Occupational exposure and effects on the male reproductive system

Exposição ocupacional e efeitos sobre o sistema reprodutor masculino

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Abstract

A significant increase in the incidence of male infertility has been described in the international literature, raising questions about its causes. Part of this effect may result from synthetic toxic substances acting on the endocrine system (endocrine disruptors), many of which are routinely used in work processes. We provide a critical review of the specialized literature on work-related chemical substances capable of causing male infertility. Pesticides such as DDT, linuron, and others, heavy metals like mercury, lead, cadmium, and copper, and substances from various industrial uses and residues such as dioxins, polychlorinated biphenyls (PCBs), ethylene dibromide (EDB), phthalates, polyvinyl chloride (PVC), and ethanol are among the main endocrine disruptors that can cause male infertility. Based on the literature, gonadal dysfunction and congenital malformation are the main alterations caused by these substances in the male reproductive system. We conclude that despite the relative lack of studies on this issue, the relevance of such risk calls for further studies as well as measures to prevent workers' exposure to the various substances.

Male Infertility; Occupational Exposure; Endocrine System

Introduction

Some chemical substances have the capacity to interfere in the functioning of the endocrine system, in the hormones' mechanism of action, and are called endocrine deregulators or endocrine disruptors [1,2,3], with the latter term adopted in this paper.

Alterations caused by endocrine disruptors can be temporary or permanent [2,4,5]. Endocrine disruptors can cause the following, among others: reproductive anomalies (morphological and functional gonadal dysfunction, e.g., infertility and decreased libido) and congenital malformations (altered embryonic and fetal intrauterine development) [2,6,7,8].

The principal effects of exposure to endocrine disruptors on male fertility are temporal reduction in sperm concentration and quality [9], high incidence of cryptorchidism and hypospadias [10], and altered sex ratio [11,12].

Despite the diversity of habits and cultures around the world, an increase in male infertility has been observed, apparently constituting an international phenomenon [13,14,15,16,17], although alterations in fertility can be said to suffer influences from physical, chemical, and/or psychological factors.

Male reproduction involves complex and delicate processes and depends on normal development and organization during the fetal period as well as during growth and puberty [18]. In-

terference in sex hormone function during these phases can thus have repercussions throughout adult life.

It is undeniable that good quality semen is essential for reproductive success. This quality appears to have been directly affected in recent years, and evidently there are now unfavorable trends in male reproductive health [19].

For example, Carlsen [20] demonstrated a 45% drop in human sperm count, from an average of 113 million per ml of semen in 1940 to 66 million in 1990, potentially jeopardizing male fertility [7,21].

Since the 1970s various authors have reaffirmed the possible significant drop in sperm quality and consequently an increase in male infertility rates [13,22]. The actual causes of increased infertility remain controversial [13,14,16,23], but research suggests that many substances to which men are exposed and than can affect their fertility may be work-related [24,25,26].

The international technological shift in industrial and agricultural development in the 20th century involved handling and exposure to various substances that are harmful to humans, some of which affecting the male reproductive system, such as pesticides, metals, estrogen-like substances, chlorinated compounds, etc. [3,13,16,27].

This raises the hypothesis that the effects of these substances on the male reproductive organs may shed light on numerous issues related to the increase in male infertility.

Some 6% of reproductive-age men present male infertility. The most frequent causes, accounting for 90% of the total, are associated with spermatogenesis. The other causes are related to alterations in sperm transport and accessory glands in the male genital tract (6%), erectile disorders (2%), ejaculatory disorders (1%), and functional alterations in the sperm and coitus (1%) [28]. There may be absence of sperm (azoospermia), a decrease in the number (oligozoospermia), alteration in form (teratozoospermia), in the motile capacity (astenozoospermia), or in the vitality (necrospermia) [29,30].

Exposure to endocrine disruptors can modify hormone metabolism by altering the synthesis and/or breakdown of testosterone, FSH, LH, or other hormones. Most steroid metabolism occurs in the liver, the main target for some exogenous toxic substances [31].

Methods

The current study reviewed the specialized literature for substances that can act as endocrine disruptors and lead to male infertility through occupational exposure.

The research consisted of a bibliographic survey and data collection in books and articles in journals or periodicals. The material collected for the study was limited to that published in the Portuguese, English, and Spanish languages, based on the review of the domestic and international literature through books, articles in indexed periodicals and websites. Due to the scarcity of material published in this area, we did not adopt any restriction on the time period researched.

