The Environmental Impact on Male Fertility

SUPAT SINAWAT, M.D., M.Sc., M.R.T.C.O.G*

Abstract

There have been several reports indicating that the quality and quantity of human spermatozoa are facing a serious decline. This leads some scientists and environmentalists to believe that the human species is approaching a fertility crisis. Several factors have been claimed to be the attributable causes of the decline in male fertility potentials. These include heavy metals and various chemical agents widely used in agriculture and industry. Moreover, other physical factors such as the increased global temperature and radiation exposure as well as the biologic factors such as the contamination of phyto- and xeno-estrogen in the environment could detrimentally affect male reproductive function. These effects can result in, not only a reduction in sperm concentration, but also alterations in sexual behavior, mood disorders and the presence of genital cancers. The knowledge in male gonadal toxicity, therefore, is very useful in understanding the impact of environment to the male reproductive system. This will lead us to protective strategies to avoid the adverse effects of environmental factors on the male fertility.

Key word : Male Fertility, Environment

SINAWAT S
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A serious decline in the quality and quantity of human spermatozoa has occurred over the past 50 years[1]. The study in Scotland revealed that men born after 1970 had a sperm count 25 per cent lower than those born before 1959 - an average decline of 2.1 per cent a year. The lower sperm count was also associated with poor semen quality[2]. These data have led some scientists and environmentalists to believe that the human species is approaching a fertility crisis. Other scientists, however, think that the available data are insufficient to deduce worldwide conclusions[3,4]. Decreased semen quality and the total sperm count over the past 50 years has been attributed to envi-

* Reproductive Biology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

ronmental toxicants, many of which act as "estrogens"[5,6]. There is still not enough evidence to determine whether this decline in semen quality is geographically localized or is a global phenomenon.

Environmental factors which have some impacts on male fertility

Fertility of males requires the competent integration of hypothalamic-pituitary-gonadal axis and the adequate production of male gametes which are capable of fertilizing the eggs. Male fertility can be affected by any chemical, physical or biological agents that alter physiologic contral processes and impairs the normal functioning of the gonads. This can occur either by a direct chemical action of the agent or indirectly *via* the metabolic products formed during the reaction process.

A potential gonadotoxic agent can interrupt the normal function of the male reproductive system at

(1) the level of hypothalamic-pituitary-gonadal axis

(2) the gonadal level directly

or (3) by altering posttesticular events such as sperm motility or function or both. Any disruption of these events mentioned above by toxicants may lead to hypogonadism, infertility, decreased libido/sexual function or all of these. The effects may lead to transient dysfunction or permanent gonadal damage.

Possible environmental toxicants that may affect the male reproductive system are :

1. Heavy metals
2. Agricultural and industrial chemicals
3. Cigarette smoking/alcohol/marijuana
4. Pharmacological agents
5. Hyperthermia/radiation
6. Diseases
7. Oxidative stress
8. Environmental hormones

Heavy metals

Heavy metals such as lead, mercury, cadmium, aluminium, cobalt, arsenic, lithium and chromium have been noted to exert adverse effects in human and experimental animals. In animals, lead exposure results in a dose-dependent suppression of serum testosterone and spermatogenesis[7]. Lead is a direct testicular toxicant and is also able to disrupt the hormonal feedback mechanism at the hypothalamic-pituitary level[8,9].

Mercury exposure can alter spermatogenesis and it has been found to decrease fertility in experimental animals[10].

Boron has a major adverse effect at the hypothalamic-pituitary axis in a manner similar to lead. Oligospermia and decreased libido were reported in men working in boric acid-producing factories[11].

Polycyclic aromatic hydrocarbon (PAHs) is another ubiquitous undefined complex mixture encountered in the environment, as a consequence of combustion as well as the use of tobacco products[12]. The toxicity of PAHs to the male reproductive system, however, has not been examined in a well-designed study.

