



Effects of mobile phone exposure on metabolomics in the male and female reproductive systems

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ABSTRACT

With current advances in technology, a number of epidemiological and experimental studies have reported a broad range of adverse effects of electromagnetic fields (EMF) on human health. Multiple cellular mechanisms have been proposed as direct causes or contributors to these biological effects. EMF-induced alterations in cellular levels can activate voltage-gated calcium channels and lead to the formation of free radicals, protein misfolding and DNA damage. Because rapidly dividing germ cells go through meiosis and mitosis, they are more sensitive to EMF in contrast to other slower-growing cell types. In this review, possible mechanistic pathways of the effects of EMF exposure on fertilization, oogenesis and spermatogenesis are discussed. In addition, the present review also evaluates metabolomic effects of GSM-modulated EMFs on the male and female reproductive systems in recent human and animal studies. In this context, experimental and epidemiological studies which examine the impact of mobile phone radiation on the processes of oogenesis and spermatogenesis are examined in line with current approaches.

1. Introduction to metabolomics: effects of EMF on male and female reproduction

Humans are often exposed to a broad array of electromagnetic fields (EMF) as technology advances. The purpose of this review is to discuss the effects of EMF-induced metabolomics on the male and female reproductive systems caused by mobile phones EMF exposure in the light of current research. Human and animal studies have identified a number of adverse health effects that can be caused by this exposure that require additional evaluations (Sepehrmanesh and Davis, 2017). Many factors, such as body weight, dielectric constant, electrolyte balance and other properties are important in the context of these effects since they change conductivity and reactivity to EMF (Tabrah et al., 1998; Vesselinova, 2015). *In vivo* and *in vitro* studies indicate that EMF exposure can alter cellular homeostasis, activate voltage-gated calcium channels and affect endocrine function, reproduction functions and fetal growth in animals. Moreover, the absorption rate of EMF in human cells is affected by polarization, amplitude, frequency, and power density. Absorption rates of different tissues affect cellular absorption of radiofrequency energy. The effects of EMF may be classified as thermal or non-thermal. In general, the thermal mechanism is understood to increase local temperature with an oscillatory current at the

radio frequency of the electrical field (Belyaev, 2005; Gye and Park, 2012). In contrast, non-thermal effects of EMF on human cells can include the generation of large and damaging reactive oxygen species (ROS). ROS generation causes oxidative damage in the target cells. In research on pregnant rats and their offspring exposed to 900 MHz, 1800 MHz and 2450 MHz EMF, Yuksel et al. (2016) reported a higher body temperature and uterus lipid peroxidation levels in newborn rats compared to a control group. This indicates that health risks caused by EMF can arise from either non-thermal or thermal effects of EMF in the female reproductive system (Yuksel et al., 2016) and that both may be involved. EMF has a high penetrating power and can accelerate the movement of charged particles of macromolecules and polymers, such as electrons and ions (Asghari et al., 2016).

EMF-induced changes observed at the cellular level may cause free radicals and Ca^{+2} mediated cell growth inhibition, protein misfolding and DNA damage. EMF has biochemical interactions arising from activation of second chemical messengers in biological materials (Belyaev, 2005; Gye and Park, 2012). Moreover, the effect of EMF exposure on reproductive functions depends on frequency and wave, polarity and information content, as well as energy, power density and total time of exposure. (Gye and Park, 2012). The main side-effects of EMF are seen through protein synthesis, which seriously affects cell

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structure and functions (Mancinelli et al., 2004). In that context, Desai et al. suggested that the EMF might enhance ROS generation by increasing nicotinamide adenine dinucleotide (NADH) oxidase activity in plasma membrane. One possible interaction mechanism between electromagnetic radiation and biological systems is a process involving free radicals (Desai et al., 2009b). Highly reactive free radical formation increases oxidative stress, a physiological or cellular condition, and molecular damage subsequently occurs, together with pronounced effects on macromolecules such as. ROS consist of highly reactive molecules formed by unconjugated electrons in free orbits. While a small concentration of ROS is essential for the maintenance of healthy cells, excessive concentrations can cause tissue damage and impair the ability of cells to undergo repair or apoptosis (Bandyopadhyay et al., 1999; Kesari et al., 2013). In the case of exposure to mobile phone radiation, an EMF-induced iron-mediated process (Fenton reaction) occurs. This reaction leads to an increase in hydroxyl free radical generation in the cells that can cause serious damage. Hydroxyl radicals are generated from hydrogen peroxide through the Fenton reaction in the presence of iron, and also EMF (D'Autreaux and Toledano, 2007; Desai et al., 2009a; Kesari et al., 2013). Kesari et al. (2013) suggested that the Fenton reaction induced by EMF accounts directly for cell death by increasing the production of free radicals that play an important role in the enzymatic and genetic action of EMF (Fig. 1) (Kesari et al., 2013).