The descriptors researched in English were the following, in addition to their Portuguese and Spanish equivalents: infertility, male infertility, azoospermia, endocrine disruptors, environmental contaminants, infertility versus occupational, effects of occupational exposure, male reproductive system, gonads, reproduction and human development, male gonadal hormone control, chronic effects of pesticides, heavy metals, and others, toxicology, male infertility, and occupational exposure to endocrine disruptors.

Male infertility and occupational exposure to endocrine disruptors

External causes include factors that are exogenous to the body, and exposure to them can occur consciously, for example in alcohol consumption or smoking, or unconsciously or accidentally as with infections or occupational or environmental contamination [28].

The numerous external causes of infertility include exposure to work-related substances; contact with toxic substances like pesticides, or exposure to extremely hot areas such as blast furnace operations [3,13,30,31,32].

Chia & Tay [33] assessed a total of 640 men who were incapable of conceiving with their wives, asking about the men's exposure to agents known to affect spermatogenesis, such as alcohol consumption, smoking, and stress. They evaluated total semen concentration, density, motility, viability, and morphology. Smoking proved to be a significant risk factor and exposure to electromagnetic fields and high stress levels may have contributed to this increased risk of infertility in occupations with these characteristics, although the factors require further in-depth study and validation of the hypothesis.

There was a significant increase in the incidence of testicular cancer in the 20th century, which could be correlated with the increase in male infertility. There has also been an increase in the incidence of prostate cancer [34]. A signifi-

cant difference is that testicular cancer occurs in young, reproductive-age men, while prostate cancer occurs mainly in elderly men, so that the latter increase is explained mainly by the increase in the population's mean age.

Several studies have correlated the increase in testicular cancer with exposure to certain substances [35]. As important as the chemical agent is the duration of exposure to the inductive agent [32].

In recent decades, the increasing incidence of testicular cancer has been associated with exposure to endocrine disruptors like pesticides and industrial residues [36,37].

Sheiner et al. [38] investigated the influence of work conditions (such as exposure to toxic substances) on reproduction. The study concluded that industrial and construction workers present an increased infertility rate as compared to other professions, due mainly to greater exposure to stress. Workers in these sectors smoked more and were more exposed to noise and physical effort as compared to other professions. These workers presented sperm abnormalities, hormonal alterations, varicocele, and/or cryptorchidism.

Among the many external causes of infertility are exposure to substances related to occupation, such as pesticides, polychlorinated biphenyls (PCBs), dioxins and furans, ethanol, phenols, phthalates, and metals like cadmium, lead, mercury etc. [7,10,36] and adverse work situations (exposure to hot areas like blast furnace operations etc.) [13,28,29,32].

Cadmium

Some toxic substances act on the testes, causing problems in spermatogenesis and spermiogenesis. One example is cadmium [39].

Industrial cadmium exposure is extremely relevant, affecting more than 1,500,000 workers a year in the United States alone [40]. Cadmium is used in pesticides, batteries, rubber processing, production of pigments, and galvanizing [41]. It is also bioaccumulative and persistent in the environment (with a half-life of 10-30 years) [14].

Cadmium can directly injure the testes. A testicular toxin and various derived compounds were shown to induce severe damage to the spermatogenic epithelium in an animal model [39]. The effect of cadmium on the testes appears to be manifested mainly in the Sertoli cells, which present more morphological changes under scanning electron microscopy. Cadmium can also interfere with the normal functions of mitochondrial enzymes [28].

Testicular lesion from cadmium is primarily vascular, and the vascular damage determines the degree of lesion in the germ cells and Leydig cells. This lesion can generate Leydig cell tumors, tubular degeneration (in high-dose exposure), and atrophy [42], in addition to inducing tissue necrosis and deficient androgen production [42,43].

In chronic exposures to lower doses, the greater availability of metallothionein, bound to cadmium, means that the testicular lesion is less aggressive as compared to cases of acute intoxication [44].

In a study by the World Health Organization (WHO) on the effects of lead and cadmium in the blood of adult men, the overall results indicate that even low-level exposure to lead (400µg/l) and cadmium (10µg/l) can significantly reduce the quality of semen, although the study did not show conclusive evidence of male endocrine reproductive alterations [45,46,47,48].