Cadmium, another heavy metal used widely in industries (electroplating, battery electrode production, plastics, alloys, paint pigments) and present in soil, coal, water and cigarette smoke, is a testicular toxicant. In animal studies, cadmium has been shown to cause testicular necrosis. It can also induce the expression of heat shock proteins, oxidative stress response genes, and heme oxygenase induction mechanism. Clinacal studies have associated cadmium exposure with testicular toxicity, altered libido, and infertility[13].

Agricultural and industrial chemicals

Agricutural chemicals implicated in male reproductive toxicity include epichlorhydrin, DDT, ethylene dibromide, kepone, and the dioxins.

DBCP, a nematocide widely used in agriculture, is a testicular toxicant and induces hypergonadotropic hypogonadism[14].

DDT, a commonly used pesticide, has estrogenic effect in males by blocking the androgen receptors[15].

Methyl chloride, used in the production of organosilicated and gasoline antiknock additives, has been reported to induce changes in semen quality, testicular size, and serum gonodotropins[16].

Cigarette smoking/alcohol/marijuana

The association between cigarette smoking and infertility has been investigated but with conflicting conclusions[17]. A detrimental effect of smoking on sperm concentration, motility, and morphology may be caused by impaired spermatogenesis secondary to various hormonal alterations[18]. Smoking and the presence on varicocele have also been proposed as having an additive detrimental effect on sperm density[19].

Chronic high-level consumption of alcohol has been shown to decrease sperm concentration and the number of normal sperm forms, and to impair sexual function in men with alcohol dependence syndrome. Alterations in the hypothalamic-pituitary-gonadal axis is contributary to the gonadotoxicity of alcohol. Avoidance of chronic, heavy alcohol use can reverse these effects[20].

Marijuana can decrease sperm number and motility and increase abnormal forms. Other "recreational drugs" such as cocaine, heroin and methadone have also been found to cause decreased testosterone and altered gonadotropin levels[21].

Pharmacologic agents

Anabolic steroids : Steroid abuse in athletes has been found associated with severe impairment of normal sperm production. This effect is due to feedback inhibition of the hypothalamic-pituitary axis by steroids and this effect can be reversed within 4 months of nonuse[22].

Chemotherapeutic agents :

1. Antibiotics : Some antibiotics such as tetracycline derivatives, sulfa drugs, nitrofurantoin and macrolide agents impair spermatozoal function and spermatogenesis[23].

2. Cancer chemotherapy usually damages the germinal epithelium. Mechlorethamine (nitrogen mustard) causes spermatogenic arrest. Cyclophosphamide affects the decondensation potential of spermatozoa due to alkylation of the nuclear proteins or DNA. This may also contribute to congenital abnormalities of the off spring[24].

The severity of germ cell damage is related to the category of the agent used, the dose, the duration of the treatment and the developmental stage of the gonad. Prepubertal and adolescent gonads are reportedly affected less by chemotherapy and radiation than the postpubertal testis[24,25].

3. GnRH agonists lead to suppression of gonadotropins and spermatogenesis. It may have the potential to be utilised as a male contraceptive agent in the near future[26].

4. Ketoconazole, an antifungal agent, inhibits testosterone biosynthesis primarily by inhibiting the activities of steroidogenic enzymes in Leydig cells without direct effect at the pituitary level[27].

5. Cyclosporin, the immunosuppressive drug used in patients who have undergone organ transplant, has hypoandrogenic effects mediated through the hypothalamic-pituitary axis[28].

Hyperthermia/ radiation

Hyperthermia results in impaired Leydig cell function, a gonadal loss in size of seminiferous tubules and the peritubular hyalinization with fibrosis of the testis[29]. Hyperthermia of testis can occur on several occasions such as in persons who uaually wear very tight underwear, in persons who spend a very long time sitting daily such as truck drivers, in persons who usually take a hot bath instead of taking a shower and in persons who have cryptorchid testis or varicoceles.

Gonadal damage due to radiation exposure (X-rays, neutrons and radioactive materials) is generally more severe and difficult to recover from than that induced by chemotherapy. A direct dose of irradition to gonads greater than 0.35 Gy causes aspermia. The time taken for recovery increases with larger doses, and doses in excess of 2 Gy will likely lead to premanent azoospermia. Leydig cells will also be affected at higher radiation doses (> 15 Gy)[30].

