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The effects of endocrine disrupting chemicals and genetic susceptibility on male infertility

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Abstract: Reproductive functions in men are impaired by many environmental, physiologic, and genetic factors. Xenobiotics (e.g. phthalate, alkylphenols, heavy metals, bisphenol A, ets) are the majority of the environmental factors which happen adverse effects with covalent interactions between intermediate metabolites and cellular macromolecules. The recent publications regarding infertility have stated that the substances do not only interfere human's normal hormone functions, but also cause the reproductive disorders such as testicular germ line cancer and prostate hyperplasia. The xenobiotics disrupting endocrine system are metabolized by the enzyme involved phase I (e.g., CYP_{450}) and II (e.g., *NAT*, *SULT*) enzymes. Most of the enzymes are polymorphic and genetic variants modify the enzyme catalytic activities. Thus, the effects of endocrine disrupting chemicals might vary between individuals. To date, the impact of genetic variability in the capacity of metabolizing xenobiotics has not been extensively studied on male reproductive functions. The relation between environmental and genetic factors and infertility has not been shown clearly. Therefore, we aimed to evaluate the interaction between endocrine disruptors' exposure and polymorphisms involved in genes (e.g., *DAZL, MTHFR, POLG)* in male infertility risk by data obtained from previously studies.

Key words: Polymorphism, endocrine disruptors, reproduction, testis, fertility

Introduction

US Environmental Protection Agency (EPA) has defined an endocrine-disrupting chemical as *"an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and regulation of developmental processes"* (Kavlock et al.

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1996). These chemicals are called as ″endocrine disruptors″ or ″endocrine disrupting chemicals″ because they (i) mimic natural hormones, (ii) inhibit the action of hormones, and/or (iii) alter the normal regulatory function of the endocrine systems (Sikka & Wang, 2008).

Today, it is distinguished some substances with endocrine properties according to their antioestrogenic, oestrogenic, antigestagenic and antiandrogenic effects. The effects of endocrine disrupting chemicals on reproductive organs have not been shown for humans; however, some studies reported exposure to endocrine disruptors might alter human fertility (Dallinga et al. 2002; Pflieger-Bruss et al. 2004; Tielemans et al. 1999).

In the past years, a plenty of studies about reproductive malfunction in male have been reported for both human and animals (Jørgensen et al. 2001). An increase of males suffering from cryptorchidism, hypospadia, testicular and prostate cancers, abnormal sexual development, alteration in pituitary and thyroid gland functions, reduced fertility and erectile dysfunction as well as immune suppression and neurobehavioral effects has been documented (Jackson 1988; Sikka & Wang 2008). It have been also suggested that exposing of endocrine disrupting chemicals in fetal life might affect a range of male reproductive disorders such as testicular cancer, cryptorchidism and hypospadia (Purdue et al. 2005).

Endocrine disrupting chemicals could be detoxified by enzymes included phase I and II enzymes (Guengerich 2001; Turesky 2004). The enzyme activities might modify the activation and/or detoxification of chemicals. Similarly, genetic variants could modify the enzymes' catalytic activities (Hart et al. 2008; Hirvonen 1999). Susceptibility to the effects of endocrine disrupting chemicals might vary individually due to polymorphisms in metabolizing enzymes. Therefore, in this review, it is pointed out the effects of the major endocrine disrupting chemicals and the genetic susceptibility on male reproductive system.

Male Reproductive System

It is necessary activation of specific pathway by hormones, especially androgen and anti-müllarian hormone in order to development of the male reproductive system. While testis formation itself does not depend on

hormone, most other aspects of masculinization are dependent on normal testicular hormone production. Moreover, development of testis cell depends on the local effect of hormones (Sharpe 2001). One of the most important hormones is androgen that is fateful in the normal development of Wolffian ducts differentiating into epididymis, vas deferens and seminal vesicles (Wilson 1978). Furthermore, testosterone is vital for meiosis and subsequent differentiation of spermatids (De Gendt et al. 2004). The action by testosterone exerts though sertoli cell, which express the androgen receptor, and have stimulation of the synthesis of various proteins and tropic factors in specific periods of spermatogenesis (Wang et al. 2009). Also, dihydrotestosterone, which is produced locally from testosterone by 5-α-reductase, is the most vital hormone for masculinization of external genitalia and prostate (Fisher 2004).

