Review Article

Does paternal occupation and lifestyle affect embryo quality?

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Summary

Man is exposed to numerous exogenous as well as environmental chemicals through various routes. During the past 50 years, the rapid expansion of chemical industries in both the developed and developing countries has resulted in release of a plethora of xenobiotics into the environment. These alien molecules, including pesticides, herbicides, cosmetics, preservatives, cleaning materials, municipal and private wastes, pharmaceuticals and industrial by-products enter our bodies in a variety of forms. Exposure to chemical contaminants, which are estrogen mimics and endocrine disruptors, has been implicated as one of the possible factors contributing to the increasing male infertility. Environmental exposures of the father to the toxicants are linked to spontaneous abortion and / or congenital abnormalities in their off spring. Where the husbands are employed in an industry (chemical dyes, plastics, formaldehyde, etc.), their wives have about 90% greater risk of stillbirth. Exposure of the fathers to polyvinyl alcohol and benzene is associated with about 50% increase in preterm delivery. Men working in the agriculture industry face more than ten-fold increased risk of having infertility in comparison to those in other jobs. Lifestyle factors, like tobacco smoking, are deleterious to reproduction. Fathers who are "regular" drinkers have babies who weigh less than babies whose fathers are only "occasional" drinkers**.** Monosodium glutamate (MSG), a common flavor- enhancer added to foods, has been found to cause infertility problem in the offspring of MSG-treated male rats which had shorter body length and reduced testis weight. There are many evidences suggesting that parental chemical exposure to chemicals such as toluene, n-hexane, xylene, ethyl acetate, carbon disulfide, ethylene glycol ethers and their acetates, styrene, trichloroethylene, tetrachloroethylene, 1,1,1-tri-chloroethane, bisphenol, phthalates, etc., can potentially produce adverse effects on the progeny, particularly decline in embryo quality. Studies need to be focused on these occupational groups, by studying specific occupational exposure assessment, which should include not just the case history (with all its potential biases), but also results of environmental and biological surveillance (past and present data). Also, the causative agents need to be identified and appropriate preventive measures taken.

Key words: Congenital abnormalities, embryo quality, environmental toxicants, lifestyle, paternal occupation

Introduction

The global explosion of human population might suggest that everything is fine with human reproduction. However, reproductive failures, fetal abnormalities and birth defects in children are much more common in the recent times than earlier. The cause of any disruption in reproduction could be the result of genetic and / or physiological events that occur in any one or in some combination of the mother, the father and the child. Alteration in paternal chromosomal configuration might be associated with pathologies in the offspring, including cancer and infertility (Aitken and Krausz, 2001). Men with severe oligo-asthenozoospermia have higher incidences of synaptic anomalies and produce abnormal spermatozoa and that, in turn, would bring about higher episodes of abnormal embryos caused through chromosomal abnormalities (Egozcue et al., 2005). Evidences show that the occupation of the parents has some connection with etiology of Down's syndrome (Olshan et al., 1989).

Historically, the picture in this regard is less clear for the father. Evidences suggest that the male parent could be the source of detrimental effects on the genetic make-up and health of the embryo and, therefore, the child. Geneticists have estimated that about 40% of the cases of human infertility are due to male factors (Gangrade, 2003). Sperm DNA damage does not impair fertilization of the oocyte or completion of the first 2 to 3 cleavages, but can

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block blastocyst formation through induction of apoptosis (Fatehi et al., 2006).

During the past 50 years, the rapid expansion of chemical industry in both the developed and developing countries has resulted in the release of a plethora of xenobiotics (molecules foreign to biological systems) into the environment (Klaassen and Casarett, 2001; Robaire and Hales, 2003). These alien molecules have been shown to cause havoc to human health. Reproduction or development can be affected by exposure to a wide variety of agents including pesticides, herbicides, cosmetics, preservatives, cleaning materials, municipal and private wastes, pharmaceuticals, industrial by-products, poly-chlorinated biphenyls (PCBs), phytoestrogens such as isoflavones, heavy metals (*e.g.,* organic mercury, cadmium and lead), chlorination disinfectant by-products in water, organic solvents, poly-aromatic hydrocarbons, particulate air pollutants, etc. (Joffe, 2003).