Diseases

Acute and subacute infection and inflammation of the male gonads and accessory glands can be associated with disturbances in both sex gland function and sperm quality. Some of these conditions such as chlamydial infection, mumps orchitis, tuberculosis, syphilis and leprosy can cause irreversible sterility. These conditions are usually assoicated with leucospermia or bacteriospermia. The pathophysiology of these conditions involves damage to the seminiferous tubules or obstruction to the passage of sperm at the level of epididymis or ejaculatory ducts[31].

Oxidative stress

Oxidative stress is a condition associated with an increased rate of cellular damage induced by oxygen and oxygen-derived oxidants. Chronic disease states, aging, toxin exposure, physical injury and exposure to many types of food can enhance this oxidative process and cause cell damage.

The generation of nitric oxide in response to infection and inflammation can contribute to poor sperm motility and function and lead to infertility. Nitric oxide along with superoxide radicals

(peroxynitrite) induces endothelial cell injury, which may result in gonadal dysfunction due to vasoactive effects of nitric oxide rather than by direct effects on gonadal cells[32,33].

Environmental hormones

Several agents that some males are exposed to in their daily lives may have estrogenic effects. These include non-ionic surfactant detergents which are used mainly in industries, cosmetic materials, and food which produces phytoestrogen such as soybean. Exposure to high estrogen *in utero* or early neonatal life has been shown to be associated with low sperm count, small testis and the increased possibility of development of testicular cancers in the young. Exposure of adult males to environmental estrogen may also have some impact on the male reproductive system[6,34].

SUMMARY

The dramatic increase in knowledge of male gonadal toxicity and subsequent changes in fertility will be of use in understanding the impact of the environment on the male reproductive system. This will lead to protective strategies which can be suggested to avoid or decrease the detrimental effects of environmental factors on male fertility.

Summary of the common gonadotoxic agents[34].

Class		Agent	Adverse effects/comments
A :	Environmental/occupational agents		
	Organochemicals	DBCP	↓ Fertility, ↓ libido; embryo fetal loss,
		DDT	birth defects, cancer; estrogenic
		PCBs	effects, poor semen quality
		Dioxins	
		Methyl chloride	
	Heavy metals	Lead	↓ HPG-axis, ↓ spermatogenesis, CNS
		Mercury	effects, testicular damage
		Cadmium	
		Cobalt	
		Chromium	
	Recreational drug	Nicotine	↓ Spermatogenesis, poor sperm function
		Alcohol	↓ HPG axis
		Marijuana	
		Steroids	
B :	Pharmacologic agents		
	Antimicrobials	Tetracyclines, sulfas, gentamicin, neomycin, nitrofurantoin	↓ Sperm function, ↓ spermatogenesis, testicular damage, ↓ sperm motility
	Antineoplastic	Nitrogen mustard, Cyclophosphamide	
	Radiations	X-rays, γ-rays	Germ cell and Leydig cell damage
	Other drugs	Cimetidine	
		GnRH analogs	↓ HPG-axis, ↓ sperm; ↓ libido,
		Cyclosporine	↓ steroidogenesis
		Lithium, Ketoconazde	
C :	Biological agents		
		Hyperthermia	↑ ROS, ↓ spermatogenesis, testicular damage, poor sperm morphology
		Infection/inflammation	↑ ROS, ↑ WBC, ↓ SOD, ↑ IL-8 ↓ sperm function
		Oxidative stress	↑ ROS, ↑ LPO ↑ cytokines, ↓ T, ↓ sperm function
		Age related	↑ ROS, ↓ HPG, ↑ LPO ↓ spermiation

DBCP, dibromochloropropane; DDT, dichlorodiphenyl-trichloroethane; ROS, reactive oxygen species.