An endocrine-disrupting chemical can cause hazard in potential target sites in the male reproductive system. Hormone balance is fundamental for a normal development of male reproductive mechanism. Hormonal imbalance has been linked to masculinization anomalies, but few studies have been accomplished to relate early hormone imbalances to long term testicular function in terms of fertility. It is seen that anomalies in development of testes in fetal and neonatal life could have long-term results for sperm production. Especially prepubertal exposure to endocrine-disrupting chemicals is more likely to have negative effects on reproductive mechanism because of being development of blood-testis barrier in humans just before puberty (Latini et al. 2006; Sharpe 2001).

Potential Targets for Endocrine Disrupting Chemicals on Male Reproductive System

Male gonads -testes- play role in spermatogenesis and androgen production. Various compartments in testis are regulated by paracrine and autocrine systems that are under endocrine influences from the pituitary and hypothalamus. While approximately 80% of the testicular mass comprises of highly coiled seminiferous tubules in which spermatogenesis takes place, the remaining 20% is made up of leydig and sertoli cells, which have main role of establishing normal spermatogenesis (Sikka & Wang 2008).

Sertoli cells or ‘nurse cells’ which form a continuous and complete lining within the tubular walls that envelope the developing sperm in spermatogenesis. Sertoli cells are under the influence of follicle stimulating hormone (FSH) and inhibit control of the luminal environment. There are various functions of sertoli cells; such as providing nourishment for the developing sperm cells, secreting fluid which helps transportation of sperm into the epididiymis, releasing the hormone inhibit whose job is regulation sperm production. The important point is the differentiation of sertoli cells for establishment of normal spermatogenesis during puberty (Sikka & Wang 2008). Several studies suggest that sertoli cells are included in the progression of spermatogenesis through a kind of paracrine signals which regulate gene expression and metabolism of germ cells (Skinner 2005).

Leydig cells generate testosterone from cholesterol by enzymatic pathway and steroidal intermediates under the control of luteinizing hormone (LH) from pituitary. The cells are found in connective tissue between the seminiferous tubules (Sikka & Wang 2008).

Spermatogenesis which spans about 80 days in man and 40-50 days in the rodent is a chronological and complex process. During the period, the immature germ cells originate within extremely specialized spermatozoa in a cyclic manner (Mandl 1964). The producing of mammalian spermatozoa starts with engagement in a differentiation pathway of diploid cells called spermatogonium, which is found in the basal compartment of the seminiferous tubules (de Rooji & Russel 2010). After that, spermatogonia undergo lots of mitotic division for generating a large population of primary spermatocytes that produce haploid spermatids by two meiotic cell divisions and spermiogenesis defines as the transformation of spermatids within elongated flagellar germ cells capable of motility. The release of mature germ cells is named as spermiation (Sikka & Wang 2008).

The endocrine-related effects are based on altered hormone biosynthesis, storage and/or release, transport and clearance as well as altered hormone receptor recognition/binding, post-receptor activation and induction of oxidative stress (Sikka & Wang 2008). While some agents such as cyanoketone, ketazone, aminoglutethimide block specific enzymes in the streoidogenesis pathway, some fungicides have ability to inhibit estrogen biosynthesis by blocking aromatase activity converting testosterone