The role of paternal factor in early human embryogenesis is gaining a lot of attention in view of the adverse outcomes of intra-cytoplasmic sperm injection (ICSI) for the management of male infertility. Spermatozoa have a role in the embryo quality, even in the early stages of development, which limit the success rate of IVF procedures (Gao et al., 2006). Paternal influence on embryonic development occurs as early as fertilization. Incorrect formation of the spermatozoon due to centrosome defects and abnormal concentrations of any of the components involved in the egg activation process can lead to failure of cleavage of the zygote or during the subsequent cell cycles (Menezo, 2006). Chromatin damage precedes the loss of fertilization potential and poor embryo quality (Cebesoy et al., 2006). Data from epidemiological studies suggest that occupation of male parents such as in welding, painting, automobile mechanic or firefighting, which involve exposure to metals, combustion products, solvents and pesticides, may be associated with an increase in spontaneous abortions, birth defects and childhood cancer (Olshan and Mattison, 1994). Exposure to ionizing radiation, welding fumes, heavy metals such as lead, organic solvents, pesticides, cancer chemotherapeutics, alcohol consumption and cigarette smoke have been evaluated for male-mediated adverse effects on pregnancy outcomes. The possibility that offspring conceived through assisted reproductive technologies due to male factor infertility might be at increased risk of adverse outcomes has been assessed (Hales and Robaire, 2001).

This review focuses on the quality of embryo, which is affected by male parent's exposure to environmental toxins at their workplace or in the environment and/or lifestyle.

Paternal exposure to environmental toxicants

Paternal exposure is anything which the father of the baby is exposed to before conception or during his partner's pregnancy. Examples include recreational drugs, alcohol, cigarette smoke, chemotherapy or radiation therapy, environmental or occupational exposures and prescription or across-the-counter medications. Bhatt (2006) found that toxic substances in the environment / workplace / lifestyle (like disinfectants, pesticides, insecticides, heavy metals, smoke, automobile gas emissions, nuclear dust and organic solvents) may cause teratogenicity, endocrine disruption, abortion, stillbirth, cancer and / or fetal disturbances.

Free radicals

All aerobic cells are routinely exposed to certain levels of reactive oxygen species (ROS) that constitute aspects of free radicals. Free radicals are defined as "any atom or molecule that possesses one or more unpaired electrons" (Warren et al., 1987). The primary suspects in the link between environmental assaults and infertility are free radicals, also called pro-oxidants. These are unstable molecules, usually containing oxygen, that are released as by-products of many natural biochemical processes in the body. Infections, chemicals, and other environmental assaults can result in production of high levels of free radicals. The free radicals can affect the genetic material. Spermatozoa are particularly vulnerable to the damaging effects of this oxidation process. The ROS affect the integrity of DNA of spermatozoa and, hence, have great potential to contribute to chromosomal abnormalities in embryos (Wyrobek et al., 1994).

Heavy metals

Occupational exposure to heavy metals such as lead and mercury is prevalent in metal foundries, battery plants, metal scrapings, automobile repair and service, glass and pottery industries, pesticide production and manufacture of electrical supplies. A tendency towards reduced semen quality has been recorded in men exposed to heavy metals (Bonde, 1993; Irgens et al., 1999). Epidemiological studies have indicated that paternal exposure to heavy metals such as lead and mercury may be associated with an increased risk of spontaneous abortion (Anttila and Sallmen, 1995) and decreased fertility (Sallmen et al., 2000b). In an another study, it was suggested that lead exposure among fertile couples could

be related to not begetting a child rather than delay of pregnancy (Sallmen et al., 2000a). Increased risk of spontaneous abortion was found in cases of pregnancies in which the father worked as a stainless steel welder, whereas pregnancies in which the father was a welder of other metals was not at any increased risk (Hjollund et al., 2000).