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REFERENCES

1. Carlsen E, Giwercman A, Keiding N, et al. Evidence for decreasing quality of semen during past 50 years. Br Med J 1992;305:609-13.
2. Brake A, Krause W. Decreasing quality of semen. Br Med J 1992;305:1498-503.
3. Fisch H, Goluboff ET, Olson JH, et al. Semen analyses in 1283 men from the USA over a 25-year period : no decloine in quality. Fertil Steril 1996;65:1009-14.
4. Paulsen CA, Berman NG. Data from men in greater seattle area reveal no downward trend in semen quality : further evidence that deteriration of semen quality is not geographically uniform. Fertil Steril 1996;65:10015-20.
5. Working PK. Male reproductive toxicity : comparison of the human to animal models. Environ Health Perspect 1988;77:37-44.
6. Sharpe RM, Skakkeback NE. Are estrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 1993;351: 1392-5.
7. Foster WP, McMahon A, Young-Lai EV, et al. Reproductive endocrine effects of chronic lead exposure in male monkey. Reprod Toxicol 1992; 7:203-9.
8. Braunstein GD, Dahlgren J, Loriaox DO. Hypogonadism in chronically lead poisoned men. Infertility 1978;1:33-5.
9. Sokol RZ. Hormonal effects of lead acetate in the male rat : mechanism of action. Biol Reprod 1987;37:1135-8.
10. Barlow SM. Reproductive hazards of industrial chemicals. London : Academci Press; 1982.
11. Weir RJ, Fisher RS. Toxicological studies on borox and boric acid. Toxicol Appl Pharmacol 1972;23:251-64.
12. Georgellis A, Topari J, Veromaa T, et al. Inhibition of meiotic divisions of rat spermatocytes by polycyclic aromatic hydrocarbons. Mutat Res 1990;231:125-35.
13. Snow ET. Metal carcinogenesis : Mechanistic implications. Pharmacol Ther 1992;53:31-65.
14. Lipschultz LT, Ross EC, Whorton MD, et al. DBCP and is effect on testicular function in man. J Urol 1980;124:464-8.
15. Kelce WR, Monosson E, Gamcsik MD, et al. Environmental hormone disruptors. Toxicol Appl Pharmacol 1994;126: 276-85.
16. Schrader SM. Principles of male reproductive toxicology. In : Brooks SM, Gochfeld M, et al, eds. Environmental Medicine. St. Louis : Mosby; 1995: 95-100.
17. Stillman RJ, Rosenberg MJ, Sachs BP. Smoking and reproduction. Fertil Steril 1986;46:545-50.
18. Vine MF, Tse CJ, Hu PC. Cigarette smoking and semen quality. Fertil Steril 1996;65:835-42.
19. Klaiber El, Broverman DM, Pokoly TB. Interrelationship of cigarette smoking, testicular varicoceles, and seminal fluid indexes. Fertil Steril 1987;47:481-6.
20. Kucheria K, Saxena R, Mohan D. Semen analysis in alcohol dependence syndrome. Andrologia 1985; 17:558-61.
21. Kolodny RC, Masters WH, Kolodner RM, et al. Depression of plasma testosterone levels after chronic intensive marijuana use. N Eng J Med 1974;290:872-6.
22. Knuth UA, Maniera H, Nieschlag E. Angbolic steroids and semen parameters in body builders. Fertil Steril 1989;52:1041-7.
23. Schlegel PN, Chang TSK, Marshall FF. Antibiotics : potential hazards to male fertility. Fertil Steril 1991;55:235-42.
24. Shalet SM. Effects of cancer chemotherapy on gonadal function of patients. Cancer Treat Rev 1980;7:141-52.
25. Oats RD, Lipshultz LI. Fertility and testicular function after chemotherapy and radiation therapy. In : Lytton B, ed. Advances in urology, chicago; Mosby Year book; 1989;2:55-83.
26. Rivier C, Rivier J, Vale W. Antireproductive effects of a potent GnRH antagonist in the male rat. Science 1980;210:93-5.
27. Bhasin S, Sikka CC, Fielder T. Hormonal effects of ketoconazole in the male rat : mechanism of action. Endrocrinology 1986;118:1129-32.
28. Sikka SC, Bhasin S, Coy DC. Effect of cydosporine on hypothalamic-pituitary-gonadal axis in the male rat : mechanism of action. Endocrinology 1988;123:1069-74.
29. Robinson D, Rock J. Intrascrotal hyperthermia induced by scrotal insulation : effect on spermatogenesis. Obstet Gynecol 1967;29:217-20.
30. Ogilvy-Stuart AI, Shalet SM. Effect of radiation on the human reproductive system. Environ Health Perspect 1993;101(supple) : 109-16.
31. Hellstrom WJG, Neal DE Jr. Diagnosis and therapy of male genital tract infections. In : Diamond MP, Decherney, Overstrect JW, eds. Infertility and Reproductive Medicine Clinics of North America. Philadelphia : W.B. Saunders; 1992: 399-411.
32. Aitken RJ, West KM. Leucocyte infiltration into the human ejaculatate and its association with semen quality, oxidative stress and sperm function. J Androl 1994;15:343-52.
33. Rossells M, Dubey RK, Imthorn B. Effect of nitric oxide on human spermatozoa : endence that nitric oxide decreases sperm motility and induces sperm toxicity. Hum Reprod 1995;10:1786-90.
34. Sikka SC. Gonadotoxicity. In : Hellstyrow WJD, ed. Male infertility and sexual dysfunction, New York; 1997:292-306.

