

IMPACT OF CIGARETTE SMOKING ON HUMAN REPRODUCTION: ITS EFFECTS ON MALE AND FEMALE FECUNDITY

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Cigarette smoking has become a serious health and societal problem today and also presents a rather challenging dilemma for the physician or the health care provider. No doubt, the physician has a difficult and yet necessary and important role to play in convincing patients of the adverse health effects smoking has on the body's ability to properly function and reproduce. The smoking behavior can be defined only as physically self-destructive and anyone who smokes should be advised to stop. The data shown in this review depicts a great deal of epidemiological evidence that smoking adversely affects female and male fertility. It also shows the biological plausibility and mechanisms of action of cigarette smoke and its components on the various reproductive processes. The argument against smoking holds true for anyone wishing to reproduce, however, it is particularly imperative for individuals having difficulty in conceiving or experiencing infertility problems. Infertility generally is defined as the inability of a couple to conceive after 12 months of trying to achieve pregnancy without the use of any means of contraception (unprotected sex). Data from 1982 reveal that infertility affects an estimated 2.4 million married couples in the U.S. and these figures continue to increase dramatically.

INTRODUCTION

A large percentage (30-35%) of men and women of reproductive age in the United States utilize nicotine via smoking cigarettes on a daily basis. An additional portion of nonsmokers, especially children, are also affected as "second hand smokers" by inhaling side stream smoke from burning cigarettes and exhaled smoke from smokers (1). It can be said today that smoking has been established as the number one preventable cause of death and disease in the United States and in other countries worldwide. Most lung cancer and emphysema, as well as a high percentage of heart attacks are caused by cigarette smoking. Recent scientific data reveal that the cancer risk from smoking is not limited to cancer of the lung. Many bladder, cervical, esopha-

geal, and pancreatic cancers are also caused by smoking. In 1987, lung cancer replaced breast cancer as the number one cancer killer of women in America. It is now generally accepted that at least 434,000 Americans die each year of smoking-related illnesses. Although 30 million Americans have given up smoking in the past 20 years, 50 million still smoke. These are not just loyal customers. They are, for the most part, addicted to cigarettes. According to a current report (2), it is suggested that if current smoking rates continue in the world, more than one-fifth of the people alive in the developed world today will eventually die of smoking-related causes, a far greater toll than previously thought.

Cigarette smoke contains a large number of substances, including nicotine, carbon monoxide, and recognized carcinogens and mutagens, such as radioactive polonium, benzo(a)pyrene, dimethylbenz(a)anthracene, dimethylnitrosamine, naphthalene, and methylnaphthalene (3). Many of these constituents, however, have never been evaluated for their toxicological effects and their impact on the human body and general health and therefore the full ingredients of cigarettes and cigarette smoke remain unknown. Inhalation of cigarette smoke, whether through active or passive smoking, leads to absorption of these substances through the pulmonary vasculature and blood borne circulation throughout the body (4).

Because of the vast amounts of scientific and clinical data concerning smoking and health and because of the recent surge of interest in the effects of smoking on reproductive health, it is the intent of this review to limit the discussion to the effects of smoking on female and male reproductive health only. Numerous other important aspects of smoking on general health care, public policy, contraceptives, and smoking prevention are beyond the scope of this review and will not be addressed.

EFFECTS OF SMOKING ON FEMALE FERTILITY

No one disagrees any longer that smoking during pregnancy has deleterious effects upon both the mother and the growing fetus. A number of studies address the effects of cigarette smoking on female fecundity. These studies include epidemiologic and animal studies which overwhelmingly support the hypothesis that cigarette smoke and its constituents have adverse effects on reproductive function. In epidemiologic studies, issues such as methodology, patient selection, selection of adequate control population, and elimination of potentially confounding variables have been sources of concern. However, in spite of all the variations and when all data is considered as a whole, the literature clearly demonstrates a reduction in the fecundity of women who smoke. Specifically, such effects include deleterious effects on menstrual cyclicality; tubal function and embryo transport; control of oocyte production and viability; age of onset of menopause; and bone metabolism.

