



Drug: A Major Cause of Infertility in Male

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ABSTRACT: Approximately 50% of known causes of primary infertility are attributed to male factor; while rapid progress is been made in improving fertility in women, the treatment of male infertility has remained very unsatisfactory. For healthy young couples, the probability of getting pregnancy per a reproductive cycle is about 20% to 25%. Their cumulative probabilities of conception are 60% within the first 6 months, 84% within the first year, and 92% within the second year of regular fertility-focused sexual activity. There are different causes of infertility, some causes are more common in some countries than others, such as pelvic inflammatory diseases (PID) and sexually transmitted infections (STI) in Africa. Some personal habits are considered risk factors for infertility, such as excess alcohol intake, cigarette smoking and other forms of drug abuse. Hence this research work is aimed at revealing that drugs such as antibiotics, alcohol, tobacco products, illicit drugs and certain medications can limit the chances of men having children in the present time, or even far into the future.

Keywords: Drug Abuse, Infertility, Reproduction, Sperm, Morphology

INTRODUCTION

Infertility or sterility is defined as the total inability to reproduce (Nieschlag, 1997), infertility has an element of time in its definition. It can be stated as failure to conceive after one year of regular unprotected intercourse with the same partner (Martini, 1991). Infertility can be classified into primary and secondary, A male without biological offspring can be said to have "primary infertility," whereas a male who is unable to impregnate his partner but who already has biological children is referred to as having "secondary infertility" (Sigman et al., 1997).

Infertility affects 13% to 15% of couples worldwide (WHO, 1983). The prevalence of infertility varies widely, with developed countries having less and more in the developing countries, where the needed resources for investigation and treatment are not available (Cates W et al., 1985). It has been estimated that in the United Kingdom, one in six couples would complain of infertility (Zargar et al., 1997)

Approximately 50% of known causes of primary infertility are attributed to male factor (Yates et al., 1989); while rapid progress is been made in improving fertility in women, the treatment of male infertility has remained very unsatisfactory (Zarate et al., 1973). This situation is partly due to paucity of our knowledge regarding the factors controlling spermatogenesis in man. The role of testosterone and gonadotropins in the maintenance of spermatogenesis is not clearly understood (Steinberger, 1971), neither is the etiology of male factor infertility easily defined (Reijo et al., 1996).

For healthy young couples, the probability of getting pregnancy per a reproductive cycle is about 20% to 25%. Their cumulative probabilities of conception are 60% within the first 6 months, 84% within the first year, and 92% within the second year of regular fertility-focused sexual activity (Remah, 2010). There are different causes of infertility (Poppe and Velkeniers, 2002; Razzak and Wais, 2002; Ikechebula et al., 2003). Some causes are more common in some countries than others, such as pelvic inflammatory diseases (PID) and sexually transmitted infections (STI) in Africa (Araoye et al., 2003). Some personal habits are considered risk factors for infertility, such as excess alcohol intake (Tolstrup et al., 2003) and cigarette smoking (Saleh et al., 2002).

There are many epigenetic factors which have been well-known as potential causes of male infertility. Environmental pollutants as well as modern-day social habits such as smoking, consumption of alcohol and drug taking have all been associated with male subfertility (Marshburn et al., 1989; Schlegel et al., 1991; Sharpe and Skakkebaek, 1993; Tas et al., 1996), while others are genetically predisposed to being subfertile (Reijo et al., 1996), certain chronic systemic illnesses are known to impair fertility potential and some bacterial or viral diseases which may or may not be associated with the male reproductive tract may also adversely affect semen parameters (Hargreaves et al., 1998), permanent azoospermia and sterility is a common side effect of cancer chemotherapy in humans (Schilsky, 1980), some may be caused by herbal concoction. This research work is aimed at revealing that drugs such as antibiotics, alcohol,

tobacco products, illicit drugs and certain medications can limit the chances of men having children in the present time, or even far into the future.

DRUGS THAT CAN ALTER THE MALE REPRODUCTIVE SYSTEM

Drug is defined by pharmacologists as any substance that, by its chemical nature, alters structure or function in the living organism (Alhassan et al., 1991).

Drugs are chemical components put together at a particular proportion, for a specific purpose, the route administration includes; orally, intra muscular, intra venous, topically, inhalation etc. It is important for men to be aware of the effect of drug abuse on their fertility. Depending on the drug and the level of use, the negative effect on sperm production and morphology has different intensities and durations. Apart from the severe effect of drugs on sperm production and morphology; they can also affect erectile function and libido.