Lead

Reproductive dysfunction has been described in men exposed to lead at the workplace, including oligozoospermia and dose-dependent astenozoospermia [48,49,50].

Blood and semen samples were analyzed from battery factory workers, showing an inverse association between plasma lead levels and sperm volume and concentration.

Significant correlations were observed between lead, dehydratase, and protoporphyrin levels and reproductive parameters, indicating a decrease in sperm density and motility and viability counts and an increase in abnormal sperm head morphology [45].

Other authors have also reported a reduction in spermatogenesis among battery workers as one of the findings in symptomatic lead poisoning [51,52,53,54].

The 1950s witnessed a reduction in gonadotropin secretion among individuals exposed to lead, while moderate exposure only led to higher FSH levels [55].

Studies on workers in lead foundry workers showed hypogonadism and decreased serum testosterone, with a reproductive and endocrine impact, especially in the hypothalamic-pituitary-testicular axis, associated with occupational exposure to inorganic lead [54,56].

Another lead foundry study evaluated exposure and damage over time. The study demonstrated a non-progressive increase in LH in individuals exposed for less than one year, while those exposed for more than three years showed a reduction in both testosterone and the testos-

terone/steroid transport protein ratio, suggesting a correlation between testicular dysfunction and duration of exposure [58].

Studies in rodents have also demonstrated both a direct effect of lead on the testes and interference in the hypothalamic-pituitary axis [59,60].

Studies in laboratory animals exposed to lead showed lower plasma LH levels after stimulation with GnHR as compared to controls, in addition to decreased inhibin/FSH ratio [61].

Continuous intrauterine exposure of male rodents also showed harmful effects on male sexual maturity and reduced neonatal sex steroid levels. In addition, exposure during puberty induced a reduction in testosterone concentrations and decreased plasma LH [62] in males exposed to high lead levels, thus suggesting secondary effects in relation to the hypothalamic-pituitary effects, with alterations in FSH levels [63].

Lead can reduce the amount of sulfated steroids excreted in the urine and can cause a reduction in testosterone levels and sperm concentration [64]. In addition to the effects on hormone levels, Assennato et al. [52] describe a reduction in sperm concentration by a direct, non-hormonal effect, in sperm production or transport. A direct effect of lead on the testes has also been shown in rodents [55,65].

Animal studies appear to confirm lead's toxic effect on the reproductive system. Excess lead intake can result in decreased sperm production and testicular weight [59].

Studies in monkeys chronically exposed to lead showed alterations in Sertoli cell function [53,66].

Lead can alter prostate secretory function [46] (concentration of zinc, acid phosphatase, and citric acid in the seminal fluid). Donovan et al. [67] showed that in animals lead, like other divalent cations, can inhibit the binding of dihydrotestosterone to specific receptors in the prostate and seminal vesicle.

A study in which men were exposed to lead in the workplace showed that increased levels were associated with decreased libido and an increase in semen abnormalities [49]. The principal source of lead contamination occurs in workplaces [28].

Mercury

Research on mercury increased after the accident in Japan in 1968, when more was learned about exposure to this metal in rats and humans [68].

Mercury can concentrate in the kidneys, cerebellum, and testes. Mercury poisoning leads to neurological disorders, kidney failure, and infertility [68].

Mercury can interfere in spermatogenesis and also affects the epididymis. It can also cause Young syndrome, associated with obstructive lesion of the upper epididymis [69].

Copper

Copper can act on FSH receptors, interfering in spermatogenesis [57]. In animals, the main endocrine alterations are in testosterone, LH [70], and FSH secretion [71].

Pesticides

The main pesticides with effects described on the reproductive system are beta-HCH, carbaryl, chlordane, dicofol, dieldrin, DDT (dichlorodiphenyl-trichloro-ethane) and its metabolites, endosulfan, heptachloro and H-epoxide, lindane (gamma-HCH), malathion, mathomyl, methoxychlor, mirex, oxychlordane, parathion, synthetic pyrethroids, toxaphene, and transnonachlor [37].