Effects on female reproduction

Overall, when female fertility is not compromised, attempts to achieve conception typically involve having sex with a male and establishing the pregnancy without any medical assistance or interference. Under normal circumstances, fertilization of an egg, subsequent attachment of the yielded embryo, and maintenance of pregnancy depend on a series of rather complex and somewhat interrelated events. Those events involve the presence of an intact, healthy female reproductive tract that can produce eggs, enable them to be fertilized in the Fallopian tubes and become embryos and then lead them into the uterus where they attach and grow and give rise to a healthy baby. Specifically, the female must have healthy ovaries that can produce eggs. Also, she must have adequate hormone levels that can properly stimulate the production of the eggs at the time of ovulation and to later support the attachment of the embryos to the uterine lining and maintenance of pregnancy. The whole process is rather complex, and cigarette smoking can interfere with almost every aspect of egg production, the fertilization process, embryo attachment, and the proper growth and development of the baby during the pregnancy. The mechanisms as to how smoking affects the above defined processes are not totally understood because of the complexity of the reproductive system and the process of fertilization, but the evidence and understanding of these modes are becoming clearer every day as more and more data become available.

Effects on fecundity

Data from several epidemiologic studies show that women "habitual" cigarette smokers had significantly increased frequency of infertility when compared to nonsmokers (21% versus 14%, respectively). A consistent and highly significant trend of decreasing fertility with increasing numbers of cigarettes smoked daily (smoking intensity) was seen especially when the women smoked more than 16 cigarettes per day (4).

Of all studies that can be evaluated for the influence of smoking on fecundity, most reveal a decreased rate of conception or fertility associated with smoking versus control patients. Appropriately,

however, emphasizing the difference between an “association” and “causation” of smoking on fecundity should be made. In evaluating causation, one must look at the strength of the association; at dose-response effect; and at the specificity of the association, its consistency, and its biologic plausibility. The strength of association of smoking and decreased fecundity, although significant, is not overwhelming in some studies. There is the suggestion of a dose-response effect in those studies, but this phenomenon needs more evaluation. The specificity of the association is not great, but the consistency of the findings is good—although not completely uniform. In some studies the association of smoking to decreased fecundity is well supported, especially in relation to primary tubal infertility. The possibility that this association is related to the different lifestyles of smokers—such as increased number of sexual partners, increased risk and frequency of pelvic inflammatory disease (PID) (5), and a direct effect of smoking on the likelihood of acquiring PID—remains an important unresolved issue.

Effects on tubal function

Data regarding effects of smoking on tubal function and subsequent tubal infertility come mainly from both human and animal studies. The smoking and nicotine-induced effects are possibly mediated via epinephrine and/or vasopressin release, which is shown to increase in blood and in urine after smoking is initiated. These hormonal changes, in turn, could bring about altered uterine tubal function which can manifest alterations in gamete transport with subsequent decrease in fecundity (6).

On the one hand, potential delay in embryo transport might decrease embryo viability or increase the frequency of ectopic tubal gestation from retained embryos. On the other hand, impairment of implantation/nidation from accelerated embryo transport and early entrance into the uterus also might affect fertility.

Ectopic tubal gestation, although not technically a decrease in fecundity, affects fertility and is often a manifestation of tubal dysfunction. An important piece of evidence linking smoking and ectopic gestation in humans comes from studies in which women with confirmed ectopic tubal gestation were

matched to both a pregnant woman who delivered and a nonpregnant control. The data showed significantly more women with ectopic gestation were smokers, compared with controls (7).

Cigarette smoking has been demonstrated to adversely affect both the humoral and cellular immune systems. Such alterations might affect tubal epithelial response to inflammation and, it is speculated, result in an increased frequency of tubal infection and subsequent infertility. Thus, overall, some human and animal studies support the possibility of altered tubal physiologic features with altered tubal transport; possible early or delayed entry of blastocyst into the uterus; and alterations in the immune system that can account for the epidemiologic association between smoking and decreased fecundity from tubal causes (8, 9).

Effects on oocytes and pre-implantation embryos

Effects of smoking on oocytes can affect female fertility. Studies in rats and mice show that smoking can cause destruction of oocytes. Such oocyte destruction in rats and mice has been shown to encompass not only primordial follicles, but growing pre-ovulatory follicles and even oocyte meiosis. These experiments demonstrate deleterious dose-response effects on oocyte/follicle destruction and function in histologic-sectioned ovaries (10). Also noted is a dose-response effect of these compounds on fertility of rats bred after exposure to smoke or its selected components. The oocyte or the process of fertilization also may be altered; nicotine has been shown to prevent cortical granule formation, inhibiting the block to polyspermy (11). A polyspermic embryo might fail to develop or later abort and lead to loss in fecundity.