to estrogen in the testis (Manavathi & Kumar 2006). Moreover, steroid hormone-binding globulin and testosterone-estrogen-binding globulin, responsible for transporting of steroid hormones, are specialized carrier proteins. For instance, DDT analogs have a potential to induce hepatic oxidase activities *in vivo*, and it might lead to decrease transport of testicular androgen as a result of increased degradation (Bulger et al. 1978; Welch et al. 1971). Moreover, the blocking of action of LH receptor may alter the serum level of testosterone because steroid hormones do not store intracellularly within membranous secretory granules testosterone are released on activation of the LH receptor (Cooper et al. 1987). Intracellular receptors such as adrenal steroid, thyroid hormones, vitamin D, retinoic acid and membrane-bound receptors provide responses of hormones from respective target tissue through direct interactions and specific binding between natural ligand and its receptor is a fundamental step in hormone function. For example, some of the environmental agents such as chloredecone, some PCBs, alkylphenols can disrupt estrogen receptor function while DDT metabolite p, p′-DDE have ability to block testosterone-induced cellular responses *in vitro* (Kelce et al. 1995; Routledge & Sumpter 1997).

Also, it is known that oxidative stress is a condition which is associated with an increased rate of cellular damage induced by oxygen and oxygen-derived free radicals usually known as reactive oxygen species (ROS). For example, nitric oxide (NO) radicals have the ability of contributing poor sperm motility leading to infertility. Also, ROS might have play a role for induction of oxidation of critical sulpha-hydroxyl (SH) groups in proteins and DNA which will alter cellular integrity and function by increasing susceptibility to attack by toxicants (Rosselli et al. 1995).

Major Endocrine Disrupting Chemicals

- *Bisphenol A* (BPA) is widely used to prevent cavities in teeth, to prevent food contents from metal contact in metal cans, to contain foods in refrigerator shelving, baby bottles, water bottles, returnable containers, as plastic materials in micro-wave ovenware, artificial teeth, nail polish, compact discs, electric insulators. Also, it is used as a part of automobiles, certain machines tools, electrical appliances (Pflieger-Bruss et al. 2004).

BPA, stated as a prototypical non-steroidal estrogen, which is documented to lead to its effects by interrupting with both androgen production and function (Welshons et al. 2003). It has also been known to have a role to damage sertoli cell function by interrupting expression and localization of tight junction proteins (Li et al. 2009; Salian et al. 2009). In prenatal, perinatal and adult rodents exposing to BPA by oral or subcutaneous administration routes, it has been indicated to cause developmental genitourinary defects, declined epididymal weight, daily sperm production or increase prostate weight even though they has been exposed to doses lower than 50 mg/kg/day, which is usually acceptable daily intake (ADI) in humans (Richter et al. 2007; Salian et al. 2009; Williams et al. 2001). Also, when exposing to lower doses such as 50 mg/kg/day, 3 mg/kg/day of BPA by subcutaneous injection (in pubertal rats and mice) and 25 mg/kg/day of BPA by oral route (in adult mice), lower concentrations of epididymal spermatozoa and testosterone is observed for both administrations (Al-Hiyasat et al. 2002; Herath et al. 2004).

Among studies conducted on human populations, Takeuchi & Tsutsumi (2002) have published the first data on BPA. They have stated a positive correlation between exposing of BPA and total/free testosterone values in men and women. It has also indicated that occupationally exposed men have higher urinary BPA concentrations than controls. In addition to that, there is a relation between BPA and lower FSH concentration (Hanoka et al. 2002). There was no meaningful correlation between semen parameters and urinary BPA concentrations in fertile men (Mendiola et al. 2010). Nevertheless, a significant inverse correlation was detected between urinary BPA concentrations free androgen index (FAI) levels and the FAI/LH ratio, as well as a significant positive correlation among BPA and sex hormone-binding globulin (Li et al. 2011). By Li et al. (2011), there has been observed a high interaction between BPA and semen quality in Chinese men (involving motility, viability, sperm count and sperm concentration), which also correlated with the educational level and longer occupation history. It has been also documented that men who had better education and a long history of occupation had lower levels of BPA, because they were not in direct contact with endocrine disrupting chemicals, unlike men working in factories.