EMF-induced free radicals can create both structural deformities and functional defects in sperm (Gye and Park, 2012). Processes relevant to this damage can involve the stimulation of protein kinases, and an increase in cyclic adenosine mono phosphate (cAMP), phosphorylation, and calcium efflux. The first target of ROS is the sperm membrane. Lipid peroxidation has been shown to be induced when O_2 is not soluble in the hydrophobic membrane or when it is in the protonated form (Evans and Halliwell, 1999; Phillips et al., 2009). Moreover, Kumar et al. (2011) reported that exposure to 2.45-GHz EMF caused apoptosis during spermiogenesis, and that caspase-3 activity affects reproductive physiology. The effect of oxidative stress on health and of microwave EMFs on chronic stress through over-production of ROS have now been revealed (Kumar et al., 2011). Excessive generation of ROS and oxidative stress may contribute to aging and various health conditions affecting female reproduction. Endothelial dysfunction caused by oxidative stress contributes to obstetric complications, such as early and repeated pregnancy loss, pre-eclampsia, intrauterine growth restriction and preterm delivery (Webster et al., 2008). Reactive oxygen and nitrogen species may have adverse effects on embryo implantation and may affect the development of reproductive disorders, such as endometriosis and pre-eclampsia (Webster et al., 2008). Despite the fact that the exact pathogenesis of pre-eclampsia is still unknown, placental ischemia/hypoxia is regarded as a significant factor through

the induction of oxidative stress, that may trigger endothelial cell dysfunction in the disease (Webster et al., 2008; Possomato-Vieira and Khali, 2016). Modified vasomotor functions are demonstrated with unsuccessful embryo implantation in preeclampsia and endometriosis, and low placental perfusion (Massé et al., 2002). Antioxidants are reported to cure such effects and can thus mitigate infertility risks (Agarwal et al., 2008b; Webster et al., 2008). Previous studies have examined the deleterious effects of EMF on reproduction in both genders in different exposure doses, and research has shown that EMF has harmful effects on sex hormones, gonadal function, fetal growth and pregnancy (Rodriguez et al., 2003; Rodriguez et al., 2004; Gye and Park, 2012). In addition, natural antioxidants can be used to reduce the side-effects of EMF exposure (Gye and Park, 2012; Nelson et al., 1995; Pourlis, 2009). In this regard, ROS over-generation can lead to disruption of normal female physiological reactions by penetrating the body's natural antioxidant defense system (Agarwal et al., 2012; Al-Gubory et al., 2010). Oxidative stress has been shown to be a significant cause of infertility in men. Sperm numbers and motility are important determinants of fertilization capacity, and oxidative stress may cause infertility in men by affecting these parameters (Makker et al., 2009; Saalu, 2010).

A significant increase has been observed in mitochondrial and cytosolic superoxide generation in human spermatozoa exposed to EMF (Agarwal et al., 2009; De Iuliis et al., 2009). The relation between loss of sperm motility and ROS over-generation is well-known in sperm biology (Darr et al., 2016). Increases in lipid peroxidation and the subsequent malondialdehyde depend on acrolein generation that can covalently bind with electrophilic aldehyde and proteins such as 4-hydroxynonenal (4-HNE) (Aitken et al., 2012). These components alkylate the sperm axonemal proteins that regulate sperm motility, and especially the heavy chain dynein. In addition, electrophiles such as 4-HNE increase oxidative stress by stimulating ROS generation through sperm mitochondria (Aitken et al., 2012). This occurs since the mitochondrial electron transport chain, another protein group alkylated by 4-HNE, generates succinic acid dehydrogenase components (Aitken et al., 2012). Even a minimal increase in ROS induced with EMF can have a profound effect on reproduction by damaging mitochondria (Aitken et al., 2012). ROS generation originating from EMF is reported to increase lipid peroxidation in spermatozoa and damage mitochondrial DNA (Aitken et al., 2012; Al-Damegh, 2012; Kesari et al., 2011; Moazamian et al., 2015).

2. The effects of EMF-induced oxidative stress mechanisms on the male genital system

The effects of EMF emitted from the mobile phone on the reproductive organs and fetal development have been extensively investigated by our laboratories (Sepehrmanesh et al., 2014) and others, and the number of studies on the impact of EMF exposure on human reproduction has increased considerably. While some studies suggest that EMF has an adverse effect on male reproductive systems, others have reported that EMF has no, or only partial, effects on testicular tissue and functions. As with other endpoints, these inconsistent results may be due to the fact that different researchers have used different frequencies, amplitudes, power densities, and that the density and exposure times of the induced magnetic fields have also not been standardized (Belyaev, 2005; Dasdag et al., 2003; Desai et al., 2009b; Yan et al., 2007). Radiation emitted by mobile phones may cause structural and functional injury in the testes, changes in semen parameters, and decreased epididymal sperm concentrations and male fertility (Kang et al., 2010). These changes depend on the length of exposure, the specific absorption rate (SAR) and the energy level of EMF. In this context, a decrease in testicular size has been reported as one effect, and studies have also reported decreases in the diameter and epithelial thickness of the seminiferous tubules (Dasdag et al., 1999; Ozguner et al., 2005; Salama et al., 2010). According to De Iuliis et al. (2009),