Evidence in humans to support the animal data of the adverse effects of smoking on oocyte viability is not convincing. The only such data come from a number of human studies that associate cigarette smoking with the decreasing age of menopause. Thus, based on animal models and human effects on age at menopause, comes a hypothesis that cigarette smoking depletes oocyte viability and/or number. This depletion in humans may result in an earlier age of the loss of reproductive function: menopause. This earlier menopause may be the endpoint

of a process taking place throughout a smoker's reproductive life—mainly the effect of smoking on oocyte meiosis, follicular maturation, and oocyte viability. Subsequently, a decrease in fecundity might result (10).

Effects on menstrual cyclicity

Data from a small number of studies on menstrual cyclicity and smoking tend to show that smokers when compared to controls (nonsmokers) have a higher frequency of secondary amenorrhea, increased vaginal bleeding, and significantly lower luteal phase urinary estrogens (12). These studies showed that current smokers, and especially heavy smokers, were more likely to have had irregular menses in the fourth and fifth decades of life than nonsmokers (13). More smokers than nonsmokers between the ages of 30 and 39 years had hysterectomies, and fewer had pregnancies. These effects also were exaggerated with heavier smoking (12). It was also reported that smokers have significantly lower concentrations of urinary estriol, estradiol, and estrone during the luteal phase of ovulatory cycles, compared with former smokers. Follicular-phase estrogens were diminished, but not significantly in smokers, and there were other estrogen-dependent phenomena such as endometrial cancer, endometriosis, and increased risk of osteoporosis (14).

Similarly, animal studies demonstrate that nicotine or cigarette smoke can, in a dose-dependent fashion, alter mechanisms controlling the release of gonadotropins and cyclicity. Most studies performed have evaluated the hypothalamus and pituitary of the female rat (15, 16). Nicotine is suggested as the primary constituent in smoke that produces these effects, although other constituents in cigarette smoke may or may not modify the nicotine-induced changes. Nicotine itself may act directly or may work through its well-described enhancement of vasopressin, which can diminish luteinizing hormone (LH) (10, 15). It has also been demonstrated that nicotine itself diminished LH in a dose-dependent fashion by delaying, blunting, or completely abolishing the LH surge in proestrus rats. Similar, but less demonstrable effects were seen on prolactin secretion. No abnormality in the pituitary response to luteinizing hormone-releasing hormone was noted, suggesting that the effect of

nicotine was not at the pituitary level (15). Others have found that there was a decrease in the percentage of rats ovulating after exposure to nicotine. Catecholaminergic and adrenergic adrenal responses (increasing cortisol) and an increase in growth hormone have been demonstrated in a number of studies, but not conclusively with human studies (16). In a most recent study, women who underwent in vitro fertilization procedures were evaluated and compared for estrogen levels, number of eggs recovered, fertilization rates, and also pregnancy rates in those who smoked one pack of cigarettes per day to those who did not smoke. Smokers experienced lower estrogen levels and egg recovery rates than nonsmokers, which could account for the decreased pregnancy rate in the smoking group (33%) as compared to the nonsmokers (57%) (17). The authors implicated nicotine as a potential reproductive toxin which resulted in lower estrogen levels and also lower egg recovery. Taken together, these clinical reports in human and animal studies emphasize the effect of nicotine/smoke on the central hormonal homeostasis of women, which may affect ovulatory cyclicity and hence fecundity.

Effects on osteoporosis

It is well documented that post-menopausal smokers have an increased risk of osteoporosis. As noted above, cigarette smoking alters metabolism via possibly hormonal alterations, and women with such metabolic changes experience a higher risk of osteoporosis. Most recent reports show that various hormones of adrenal origin were elevated with smoking, suggesting the induction of a partial enzymatic blockage in the adrenal gland. This result may be related in part to the reported ability of nicotine to stimulate adrenocorticotropic hormone release, leading to elevated cortisol which may lead to osteoporosis and osteopenia (18,19).

In general, a strong association exists between smoking and decreased female fecundity and fertility. Epidemiologic data suggests that for the former smoker, the risk to fecundity is minimized. Thus, stopping smoking may diminish the risks and assist in achieving proper conception. Therefore, it seems more prudent for all women wishing to conceive to stop smoking, especially those who experience some sort of subfertility.