An extensive study carried out in 3702 Danish metal workers exposed to welding showed that the probability of their fathering a child slightly decreased with every year of exposure to welding fumes (Bonde et al., 1990). This effect is especially true for those involved in mild steel welding as compared to stainless steel welding. It was hypothesized that spermatogenesis is decreased in welders either due to exposure to hexavalent chromium during welding or chronic exposure to radiant heat and fumes containing hexavalent chromium. Hexavalent chromium has been found to be mutagenic and, interestingly, when administered to a male rodent, it increased the incidence of lung tumors in its offspring (Anderson et al., 1994).

Ionizing radiation

Increased risk of stillbirth with increasing preconceptional exposure to ionizing radiation was reported for fathers working at the Sellafield nuclear site in Cambria, United Kingdom (Parker et al., 1999). A subsequent study carried out by Doyle et al. (2000) based on a large cohort of nuclear industry workers in the United Kingdom, found no evidence of a link between exposure to low level ionizing radiation before conception and an increased risk of adverse reproductive outcome among men working in the nuclear industry. Thus, a link between preconceptional exposure to low level ionizing radiation and increased risk of male-mediated adverse reproductive outcomes remain controversial.

Organic solvents

Several organic solvents to which men are occupationally exposed have been studied for their potential adverse effects on progeny outcome (Hales and Robaire, 2001). These include toluene, n-hexane, xylene, ethyl acetate, carbon disulfide, ethylene glycol ethers and their acetates, styrene, trichloroethylene, tetrachloroethylene and 1,1,1-tri-chloroethane. Wives of men exposed to perchloroethylene in the dry-cleaning industry (Eskenazi et al., 1991) and ethylene glycol ethers in semiconductor manufacturing had slightly prolonged gestation period (Correa et al., 1996). A study conducted in Finland, in which male workers were monitored for their organic solvent exposure, found an increased duration of pregnancy (Sallmen et al., 1998). Exposure of the father to polyvinyl alcohol and benzene was associated with about 50% increase in the incidence of preterm delivery (Savitz et al., 1989). Pregnancy outcomes among wives of male chemical workers who had high level exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin reflected enhanced risk of low birth weight or preterm delivery and birth defects through the paternal route (Lawson et al., 2004).

Analysis of semen quality in styrene-exposed men revealed a decline in sperm density, total sperm count and the proportion of sperm with normal morphology (Kolstad et al., 1999b). However, a multi-center study of European workers exposed to styrene in the reinforced plastic industry found no detrimental effect of styrene exposure on male fecundity (Kolstad et al., 1999a).

Pesticides and other polychlorinated hydrocarbons

Men working in the agriculture sector are at more than ten-fold increased risk of infertility in comparison to those in other occupations (Strohmer et al., 1993). Exposure of the father to pesticides during the preconception period or prior can also increase the risk of having anencephalic child (Lacasana et al., 2006). Men engaged in agricultural practices adopting use of pesticides are at increased risk of fetal death from congenital anomalies, particularly where pesticides are used massively (Regidor et al., 2004). There is serious concern about the effects of pesticides in the male parent on reproduction and the health of children born to him. Though, results from a multi-center study in Europe of paternal pesticide exposure during the spraying season found no effect on semen quality or fertility, as assessed by time to pregnancy (Thonneau et al., 1999), paternal pesticide exposure has been otherwise reported to decrease fertilizing ability of sperm in those seeking IVF treatment (Tielemans et al., 1999). Pre-conceptional paternal pesticide exposure is reportedly associated with an increased risk of acute lymphoblastic leukemia in children aged 0–9 years (Infante-Rivard and Sinnett, 1999).