There might be a correlation among urine BPA levels and sperm

abnormalities and sperm DNA fragmentation (suggesting apoptosis) in men from an infertility clinic (Meeker et al. 2010), however; there is no negative effect of BPA on human sperm samples with direct administration. It could be suggested that the negative actions could be induced during spermatogenesis and epididymal transit and without a direct effect on spermatozoa (Wang et al. 2009).

- *Alkylphenols* (AP) involve a phenol group and an alkane. The most common member of the AP family is 4-nonylphenol, defining about 85% of the AP market (Ying et al. 2012). APs are used for producing AP ethoxylates, tris-nonylphenyl-phosphite and AP-formaldehyde condensation resin. APs are used as surface active agents in cleaning/washing agents, paints, cosmetics, spermicides. While 4-nonylphenol has been used in the preparation of lubricating oil additives, plasticizers; polyvinyl chloride (PVC) has been used in the food processing and packaging (Jobling et al. 1995). Additionally, AP ethoxylates, mostly nonylphenol and octylphenol, are commonly used in detergents, disinfectants, surface cleaners, cosmetic products, spermicides and pesticides (Tubau et al. 2010). It is known that both nonylphenol and octylphenol have weak estrogen-receptor binding potency (1.000-1.000.000 lower than 17-β-oestradiol). To date, data about reproductive toxic effects of 4-nonylphenol is generally taken from *in vivo* animal studies or *in vitro* systems (Routledge & Sumpter 1997). There are several studies about the effects of endocrine disruption by APs in laboratory rodents. It has not been observed any developmental reproductive anomalies when neonatal rats were exposed (8 mg/kg/day for up to 15 days post partum) by intraperitoneal administration of 4-nonylphenol. Nevertheless, significant testicular damage and a reduction in spermatogenesis has been determined when exposure of juvenile rats to administration of 100 mg 4-nonylphenol/kg/day for 30 days. Another study has shown a significantly increased rate of sertoli cell apoptosis when cultured *in vitro* with 4-nonylphenol for 72 h (Tan et al. 2003), whereas it has been stated that 4-octylphenol may induce a lower epidiymal sperm count in pubertal rats by administration of 3 mg/kg/day for 2 weeks (Herath et al. 2004). It has also been documented that several 4-nonylphenol isomers may inhibit testosterone biosynthesis in rats (Li et al. 2011), but there are a few *in vitro* studies that indicate a biphasic effect with an increase production of testosterone at low-dose exposure of

4-octylphenol or 4-nonylphenol and a decrease production of testosterone at high-dose exposure (Preuss et al. 2010; Wu et al. 2010).

Although there is a significant amount of present data on the effects of APs in rodents and rats, studies about human is lacking (Ademollo et al. 2008).

- *Phthalates,* mainly include butylbenzylphtalate (BBP), di-n-butylphthalate (DBP), di-(2-ethylhexyl)-phthalate (DEHP), are used as plasticizers. Phthalates are widespread in the environment. Especially DEHP, easily released into the environment due to its low vapor pressure and low water solubility, is a component of infant toys, indoor constructions, food packaging products and biomedical devices (Thomas & Thomas 1984). Phthalates are stated as reproductive and developmental toxicants because of being one of the main groups of antiandrogenic substances (Grady & Sathyanarayana 2012). Their antiandrogenic effects can be exerted by directly inhibiting testosterone synthesis in leydig cells, which has been considered to be due to *CYP17* dysfunction (Foster 2005). Some phthalates have played a role to interrupt the patterns of gene expression which have regulation of cholesterol and lipid homeostasis or insulin signaling, which might result in lower testosterone synthesis (Liu et al. 2005).

In rats exposed to phthalates during prenatal period, specific developmental reproductive anomalies identified as phthalate syndrome have developed. Cryptorchidism, smaller testes and penis size and alterations of vas deferens and epididymis like a shorter anogenital distance are involved in the syndrome (Foster 2005). It has been known that DEHP rapidly breaks down to its metabolite (MEHP) and 2-ethylhexanol after oral administration. If DEHP enters the blood directly, the breakdown carries out slower. The main part of DEHP and its metabolites are excreted within 24 h in urine and feces (Pflieger-Bruss et al. 2004). BBP and DBP were revealed estrogenic activity *in vitro,* but not *in vivo* (Jobling et al. 1995). Although it has been not demonstrated estrogenic activity of DEHP so far, the reproductive toxicity of DEHP has been determined in many animal studies. The toxic actions of DEHP were determined to be mediated through MEHP, which is the first metabolite of DEHP (Pflieger-Bruss et al. 2004).