EFFECTS OF SMOKING ON MALE REPRODUCTION

The subject of possible detrimental effects of cigarette smoking on reproductive performance and specifically on semen parameters in the male is of great interest, but the data available are somewhat inconclusive. However, because of the recent desire to better understand and treat infertility in both males and females, cigarette smoking has become an important parameter for assessment for possible side effects on male reproduction. Using information available with other toxins on reproduction (20), scientists rationalize that male reproduction can be impaired by a small but increasing number of environmental and occupational exposures. Chemical agents may affect male reproduction via direct effect on the testicular function and spermatogenesis. Those mechanisms may involve the hormonal control of spermatogenesis or via direct effect upon the germ cells and Sertoli cells of the seminiferous epithelium. Such alterations in the spermatogenetic capacity in the male may lead to infertility and/or production of mutated spermatozoa which may subsequently cause an adverse pregnancy outcome if the mutated spermatozoa were to fertilize an egg. Twenty-eight million men or 36% of the adult population individually smoke an average of 20 cigarettes per day in the United States. Although there is some evidence to the contrary, a number of studies have shown higher incidences of abnormal morphology (21, 22), decreased motility, and sperm density in men who smoke (23, 24). Furthermore, fluctuation in androgen and gonadotropin hormone levels have been documented in male smokers. Reproductive problems such as fetal loss traditionally have been associated with women, and reproductive research—including that dealing with the effects of tobacco—has centered on women. The growing realization of a paternal component of reproductive impairment suggests that studying men is also appropriate and important.

Effects on sperm parameters

Sperm density was reduced in smokers in several studies in which mean values for smokers and nonsmokers were reported. In general, density averaged 22% lower in smokers than in nonsmokers,

with the greatest reduction as much as 57%. Additional studies include evaluations of sperm motility. Of these, for the most part, a lower proportion of motile sperm was found among smokers, compared with nonsmokers. In these studies in which impairment was reported, the level of impairment averaged 20% lower motility in smokers (21, 28).

Other studies include evaluations of the proportion of sperm with normal morphologic features (21, 22, 25). The majority of these studies showed a lower proportion of such sperm among smokers, and the magnitude of the decrease averaged 17%. Of the four evaluations of the relationship of morphologic features with differing levels of smokers, two showed increasing levels of smoking associated with increasing levels of abnormally shaped sperm, and two showed no such association.

Most recently, severe changes in the number and the arrangement of the microtubules of the sperm axoneme were noted in a smoker when compared to a nonsmoker group of men (29). Under the conditions of this study, smoking severely affected the ultra structure of the flagellum and consequently the motility and progressive motility of the spermatozoa. In an additional study it was shown, for the first time, that exposure of spermatozoa to seminal plasma from smokers resulted in a significant reduction in sperm viability and possibly their fertilizing ability (30).

There is a clear indication that smoking results in fewer sperm, less motile sperm, and a lower proportion of normally shaped sperm. The perspective afforded by the literature as a whole varies with the conclusions of individual investigators, even those whose results support the existence of an effect. The pitfall of drawing faulty conclusions based on small numbers of subjects needs careful attention in future studies of sperm and in critically appraising such work.

Effects on hormonal parameters

There are also ample experimental data to support the acute and chronic adverse effects of smoking (especially nicotine exposure) on the hypothalamic/pituitary/testicular axis, showing effects on LH, testosterone, adrenal corticotropin hormone, growth hormone, thyroid stimulating hormone (TSH), and prolactin concentrations. Lower testosterone and

higher follicle stimulating hormone levels have been found in male smokers. It has been suggested that nicotine may suppress testicular and androgen production by altering Leydig cell function. Alternatively, it has been theorized that cigarette smoking may induce increased release of catecholamines from the adrenal medulla, leading to elevated levels in renal veins, retrograde flow along the internal spermatic vein in men with testicular varicoceles, culminating in seminiferous tubule damage (31). Smokers with varicoceles had a ten-fold greater incidence of oligospermia as compared to non-smokers with varicoceles and a five-fold greater incidence of oligospermia as compared to smokers without varicoceles. These animal and human experimental data support the epidemiologic observation of male smokers' alterations in sperm morphologic features, concentration, and motility and give plausibility to the suggestion that cigarette smoke is directly or indirectly toxic to spermatogenesis.