ผลกระทบของสิ่งแวดล้อมต่อภาวะเจริญพันธุ์ในเพศชาย

*สุพัชญ์ สีนะวัฒน์, พ.บ.**

ในช่วงสองทศวรรษที่ผ่านมานี้มีการศึกษาหลายรายงานที่บ่งชี้ว่าคุณภาพของน้ำอสุจิตลอดจนความเข้มข้นของตัวอสุจิในน้ำอสุจิมนุษย์ มีแนวโน้มลดลงเรื่อย ๆ การศึกษาในสหราชอาณาจักรพบว่า ความเข้มข้นของอสุจิลดลงในอัตรา 2.1% ต่อปี ซึ่งนับว่าน่าเป็นห่วงเป็นอย่างยิ่ง ปัจจัยหลายชนิดอาจมีส่วนร่วมในการก่อให้เกิดการเปลี่ยนแปลงเหล่านี้ โดยเฉพาะอย่างยิ่งสภาวะแวดล้อมที่แย่ลงเรื่อย ๆ สารต่าง ๆ ในสิ่งแวดล้อมที่อาจทำให้ความสามารถในการเจริญพันธุ์ของผู้ชายลดลงได้แก่ โลหะหนัก สารเคมีที่ใช้ในการกสิกรรมหรืออุตสาหกรรมต่าง ๆ อุณหภูมิของโลกที่เพิ่มสูงขึ้นเรื่อย ๆ รังสีต่าง ๆ ตลอดจนฮอร์โมนที่ปนเปื้อนอยู่ในสิ่งแวดล้อม ซึ่งนับวันจะมีมากขึ้นเรื่อย ๆ ปัจจัยเหล่านี้นอกจากจะทำให้คุณภาพของอสุจิลดลง ซึ่งหมายความถึงการลดลงของความสามารถในการเจริญพันธุ์ของมนุษย์แล้ว ยังอาจสัมพันธ์กับความผิดปกติอื่น ๆ ของระบบสืบพันธุ์ เช่นการเปลี่ยนแปลงทางอารมณ์และความต้องการทางเพศ ตลอดจนมะเร็งของอวัยวะสืบพันธุ์อีกด้วย

คำสำคัญ : ภาวะเจริญพันธุ์, สิ่งแวดล้อม

สุพัชญ์ สีนะวัฒน์
จดหมายเหตุทางแพทย์ ฯ 2543; 83: 880–885

* หน่วยชีววิทยาการเจริญพันธุ์, ภาควิชาสูติศาสร์และนรีเวชวิทยา, คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น, ขอนแก่น 40002