There was a correlation between the exposure of DEHP-contaminated air and an increase in sperm DNA fragmentation and a decrease in sperm motility in PVC factory workers. In a study, it has been demonstrated that sperm anomalies (e.g., reduced sperm count and motility, depolarized mitochondrial membrane, higher levels of ROS in semen and higher lipid peroxidation) were present in infertile men having DEHP levels of up to 0.77 μg/mL in semen in India (Huang et al. 2011).

Although DBP could suppress steroidogenesis in testes mice and rats, no evidence could be stated in human. Nevertheless, it has been noted that there was a negative effect on testicular germ cell development (Latini et al. 2006). Moreover, a study has been demonstrated that there was a reverse relationship between an interquartile increase in MEHP and the testosterone, estradiol and free androgen indices. When combined with the results from animal studies, it concludes that phthalates and their antiandrogenic effects may be related to genitourinary developmental anomalies (Knez 2013).

- *Heavy metals* such as aluminum, antimony, arsenic, boron, cadmium, chromium, cobalt, lead, lithium and mercury have given rise to negative effects on the reproductive system of human and animals (Sikka & Wang 2008). There are many reports available about lead-induced toxicity (Gilfillan 1965). Despite of the fact that testicular biopsies which impart peritubular fibrosis, vacuolation, and oligospermia, supporting lead is a direct testicular toxicant (Lagos-Cabré & Moreno 2012), some studies indicate that exposing to lead can disrupt the hormonal feed-back mechanism at the hypothalamic-pituitary level (Sokol 1987). Boron, used in the manufacture of glass, cements soaps, carpets, and crockery, and leather products, results in oligospermia and decreased libido in men who worked in boric acid-producing factories (Weir & Fisher 1972). Cadmium is considered as a testicular toxicant and used in industries such as electroplating, battery electrode production, galvanizing, plastics, alloys, paint pigments. It is found in soil, coal, water, and cigarette smoke and it has correlated with testicular toxicity, alteration of libido and fertility (Sikka & Wang 2008). Mercury is found in the manufacture of thermometers, thermostats, mercury vapor lamps, paint, electrical appliances, and in mining and has caused to decrease fertility and might alter spermatogenesis in animals (Sikka & Wang 2008). Male rats and mice exposed to arsenic

exhibited steroidogenic dysfunction that possibly led to infertility (Jana et al. 2006). It was suggested that chronic arsenic exposure may contribute to male infertility in Mexican and has a negative impact on erectile function in Taiwanese men (Leke et al. 1993).

Pesticides are one of the major groups in endocrine disrupting chemicals (Tielemans et al. 1999). Organochlorine compounds, widely used as pesticides, include a wide group of substances such as DDT and metabolites, gamma-hexachlorocyclohexane (γ-HCH), polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-p-dioxins (PCDDs) (Dallinga et al. 2002). Additionally, agriculture chemicals involve epichlorhydrin, ethylene dibromide, kepone and dioxin (Mattison 1983). Dibromochloropropane (DBCP), a nematocide largely used in agriculture, is known as a testicular toxicant and induced hypergonadotropic hypogonadism (Potashnik & Yanai-Inbar 1987; Tielemans et al. 1999). Vinclozolin, fungicide known as an antiandrogenic, might be lead to hypospadia, cryptorchidism declined sperm counts and testicular tumour in males (Skakkebaek et al. 2001). Although PCBs and congener compound has been banned in most industrialized countries, it is not negligence human exposure due to the availability of PCB in capacitors and transformers (Kimbrough 1995).