Antibiotics: Antibiotics such as amoxicillin and tetracycline are commonly prescribed for a multitude of conditions (Hargreaves et al., 1998), in most cases these antibiotics are used in treating infections that are unrelated to infertility. In addition, some patients requiring assisted conception occasionally show evidence of infection on the male reproductive tract. The antibiotics co-trimoxazole and erythromycin are routinely used by urologists and fertility specialists to treat bacterial infections occurring prior to in-vitro fertilization (IVF) treatment, or when high concentrations of leukocytes are present in the semen of these patients, irrespective of microbial evidence of infection. Patients on a course of antibiotics often demonstrate below-average semen parameters. While in some instances this may be caused by the infection itself, it is likely that the antibiotics have a direct effect on sperm function (Hargreaves et al., 1998). Studies also have shown that antibiotics considerably impair sperm motility characteristics (Gilman et al., 1985; White, 1954; Schlegel et al., 1991) and functional integrity of mature sperm (Andrews and Bavister, 1989). Perfloracin produced toxic effect on testicular function in animals (Adikwu and Bramaifa, 2012) Table 1. Infact treatment with appropriate antibiotics may suppress the antibody response either through a direct immunosuppressive effect of the antibiotic or through a decrease in the antigenic load of killed sperm secondary to eradication of the infection (Greskovich et al., 1991).

Alcohol: Studies show that a man's drinking patterns before conception of a child can influence the health of future children (Hegedus et al., 1984). The use of alcohol by men prior to conception may result in physical problems in offspring which may not show up until the child is several years old. Other effects are low sperm count, poor sperm motility and poor sperm morphology. Studies of male offspring of alcoholics have provided

evidence of specific cognitive impairment as a result of chronic alcohol consumption (Hegedus et al., 1984, Tarter et al., 1989, Yen and Jaffe 1991). Sons of early onset alcoholics were impaired on tests measuring attention and verbal intellectual capacity compared with control subjects, Cicero (Cicero et al. 1994) offered three possible mechanisms to explain the effect of paternal alcohol consumption on offspring (Yazigi et al., 1992), alcohol could directly affect the characteristics of sperm by causing genetic mutations; (Yazigi et al., 1991) sperm could be subjected to a selection process, such that only a specific sperm population is functionally intact following prolonged alcohol exposure; and (Pichini et al., 1994) alcohol consumption could alter the chemical composition of semen so as to influence the activity of ejaculated sperm. Numerous studies have indicated that alcohol abuse in men can cause impaired testosterone production and shrinkage of the testes (i.e., testicular atrophy) (Adler 1992). Those changes can result in impotence, infertility, and reduced male secondary sexual characteristics. National institute of alcohol abuse and alcoholism (1994) published that in men; alcohol metabolism contributes to testicular injury and impairs testosterone synthesis and sperm production.

Tobacco: Tobacco is a preparation of the nicotine-rich leaves of an American plant called *Nicotiana tabacum*. It is cultivated in warm regions and it is a valuable cash crop in the USA, Cuba and China. It can be consumed, used as a pesticide and in the form of nicotine tartrate used in some medicine (Wikipadia, Retrieved, 2012).

Tobacco use and male fertility has always been controversial (Kumar and Gautam, 2006), reports suggest that tobacco use primarily through may be detrimental to sperm function and there have also been reports to contradict this facts (Sofiktis et al., 1995; Kunzie et al., 2003; Tummer et al., 2002; Vogt et al., 1986). Chewing of tobacco has been reported to cause decline in sperm morphology from normal to abnormal and oral cancer (Kumar and Gautam, 2006). Tobacco smokers are 60% more likely to be infertile than non-smokers (Regulated Family Services, 2009), incidence of impotence is approximately 85% higher in male smokers compared to non-smokers (The Tobacco Reference Guide, 2006). It is the key cause of erectile dysfunction (Peate, 2005; Korenman, 2004), this is due to the fact that it enhances arterial narrowing (Kendirici et al., 2005).

Cannabis (Marijuana): The use of cannabis for both recreational and medicinal purposes has long been a tradition dating thousands of years (Brecher, 1972; Mechoulam, 1986). Cannabis preparations are largely derived from the female plant of *Cannabis sativa* (Kalant et al., 1988). Cannabis is also known as marijuana, the name which is from the Mexican Spanish marihuana (Company, 2007). Chemically, the major psychoactive compound in cannabis is delta-9-tetrahydrocannabinol

(Δ^9 -THC); it is one of 400 compounds in the plant, including other cannabinoids, such as cannabidiol (CBD), cannabinol (CBN), and tetrahydrocannabivarin (THCV), which can produce sensory effects unlike the psychoactive effects of THC (Fusar-Poli et al., 2009).