Smoking and impotence

Recent results generated in our facilities indicate that men that smoke can suffer from some degree of impotence or reduction in their sexual frequency. In these preliminary studies, nonsmoker men were found to experience higher sexual frequency (sexual intercourse/month) than men who smoked. The 33-year-old nonsmoker men married to 29-year-old women were compared to 31-year-old men who smoked at least 30 cigarettes per day for a duration of 11.6 years and were also married to 29-year-old women. The 132 nonsmoker men had intercourse (sexual frequency) 11.6 ± 2.7 times per month as compared to the 158 smoker men with a frequency of only 5.7 ± 1.8 times per month. When the sexual satisfaction was rated on a scale from zero to 10 (10 being maximal sexual satisfaction) by their female sexual partners, again, the nonsmoker men scored higher (8.7 ± 1.1) as compared to that of the smokers (5.2 ± 1.1). Although these data are somewhat preliminary, the biological trends established in this study are of great significance. At the present time, the mechanism of action of cigarette smoking on the sexual habits of these men is not completely understood, although it is possible to postulate that smoking could be acting at different levels in the

body to diminish the smokers' sexual frequency and desire. One possible mechanism could be the direct influence of cigarette smoking on these men's general health, which could subsequently affect their sexual desire; another probable mode could be through the overall direct effect that smoking has on the sex hormones and their influence on the sex drive and functionality of their reproductive system.

Effects on DNA stability

Evidence suggests that tissues that turn over rapidly, including sperm produced by the testes, may be particularly sensitive to the mutagenic and carcinogenic materials found in cigarette smoke (32). Smokers have increased numbers of sister chromatid exchange in peripheral lymphocytes and increased numbers of covalent deoxyribonucleic acid (DNA) adducts in placentas, compared with nonsmokers (33, 34).

A solid body of experimental evidence suggests that exposure to nicotine, cigarette smoke, and/or polycyclic aromatic hydrocarbons is able to produce testicular atrophy, block spermatogenesis, and alter sperm morphologic features in experimental animals (10). These effects may be seen in a time-dependent and dose-dependent fashion. Cigarette smoke condensates have been demonstrated to possess compounds that are able to produce DNA mutations, either directly or after metabolism, by enzyme systems similar to those found in rodent and human gonads.

MODE OF SMOKING ACTION ON MALE REPRODUCTION

On the basis of all data available, the mode by which smoking may affect sperm parameters is believed to be via three mechanisms. First, via a reduction in testosterone concentration in testicular tissues as a consequence of impaired Leydig cell function, which may result in disturbed spermatogenesis and which subsequently may affect other testosterone dependent organs, such as the epididymis. Furthermore, such a disturbance could be most severe at the level of spermiogenesis as suggested by other testicular stresses which may explain the disorder in morphologic characteristics

observed in several studies. Second, spermatogenesis may be affected by direct effect of nicotine on testicular tissue. During smoking and inhalation of cigarette smoke, rapid absorption of volatile components such as carbon monoxide and nicotine occurs, and over 90 percent of the nicotine inhaled may be absorbed. Third, spermatogenesis may be interfered with by the catecholamines which are found to be secreted in greater concentrations by the adrenal medulla at the time of smoking or exposure to nicotine.

CONCLUSIONS

Smoking presents a challenging dilemma for the physician and the smoking public. Day by day, data generated from studies strengthen the medical case against smoking, which is now proven beyond a reasonable doubt. At least 434,000 Americans die each year of smoking-related diseases. Over 50,000 studies of its health effects show that smoking is harmful. In this article, it was the intent to review increasing epidemiologic evidence that smoking adversely affects female and male fertility. The biologic plausibility and mechanisms of action of cigarette smoke and its components on these reproductive processes were presented. The argument against smoking holds true for anyone wishing to conceive, but it is particularly imperative for individuals (male or female) having difficulty in conceiving; or females having prior miscarriages. Of those women smokers who are fortunate enough to conceive, all must be counseled to stop smoking, or otherwise risk exposing their fetus to the effects of the fetal tobacco syndrome. Because of the overwhelming evidence of the negative effects of smoking on general health and specifically on reproductive processes, now, growing numbers of physicians are getting involved. Several studies over the last decade have given evidence that more people are likely to stop smoking if their physician advises them to, as compared with making the decision to stop smoking on their own. In surveys, most smokers also say that being told to quit smoking by their physician would be the most effective way to persuade them to give up the habit.

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