Even though organochlorides accumulate in the adipose tissue, DDT and metabolites, γ-HCH, PCBs and PCDDs are also present in the fluids of human reproductive tract, e.g. seminal fluid, cervical mucus, and follicular fluid (Dallinga et al. 2002; Hanf et al. 1995). Dermal exposure to γ-HCH, which is used in therapy of ectoparasitic and also treatment of scabies and pediculosis, is some of relevance. Although in Europe the amount of γ-HCH formulation is 0.3%, the ADI for γ-HCH, which is present in different formulations and in various concentrations, is 0.01 $mg/kg^{-1}/day^{-1}$ according to World Health Organization (WHO). When exposure to γ-HCH during lactation, reduced testicular weights and the number of spermatozoa and spermatids at adulthood in male rat offspring has been documented (Dalsenter et al. 1997). It has been documented the effects of exposing PCBs on male reproduction *in vivo* such as reduced mating in rat, decreased concentration of testicular spermatozoa in mouse, lowered weight of the ventral prostate in rat seminal vesicles both rat and mouse (Alhlorg et al. 1992). Ensslen et al. (Ensslen et al. 1990) reported

a relationship between standard semen parameters such as motility, morphology, sperm count and the concentration of PCB and γ-HCH in the seminal plasma. Tielemans et al. (1999) noted decreasing human sperm fertilizing ability *in vitro* when pesticide exposure. Moreover, fertilization rates in the IVF (*in vitro* fertilization) treatment were importantly declined for couples with male partners as exposing pesticides. Dallinga et al. (2002) suggested importantly declined sperm counts in relation to an increased PCB metabolite among a subgroup of men with normal semen quality. Data about correlation between chlorinated hydrocarbons and human male fertility are controversial because of being most of the available data from animal models (Pflieger-Bruss et al. 2004).

Many synthetic pharmacological agents, phytoestrogens and anabolic steroids affect normal endocrine functions, severe oligozoospermia *etc.* (Knuth et al. 1989). Addition to that, it is known that antibiotics and cancer chemotherapy generally affect harmfully the germinal epithelium (Schlegel et al. 1991; Shalet 1980). Abnormalities in progeny were observed with cyclophosphamide treatment. It has been documented that men who have chronic low-dose cyclophosphamide treatment may be affected by decondensation potential of spermatozoa due to the alkylation of nuclear proteins or DNA. This probably affects pre- and post-implantation loss or stimulates congenital abnormalities in offspring (Qiu et al. 1992). Furthermore, usage of many antimicrobials such as tetracycline derivatives, sulpha drugs, nitrofurantoin, and erthromycin impair spermatogenesis and sperm function (Schlegel et al. 1991). Mechlorethamine, widely used as nitrogen mustard in 2nd World War, leads to spermatogenic arrest (Spitz 1948). Also, many commonly used cytotoxic agents lead a dose-dependent progressive decrease in sperm count, results in azoospermia (Meistrich 1982). Also, flutamide, used in treatment of prostate cancer, has an antiandrogenic effect (Skakkebaek et al. 2001).

Genetic Susceptibility

It is stated that male infertility is result from chromosomal abnormalities or mutations of genes involved in germ cell production and function in about 30% of overall (Vogt 2004). Even though it is considered that there are many more cases which should have a genetic background,

chromosomal aberration and micro-deletion of the Y chromosome crucial, genetic reasons of azoospermia/serious oligozoospermia (Carrell et al. 2006; Vogt 2004). Approximately 4000 genes involved in human spermatogenesis (Venables & Cooke 2000). Spermatogenetic failure results from both of gene mutations and genetic polymorphism. In a particular, single nucleotide polymorphism (SNP) is correlated with male infertility (Nishimune & Tanaka 2006).