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is one of the most toxic man-made chemicals. A study conducted by Mocarelli et al. (2000) reveals that a population exposed to TCDD was linked with lowered male to female sex ratio in offspring whose parental exposure was through paternal route rather than maternal. Published reports suggest that there may be an increased risk of fetal death among the progeny of Vietnam War veterans who

were exposed to these chemicals (Arbuckle and Sever, 1998). However, the relative risk of fetal death ranged from 0.87 to 3.2, and no causal relationship has been established to date. Some studies have attempted to assess the level of exposure to chlorinated hydrocarbons. In addition to the effects on sperm maturation in the epididymis, they may affect primordial germ cells in the embryo. *In utero* exposure of hamsters to polychlorinated biphenyls and polychlorinated dibenzofurans through contaminated cooking oil resulted in sperm with increased abnormal morphologies, reduced motility and reduced capacity to penetrate the oocytes (Guo et al., 2000). In a case-control study of paternal employment as a fire fighter and the risk of birth defects among offspring, when compared with policemen, firemen had increased risk of having children with ventricular as well as atrial septal defects (Olshan et al., 1990).

Although, reports show an association between paternal exposure to pesticides and birth defects (nervous system anomalies, cardiovascular anomalies, oral clefts, hypospadias, epispadias, musculoskeletal anomalies and non-specific anomalies (Lin et al., 1994), negative findings have also been reported by some investigators especially in the case of men engaged in agriculture and exposed to pesticides, on the basis of which it was suggested that exposure to pesticides is not associated with the specific anomalies and not at all with birth defects (Garcia et al., 1999).

Dimich-Ward et al. (1996) conducted a nested case-referent study within a cohort of 9512 fathers who had worked for at least 1 year in saw mills. Expert evaluators were asked to estimate the hours of exposure, applied to specific time windows before birth, in which chlorophenate (a wood preservative) was used. It was reported that offspring of fathers with a cumulative exposure were at increased risk of developing congenital anomalies of the eyes and genital organs. Fathers with higher cumulative exposure during the three months period before conception had a 5.7 times greater risk of having infants with congenital cataracts.

Anticancer drugs

Decrease in fertility to the extent of about 60% has been found in men who had undergone chemotherapy for cancer with alkylating agents (Byrne et al., 1987). It was suggested that the infertility observed in humans after radiation and chemotherapy may be due to failure of differentiation of spermatogonia rather than death of stem cells. Fertility may be restored by hormone treatment (Meistrich, 1998). Paternal exposure to chemotherapeutics may have adverse effects on offspring. In the rat, chronic low-dose paternal exposure to the anticancer drug, cyclophosphamide, increased pre- and post-implantation loss and malformations, disrupting embryo development and dysregulation of zygotic gene activation (Hales et al., 2005). Epidemiological studies have failed to demonstrate any increase in the risk of malformations or childhood cancer in the children of men who survived after cancer treatment (Byrne et al., 1998; Byrne, 1999). In such studies, termination of exposure to chemotherapeutic agents usually occurs well before conception is attempted. Therefore, these studies had tested only the long-term consequences of such exposures on the quality of male germ line stem cells. Animal experiments have produced clear evidence that paternal exposure to cancer therapeutic agents can bring about adverse effects on the offspring (Robaire and Hales, 1999; Trasler and Doerksen, 1999; Brinkworth, 2000). There appears to be little risk of fathering abnormal progeny after a prolonged period of discontinuation of drug use.

Lifestyle factors

Lifestyle factors including cigarette smoke, alcohol and caffeine have been projected as affecting male reproductive health. Whereas, in the earlier years the focus was on semen quality and/or fertility, in the recent times the emphasis is on direct adverse effects on chromatin of sperm due to the concern that the damage, thus induced could be transmitted to offspring causing transgenerational health hazards (Robbins et al., 2005).