Cannabis may be smoked in a "joint", which is the size of a cigarette, or in a water pipe. Tobacco may be added to assist burning. Smokers typically inhale deeply and hold their breath to maximize absorption of THC by the lungs. Marijuana and hashish may also be eaten, but cannabis is mostly smoked because this is the easiest way to achieve the desired psychoactive effects (Hollister, 1986). THC to animals lowers testosterone secretion, impairs sperm production, motility, and viability, and disrupts the ovulatory cycle (Bloch, 1983). In the rhesus monkey, THC reduced testosterone levels by 65% (Smith et al., 1976). Reductions in testicular size have been observed in rodents (Dixit et al., 1974) and dogs with administration of cannabis extract. Degeneration of the seminiferous tubules may provide an explanation for this observation (Dixit et al., 1977) and is dose dependent, with lower doses showing no appreciable effect (Thompson et al 1973). Abnormal sperm morphology has been characterized in rodents exposed to marijuana smoke (Huang et al., 1979) or Δ^9 -THC (Zimmerman et al., 1979) for a 5-day period. In vitro studies have demonstrated that cannabinoids directly inhibit Leydig cell function (Dalterio et al., 1977). In humans, effects on sperm production and morphology have also been observed. Dose-related oligospermia has been observed in chronic users (Kolodny, 1974; Issidorides, 1979).

Steroids: Anabolic steroids are the man-made derivatives of the male sex hormone testosterone (Bhasin et al., 1996; 2001). Anabolic steroids were reportedly first used during World War II when they were given to German troops to enhance their aggressiveness. The first use in athletics was reported by the Russians in 1954. A team physician from the United States recognized their use at that time and in the late 1950s conducted tests of the drugs in American athletes. The use of anabolic steroids has become increasingly popular among athletes since that time (Haupt and Rovere 1984).

Steroids produce both masculinizing and tissue-building effects (Wadler and Hainline 1989) which accelerate training (Trager, 1988) and enhancing athletic performance. At first, anabolic steroids were used almost exclusively by weight lifters and shot-putters as well as hammer, discus, and javelin throwers. However, their use later spread to football players, swimmers, and other track-and-field participants. Today, the use of anabolic steroids by athletes has reached almost epidemic proportions (Wilson and Griffin 1980); however the severity of side effects is quite variable. It depends on several factors such as type of drug, dosage, duration of use and the individual sensitivity and response (Kuipers, 1998). The original medical applications of anabolic steroids were for breast

cancer, aplastic anemia, treatment of an gioneurotic edema, growth failure in young males, stimulating sexual development in hypogonadal males, and possibly for the treatment of osteoporosis, however, these uses are limited (Robert, 2012).

Steroids have been reported to cause testicular atrophy (Kuipers, 1998), decreased sperm count, impotency and transient infertility (Jay and Nicholas 2006), oligozoospermia and sometimes azoospermia (Schurmeyer et al., 1984), impairs the percentage of morphologically normal semen (Torres-Calleja et al., 2001).

Cocaine: For over a thousand years South American indigenous peoples have chewed the leaves of *Erythroxylon coca*, a plant that contains vital nutrients as well as numerous alkaloids, including cocaine (Altman et al., 1985). Cocaine increases alertness, feelings of well-being and euphoria, energy and motor activity, feelings of competence and sexuality. Athletic performance may be enhanced in sports where sustained attention and endurance is required. Anxiety, paranoia and restlessness are also frequent. With excessive dosage, tremors, convulsions and increased body temperature are observed (World Health Organization, 2004). Cocaine is a powerful nervous system stimulant (World Health Organization, 2004). Its effects can last from 15–30 minutes to an hour, depending on the route of administration (World Health Organization, 2007). Cocaine use is frequently linked with stimulated sexual behavior; increasing libido and sexual responsiveness. Animal studies with radio labeled indicate that the drug is deposited in genital and extragenital organs, including the epididymis and seminal vesicles (Yazigi et al., 1992). Animal studies have demonstrated that rats treated chronically with cocaine had a significant increase in spermatozoa with heads separated from tails and other anomalies (Abel et al 1989). In human studies, cocaine use has been associated with depressed sperm counts, low sperm motility, and an increase in numbers of abnormal spermatozoa (Bracken et al., 1990, Hurd et al., 1992). In vitro binding studies with radiolabeled cocaine have demonstrated that cocaine binds with high affinity to human spermatozoa, leading to the suggestion that sperm may act as a vector to transport cocaine into an ovum (Yazigi et al., 1991).