The spermatogenesis locus of azoospermia factor (*AZF)* is in Yq11, which has been mapped into distinct five micro-deletion intervals designated as *AZF*a, *AZF*b (or P5/proximal P1), *AZF*bc (composing of two possibilities P5/distal P1 and P4/distal P1) *AZF*c (or *b2/b4)*. However, smaller deletions, removed only portion of the *AZF*c section, have been named as polymorphism importantly correlated with infertility, particularly oligozoospermia (Repping et al. 2003). These are named *gr/gr* deletions, which arise by the homologous recombination, have been widely analyzed in large populations of men from different countries. It was found that *gr/gr* deletions has been observed in 1.9% of controls with normal spermatogenesis and this ratio raised increasingly in men with oligozoospermia (4.3%), serious oligozoospermia (6.5%) and azoospermia (8.6%). Also, a study included meta-analysis of all studies with 4561 patients and 3426 controls, showed that *gr/gr* deletions are importantly to arise among infertile men, notably with lower sperm concentration. Additionally, it should be considered a polymorphism rising the probability of arise infertile (Repping et al. 2003; Zhang et al. 2007).

The other important enzyme is DNA polymerase gamma (*POLG*) is the nuclear enzyme whose job is replication and repair of mitochondrial DNA (mtDNA), encoding proteins involved in the respiratory chain and oxidative phosphorylation system and being included in spermatozoa widely (Folgero et al. 1993). *POLG* gene that encodes the catalytic subunit of *POLG* has a polymorphic CAG repeat region which contain 10-codon repeat on both alleles, indicating a positive selection. A large multinational study has showed that the absence of the 10-codon repeat on both alleles has observed in 9% of 99 infertile males who have impaired sperm quality, but only in 1.5% of 522 healthy controls and in none of the 98% fertile control individuals (Rovio et al. 2001). There was no association between *POLG* polymorphism and infertile males or sperm quality from studies in

Italy, France and New Zealand (Aknin-Seifer et al. 2005). A study from Portugal and United Kingdom has stated a possible association between the *POLG* polymorphism and asthenozoospermia, but the small number of subjects reduces the value of the finding (Amaral et al. 2007).

Y chromosome has deleted in azoospermia-like (*DAZL)* which is an autosomal homologue of deleted in azoospermia gene family (*DAZ)*. *DAZL* is deleted in about 3-8% of men with azoospermia or severe oligozoospermia. It is located on chromosome 3 and is important for germ cell lineage development in several species (Ruggiu et al. 2000). An analysis of *DAZL* infertile men identified two SNP at nucleotide position 260 (exon 2) and 386 (exon 3), resulting in the amino acid exchange T12A and T54A respectively. While T54A exchange was found to be significantly associated with infertility in Chinese men from Taiwan, this finding could not be associated in German, Italian, Japanese and Indian men (Becherini et al. 2004; Thangaraj et al. 2006).

FSH is important for gonadal function and has a common polymorphism in exon 10 of follicle-stimulating hormone receptor (*FSHR)*, which exchanges an asparagine for a serine at amino acid position 680 in the intracellular domain, plays an apparent role for determining FSH sensitivity in women duration of the menstrual cycle, follicular growth dynamics and response to ovarian stimulation (Gromoll & Simoni 2005). Although a few studies have investigated possible correlation between N680S with serum FSH concentration and testis volume/sperm parameters in fertile and infertile men, no association has been found (Ahda et al. 2005; Asatiani et al. 2002; Galan et al. 2005; Pengo et al. 2006). According to The National Centre for Biotechnology Information (NCBI) SNP database, the *FSHR* gene hosts over 900 SNPs and some of them, alone or as a haplotype, influence testicular function (Gromoll & Simoni 2005). Ahda et al. (Ahda et al. 2005) stated the haplotype formed by three SNPs at nucleotide position -29 in the promoter and amino acid positions 307 and 680 in exon 10 might be a risk factor for azoospermia in German men.