A recent study by Dalvie [72] attempted to elucidate the effects of the pesticide DDT on workers from the province of Limpopo in South Africa. The study hypothesis was that there could be long-term reproductive effects on malaria vector control workers who were regularly exposed to DDT. The study measured sperm count, density, and motility. Normal morphology recording included 2.5 ± 1.8% of the individuals. Most (84%) of the morphological counts were below the WHO and Tygerberg criteria, with the highest individual recording at 6%, which is precisely on the subfertility line according to the Tygerberg criterion. Persistent problems with sexual function extended to 10-20% of the patients. The most prevalent genital abnormality (71%) was abnormal testicular placement [72].

According to several studies, DDT and some organic solvents lead to decreased fertility and altered sperm counts [42,73].

DDT can also delay puberty [7,28,42,74,75]. The estrogenic activity of DDT isomers is very weak as compared to estradiol (10^3-10^6 less powerful), but the properties of bioaccumulation and long half-life indicate that human exposure levels can cause estrogenic effects under certain circumstances [7,76] and act as an androgenic agonist at high doses [77,78,79].

DDE, a metabolite of DDT, has anti-androgenic action and can also jeopardize estrogen metabolism in its synthesis or breakdown and physiological elimination [77,78]. According to Je-

quier [28], DDE can suppress the spermatogenic epithelium in humans.

Exposure to the pesticide DBCP (1,2-dibromo-3-chloropropane) in rodents profoundly affected the germ cells and androgen-dependent sexual differentiation (there was a reduction in testicular mass, androgen levels, and size of the hypothalamus) [19,75].

DBCP can reduce sperm production. Exposure to this product can be associated with a reduction in the number of male births [3,7,76]. It can reduce the concentration of ejaculated sperm in exposed workers as compared to samples in unexposed men [80]. Removing workers from the exposure site allows a return to normal values, while those suffering azoospermia remain sterile. Testicular biopsies show that the target of DBCP is the spermatogonium [79].

A study on farm workers who handled pesticides showed the action of the latter over a three-year period on testosterone metabolism. A significant increase was observed in FSH, PRL, and testosterone. An immediate effect was the temporary reduction of testosterone levels. There was also a reduction in estradiol levels. An important caveat is that the study involved a small number of workers [42].

According to Gray [81], the pesticide linuron displays anti-androgenic activity. It increases the incidence of testicular tumors in rodents. It can lead to pituitary stimulation, with an increase in LH [42].

The pesticide vinclozolin can have anti-androgenic effects. The metabolites of vinclozolin, M1 and M2, but not the substance itself, competitively inhibit the binding of androgens to the androgen receptor in mammals [82]. Exposure of adult and pubertal rats to the pesticide altered the hypothalamic-pituitary function [83].

Exposed workers in factories producing lindane showed a significant increase in LH, a non-significant increase in FSH, and a slight decrease in testosterone [84].

Studies have shown that lindane can accumulate in the testes, damaging the germinal epithelium and the number of spermatids and Sertoli cells in humans [84].

The pesticide procimidone binds to the androgen receptor, acting as an antagonist in monkey cells, and in the laboratory it is capable of inhibiting the transcription induced by dihydrotestosterone [81]. In rats it induced hypospadias and smaller accessory glands and reduced the size of various androgen-dependent tissues such as: prostate, seminal vesicle, and glans penis, even when these rodents were exposed to low doses [74].

Endosulfan is a xenoestrogen that is capable of increasing prolactin expression and competing with estrogens for the estrogen nuclear receptor [84]. According to Saiyed et al. [31], exposure to endosulfan in boys can delay sexual maturity and interfere with hormone synthesis.

Dioxins

Dioxins are the result of various industrial processes and are considered the most toxic anthropogenic agents. Studies with dioxin in sexually mature laboratory animals showed the effects of exposure to relatively high doses. The animals displayed decreased spermatogenesis, decreased testicular weight, and abnormal testes with reduced fertility [85].

A study on sexually mature laboratory animals exposed to high doses of dioxins showed alteration of accessory sex organs [85].

Dioxins can affect libido and fertility, causing changes in the sexual behavior of male fish, birds, mammals, and reptiles [83,86,87]. Tetrachloro-dibenzo-p-dioxin (TCDD) can interfere with libido [73].

A study showed similar effects in animals exposed to dioxin in uterus. This study reported that sperm counts have dropped and alterations in the male reproductive tract have increased since the 1950s [14,88].

TCDD can have an anti-androgenic and anti-estrogenic effect [89], inducing a decrease in the testicular response to LH [89,90].