Opiates: It was reported from Iran that heroine increases infertility through decreasing the motility and viability of sperms. (Simin and Zahra, 2007). Heroin reduces sexual feelings, may decrease libido, cause erectile and ejaculatory dysfunction. High-dose methadone and Buprenorphine is well known to be associated with sexual dysfunction (Miran et al., 1980; Bliesener et al 2005; Palha and Esteves, 2002).

Chemotherapy: Permanent azoospermia and sterility is now recognized as a common side effect of cancer chemotherapy in humans (Schilsky et al., 1980). Treatment of lymphomas with combination chemotherapy

with or without radiation therapy (XRT) can result in long-term or permanent azoospermia (Pryzant et al., 1993).

Testicular exocrine function is even more affected by chemotherapy. The differentiating spermatogonia appear to be most vulnerable to the cytotoxic effects of chemotherapy (Meistrich, 1986). Previous studies have shown that the majority of patients with testicular germ cell tumours have reduced sperm counts at diagnosis (before chemotherapy) (Baker et al., 2005), and this will further deteriorate during treatment (Drasga et al., 1983;

Hendry, 1983; Fossa et al., 1985; Kreuser et al., 1986; Nijman et al., 1987), but it has been reported that duration and severity of the spermatogenic depression depends upon the dose and duration of chemotherapy and baseline testis function prior to therapy, and despite an early depression in spermatogenesis, a reasonable number of patients show recovery within 1–2 years after treatment with variable sperm counts in their ejaculates (Nijman et al., 1987; Costabile, 1993; Howell et al., 1999) Table 1.

Table 1. Summary of Drugs with Their Effects on the Male Reproduction System

Drug	Effect	Reference
Antibiotics	Impaired sperm motility, Decreased sperm count, Mature sperm malfunction, Gonadotoxic and Erectile dysfunction	Gilman et al., 1985; Hargreaves et al., 1998; White, 1954; Andrews and Bavister, 1989; Yanagamachi 1994; Crotty et al., 1995; Nudell et al., 2002
Alcohol	Low sperm count, Low motility, Morphological alteration, Genetic mutations, Physical problems in offspring, Increase leukocyte in seminal fluid, Erectile dysfunction, Gonadotoxic and Gonadotoxic	Hegedus et al., 1984; Tarter et al., 1989; Cicero et al. 1994; Yazigi et al., 1992; Pichini et al., 1994; 1989, Yen and Jaffe 1991; Close et al., 1990; Martini et al.; 2004, Nudell et al., 2002
Marijuana and Cannabis	Abnormal sperm morphology, Reduce sperm production and motility, Alter morphology, Oligospermia, Increase leukocyte in seminal fluid and Gonadotoxic	Huang et al., 1979; Kolodny, 1974; Issidorides, 1979; Close et al., 1990; Fody and Walker, 1985; Nudell et al., 2002
Tobacco	Morphological alteration, Impotency, Erectile dysfunction, Alter spermatogenesis, Lower sperm penetration, Gonadotoxic and Increase leukocyte in seminal fluid	Kumar and Gautam, 2006; The Tobacco Reference Guide, 2006; Peate 2005; Korenman, 2004; Reina et al., 2007; Close et al., 1990; Saleh et al., 2002; Nudell et al., 2002
Steroids	Testicular atrophy, Decreased sperm count, Oligozoospermia, Azoospermia, Impotency and Alter morphology	Kuipers, 1998; Jay and Nicholas 2006), (Schurmeyer et al. 1984), Nudell et al., 2002, Torres-Calleja et al., 2001.
Cocaine	Reduce sperm count, Physical problems in offspring, Increase in spermatozoa with heads separated from tails, Low sperm motility, Gonadotoxic and Increased numbers of abnormal spermatozoa	Abel et al 1989; Bracken et al., 1990; Hurd et al., 1992; Brecken et al., 1990; Yazigi et al., 1991; Nudell et al., 2002
Heroin	Impaired sperm quality, Gonadotoxic, Erectile dysfunction	Chan et al., 1979.; Nudell et al., 2002
Chemotherapy	Permanent azoospermia	Schilsky et al., 1980; Pryzant et al., 1993; Nudell et al., 2002

DISCUSSION

Since research shows that certain drugs taken by men affect their fertility, it will be of great benefit for individuals to discuss any drug that they have been taking with and their potential impact on fertility with physician, while illicit drugs; cigarette and alcohol should be avoided. To protect men from potential reproductive hazards, further investigation is recommended to determine the effects of more drugs on sperm at various

dose ranges as this can lead to a healthier generation of men.

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