Androgen is involved in male reproductive system and so, androgen signaling is one of the most important candidate pathways to expect a genetic polymorphism predisposing to male infertility (Gottlieb et al. 2005). Exon 1 of the androgen receptor gene, *AR*, includes two polymorphic

trinucleotide repeat stretches, a $(CAG)_n$ with a normal range between 9 and 37 repeats, and a $(GGN)_n$ repeat, which usually include 23 codons (La Spada et al. 1991). A correlation between *AR* polymorphism and testicular function (e.g. sperm production, reproductive hormone profiles) in healthy men was dealt with several studies, and there was an inverse association with an increasing $(CAG)_n$ (Harkonen et al. 2003; Mifsud et al. 2001). On the other hand, a study was shown that *AR*-CAG polymorphism was indicated as a possible modifier for response to some organohalogen pollutants (Giwercman et al. 2007). SNP in estrogen receptor alpha *(ER1)*, the (TA)n repeat in the promoter region of *ER1* and the *RsaI* polymorphism in *ER2* have been studied in relation to male fertility, postulating a negative influence on spermatogenesis if stronger estrogen effects are conferred. Additionally, a specific haplotype (AGATA) in *ER1* has been studied in men with maldescended testis, but revealed contradictory results (Galan et al. 2005; Galan et al. 2007).

Many xenobiotics have capacity inducing or inhibiting enzymes, which exhibit alteration in their activity (Gonzalez 1992). Besides, genetic variability, tissue-specific differences, catalytic characteristic of xenobiotic-metabolizing enzymes might have remarkable individual variations (Gonzalez 1992; Nebert et al. 1996). Existence of phase I and II enzymes in testicular tissue of laboratory animals has been determined. Nevertheless, the effects of genetic variability in metabolizing xenobiotics on male reproductive system have not been widely studied (Nebert et al. 1996).

Depending on *CYP1A1* genotype, endocrine and paracrine regulation of testicular function could be interfered by extra-hepatic generation of reactive metabolites of xenobiotics (Morel et al. 1999; Nebert et al. 1993). In a study conducted by Hayashi et al (1991), for both *Msp* I and *Ile-Val* polymorphism, a high frequency was observed among normozoospermic men. Pajarinen et al. (1996) observed the correlation between glutathione S-transferase M1 polymorphism (*GSTM1*) and alcohol-induced disorders of spermatogenesis in an autopsy series. Also, there might have been a correlation between deletion of both *GSTT1* and *GSTM1* and increased risk of hypospadias (ShekharYadav et al. 2011). *GSTM1* polymorphisms were found to be related to a susceptibility to infertility in men with varicocele testes (Chen et al. 2002; Frosst et al. 1995). It is known that

methylenetetrahydrofolate reductase (*MTHFR*) is one of the key enzymes in folate metabolism and reduces 5-10-methylenetetrahydrofolate to its active form 5-methyltetrahydrofolate. *S*-adenosylmethionine is formed as methyl donor for DNA and protein methylation, and it is vital for spermatogenesis. The common polymorphism of *MTHFR* is C677T, which reduces the enzyme activity by about 35% in heterozygote (CT) and 70% in the homozygote (TT) form (Stuppia et al. 2003). Bezold et al. (2001) firstly studied the SNP, in relation to male fertility with 255 patient which have fertility and 200 controls and found an importantly different distribution (homozygous genotype 18.8 vs 9.5%) and after seven studies have been published to date with 1843 patients and 1791 controls being examined (Dhillon et al. 2007; Ebish et al. 2003; Lee et al. 2006; Park et al. 2005; Stuppia et al. 2003). In Han-Chinese population, it was observed that men carrying in *CYP2C9* rs4918758, in *CYP2C19* rs4986894, and in *CYP1A1* rs1048943 minor alleles might have genetic susceptibility to male infertility risk when coupled with 4-tert-octylphenol exposure (Qin et al. 2013).

Conclusion

Human is exposing a great deal of chemicals which have serious effects on hormonal balance in the environment during whole life. The situation have ability to not only alter normal differentiation and growth of reproductive tract when sexual developmental time, but also to result in genetic variability/differences. Especially, workers exposing to these chemicals in the industry may have more possible risks than men who live in urban areas.

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