Smoking

Tobacco smoke is deleterious to reproduction. Benzo[*a*]pyrene (B[*a*]P) is a potent carcinogen in cigarette smoke. Its reactive metabolite adducts with DNA, which can result in mutations (Zenzes et al., 1999). This can result in both male and female infertility. Women who smoke, reportedly, have lower estrogen and progesterone levels, poor LH surge (causing irregular menses and ovulation), longer time to conceive, increased risk of miscarriage, bleeding during pregnancy, babies of low birth weight during IVF and earlier menopause. Male smokers have been shown to have decreased sperm counts, impaired sperm motility, more abnormal sperm and reduced testosterone levels; they can potentially contribute to congenital abnormalities and asthma in their children. Heavy paternal smoking may increase the risk of childhood cancer in the offspring (Ames et al., 1994). According to a report, heavy smokers had 19% lower sperm counts than non-smokers (Ramlau-Hansen et al., 2007). Ji et al. (1997)

found that the more a man smokes prior to his wife's conception, greater will be the risk the child will have for developing cancer by the age of five years.

Alcohol

Fathers who consume alcohol regularly have babies who weigh one-third a pound higher than babies whose fathers are only occasional drinkers (Abel, 1994). Alcohol use in males can affect spermatogenesis and/or sperm physiology and may even cause impotence. It is reported that 75% of children with fetal alcohol syndrome have fathers who were alcoholics (Little and Sing, 1986). Although, paternal alcohol consumption has been shown to affect the growth and behavior of the offspring, the mechanisms underlying these effects still remain to be elucidated. Alcohol-induced reduction in cytosine methyltransferase mRNA levels may reflect altered genomic imprinting caused by reduced DNA methylation, which in turn may lead to the expression of normally silent paternal alleles (Bielawski et al., 2002).

Recreational drugs

Cocaine exposure of males before the wife conceives is linked to abnormal development in the offspring, since cocaine can bind with high affinity to human spermatozoa. Therefore, sperm may act as a vector of cocaine transport to the ovum (Cone et al., 1996). Use of methamphetamine, cocaine and marijuana is associated with increased risk of a variety of birth defects affecting specific organ systems (Forrester and Merz, 2007).

Merijuana, containing the chemical $^{\Delta 9}$-tetrahydrocannabinol (THC), may be directly toxic to the egg. The THC is structurally similar to testosterone and binds to the receptors to which testosterone should bind. A cardiac birth defect is attributable to paternal use of marijuana (Wilson et al., 1998).

Monosodium glutamate (MSG), a common flavor-enhancer added to foods like accent, flavored potato chips, Doritos, cheetos, meat seasonings and many packaged soup was found to cause infertility in test animals. Male rats fed MSG before mating had less than 50% success rate (5 of 13 animals), whereas those not fed MSG had over 92% success rate (12 of 13 animals). Also, the offspring of the MSG-treated males had shorter body length, reduced testes weights and evidence of overweight at 25 days of MSG treatment (Pizzi et al., 1979).

Mobile phone

Radiation may harm sperm by damaging DNA, disrupting Leydig cells or causing shrinkage of the seminiferous tubules. Where men use their mobile phones for more than four hours a day, 40% drop in sperm motility and viability was reported (Behari and Kesari, 2006).

Conclusions

Although, positive associations between occupation of the male parent and his fertility and much beyond have been reported, several methodological limitations and some controversial findings preclude definite inferences on the relationship between paternal occupational exposures to toxicants and birth defects. In humans, length of time for an A_1 spermatogonium to develop into a structurally mature spermatozoon in the testis is 64 ± 4 days. Paternal exposures to toxicants before conception could theoretically contribute to the genetic defects in subsequent generations, expressed as congenital abnormalities in the offspring. A toxic agent can be retained in the body and gradually released over a long time after exposure. Paternal exposure at the workplace or lifestyle of the father can affect his fertility and/or the health of the offspring. Future studies should be focused on these specific occupational groups. Specific occupational exposure assessment should include not just the history (with all its potential biases), but also data /information on environmental and biological surveillance. The causative agents should be identified and appropriate preventive measures taken. In doing so the rate of birth defects associated with occupational exposure can be minimized.

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