female gametes and play roles in adhesion formation (112).

Inflammatory bowel disease—ulcerative colitis (recurrent ulceration of the colon) and Crohn's disease (regional inflammation of the ileum)–occur most frequently in reproductive-age individuals, with approximately equal frequency between the sexes (62,88)168), Ulcerative colitis does not appear to impair fertility (168), on the other hand, a preponderance of reports suggest that Crohn's disease is associated with diminished fertility; mechanisms are not well established.

Another miscellaneous cause of subfecundity is cervical incompetency (52). If the cervix is not strong enough to support the added weight as a pregnancy progresses, it will dilate prematurely and spontaneous abortion can occur.

premature menopause, defined as the cessation of menses prior to age 40, has been estimated to occur in 1 to 3 percent of American women. Furthermore, estimates state that approximately 10 percent of women with amenorrhea have premature menopause, meaning that in total at least 130,000 women in the United States suffer from this problem (6).

UNEXPLAINED INFERTILITY

In approximately 3 to 20 percent of infertile couples, no clinically apparent cause of infertility is demonstrable using standard techniques (34,127, 159). Although couples cannot be placed in this category until a thorough investigation has been performed by an infertility specialist, couples with unexplained infertility may actually suffer from subclinical expression of acknowledged causes of infertility that could be revealed by further testing or continued observations. Laparoscopy performed on 50 women whose couple evaluations were normal revealed that 28 (56 percent) demonstrated either previously unsuspected peritubal adhesions or endometriosis (187). Of those who had abnormal findings, 16 received appropriate treatment and 50 percent became pregnant within a year of treatment, versus 10 percent in the women who had no abnormalities (187). Other candidates for causes of unexplained infertility include numerous immunological abnormalities (127), luteal phase cysts, poor progesterone surge, abnormal sperm-mucus penetration, abnormal sperm-egg penetration (75), and factors known to prevent the sperm from penetrating the egg (58) (as demonstrated by a sperm penetration test).

Reports disagree on the prognosis for couples with unexplained infertility. Some claim these couples have a higher probability of conceiving than the general infertile population (15); others claim lower (90).

SUMMARY AND CONCLUSIONS

The factors contributing to infertility are often multiple and the boundaries between them are not clear. Accepting this limitation, certain general statements can be made.

In women, the main contributors to infertility are hormonal disturbances, blocked or scarred fallopian tubes, and endometriosis. Hormonal disturbances can arise from a number of different sources, and they can result in abnormal or nonexistent ovulation. Blocked fallopian tubes result most often from infection by pelvic inflammatory disease (often caused by sexually transmitted diseases) and inhibit or prevent transport of the egg and sperm. Endometriosis is characterized by the presence of cells of the uterine lining outside of the uterus and may interfere with nearly every phase of the reproductive cycle.

In men, most cases of infertility result from abnormal or too few sperm, although sometimes the transmission of sperm is a problem. A number of factors, including testicular varicoceles, environmental hazards, drug abuse, and cancer, have been implicated in male infertility, although much less is known about factors leading to male infertility than about those leading to female infertility.

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