The effects of high exposure to TCDD and "TCDD-like" compounds on important sites for development and reproduction have been recognized for years [89]. The reproductive system has even been considered the most sensitive "end point" for dioxins [83,89].

PCBs

According to Brouwer et al. [85], PCBs can affect not only estrogen levels but also those of androgenic, thyroid, pituitary, corticosteroid, and other hormones.

Some of the analogs or metabolites of PCBs act as endocrine disruptors [85]. Both estrogenic and anti-estrogenic effects can be induced by these substances [91,92]. The levels of some PCB analogs were inversely correlated to sperm motility in semen samples in which the sperm concentration was less than 20 million/ml [92].

Boys born to women exposed to PCBs presented penile underdevelopment [42,90]. Other studies have described a powerful gonadotoxic action of PCBs, and exposure to these agents induced major testicular alterations [28].

Ethylene dibromide (EDB)

EDB, a substance used to remove lead traces from gasoline [93], has testicular and post-testicular effects. A study of workers exposed to this substance indicated an increase in the number of abnormal sperm and decreased sperm concentration [94]. Even short exposure can reduce sperm velocity and semen volume [31,95].

Phthalates

Phthalates are substances used in the manufacturing of automobiles, medical supplies, plastics, beverage containers, coating of metal cans etc. [42]. One of the principal forms of exposure is through food, in addition to medical materials and by occupational contact [96]. Phthalates can alter reproductive development regardless of binding to androgen or estrogen receptors. Some phthalate esters inhibit steroidogenesis in Leydig cells, displaying an anti-androgenic effect [88]. Through exposure by food, they can cause testicular atrophy and reduced fertility [30,74]. In pubertal male rats, phthalates can alter testicular function, producing malformations in androgen-dependent tissues [74].

Data have demonstrated that perinatal exposure to a variety of phthalate esters alters the development of the male reproductive tract in an anti-androgenic way, causing underdevelopment and agenesis of the epididymis at relatively low doses [81].

Others

Polyvinyl chloride (PVC) in exposed workers is associated with cancer of the testes [42].

In rats, ethanol can cause a decrease in plasma testosterone and LH levels [5].

Final remarks

The themes approached in the field of workers' health are important for any country's economic system. The issue of male infertility caused by occupational exposure is pertinent worldwide. Protection of workers against exposure may also allow preventing other alterations and injuries to the human body.

In addition to the reproductive system, endocrine disruptors can interfere in other areas such as the immune and endocrine-metabolic systems and can even cause diseases like cancer. The effects of chronic exposure can interfere in growth, physiology, behavior, and reproduction. Monitoring chronic effects requires sufficient time for the manifestations to occur.

Progress is needed in the knowledge of possible effects of exposure on male fertility. Such progress will allow the development of preventive measure within the field of workers' health. Studies in this field should be encouraged, since they are scarce in light of the almost unlimited range of substances to which workers are potentially exposed.

Resumo

*Um significativo aumento da incidência de infertilidade masculina tem sido descrito na literatura mundial, o que gera questionamentos sobre suas causas. Parte deste efeito pode dever-se à ação de substâncias tóxicas sintéticas sobre o sistema endócrino (*endocrine disruptors *ou interferentes endócrinos), sendo muitas delas utilizadas em processos laborais. Realizou-se revisão crítica da literatura especializada sobre fatores químicos de origem laboral capazes de provocar infertilidade masculina. Entre os principais* endocrine disruptors *que podem causar infertilidade masculina destacam-se agrotóxicos, como DDT, linuron e outros; metais pesados, como mercúrio, chumbo, cádmio e cobre; além de substâncias de utilidades variadas ou que correspondem a resíduos de processos industriais, como dioxinas, bifenilas policloradas, dibromoetileno, ftalatos, PVC e etanol. Disfunção gonadal e má formação congênita foram as principais alterações descritas como causadas por estas substâncias sobre o aparelho reprodutor masculino. Conclui-se que, apesar da escassez de estudos sobre o tema, a relevância do risco faz com que estes sejam estimulados, assim como que se tomem medidas preventivas para se evitar a exposição de trabalhadores a substâncias que carreiem tais riscos.*

Infertilidade Masculina; Exposição Ocupacional; Sistema Endócrino

Contributors

E. K. R. Queiroz and W. Waissmann participated equally in the design, elaboration, formatting, and revision of the article.

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