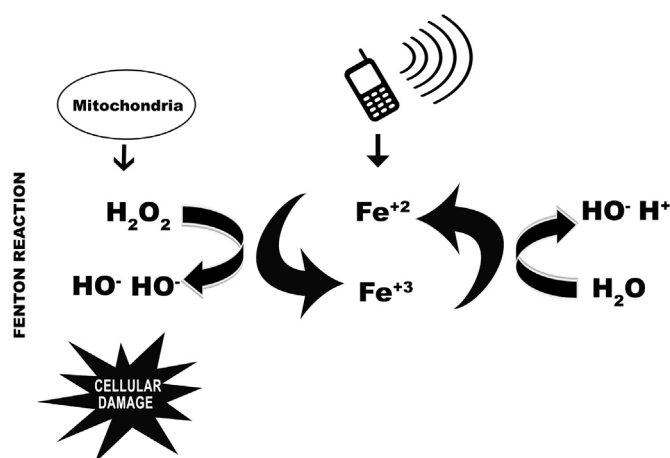


Fig. 1. Diagram showing the role of Fenton reaction EMF-induced cellular damage (modified from Phillips et al., 2009).

the underlying mechanisms involved in cellular damage to the male reproductive system caused by EMF are unclear. However, sperm cells are particularly vulnerable to oxidative damage due to the absence of antioxidant enzymes as well as substrates to protect against free radical attack on their surfaces (De Iuliis et al., 2009). Another study of male rats reported that mobile phone exposure increased glutathione levels. In addition, exposure to 900 and 1800 MHz GSM mobile phones (1 h per day for 28 days) has been demonstrated to reduce glutathione concentrations and to increase lipid peroxidation in male rats (Mailankot et al., 2009). The rise in ROS production resulting from exposure to 0.9 W/kg EMF for 35 h (2 h/day) in standby mode increases protein kinase activity. Additionally, the EMF emitted by mobile phones has also been reported to adversely impact the fertilization capacity of spermatozoa (Kesari et al., 2010, 2011). Esmekaya et al. (2011) determined that exposure to 900 MHz EMF (1.20 W/kg and 20 min/day for 3 weeks) causes oxidative damage in testicular tissue by enhancing nitric oxide and inhibiting antioxidant mechanisms (Esmekaya et al., 2011).

2.1. Mobile phone and sperm motility

Many studies have investigated the effects of EMF on the male reproductive system (Gul et al., 2009; Odaci and Ozyilmaz, 2015; Odaci et al., 2016; Sepehrmanesh et al., 2014). While some authors believe that the both the thermal and non-thermal effects emitted by mobile phones are deleterious to health, others have concluded that the non-thermal effects are minimal. (Black and Heynick, 2003; Jauchem, 2003; Meltz, 2003). In this context, studies have clearly shown that temperature increases caused by mobile phones can adversely affect sperm maturity and motility (Fig. 2) (Bonde et al., 1996; Brusick et al., 1998; Fejes et al., 2005).

Oxidative stress is also considered an important cause of male

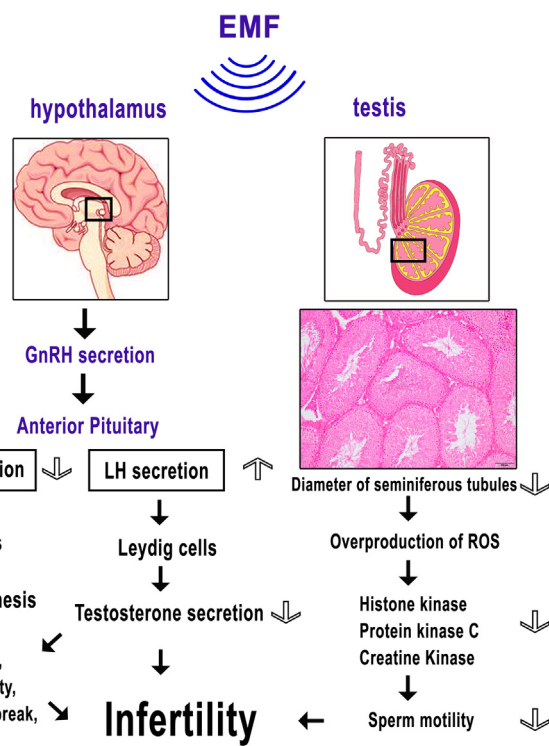


Fig. 3. Potential effects of EMF emitted from mobile phones on the association between the central nervous system and the reproductive system and the role of EMF on male infertility (Kesari et al., 2013).

infertility. In this context, ROS, which originate from spermatozoa and leukocytes, affect sperm motility and can cause infertility (Figs. 2 and 3). The plasma membrane of spermatozoa has a multiple redox system which resembles NADH, an important source of superoxide anions. Studies have shown that EMF stimulates NADH oxidase in the plasma membrane of mammalian cells (Maneesh et al., 2005a, 2005b).

ROS are maintained at physiologically low levels by intracellular free radical scavengers. Glutathione (GSH), an important scavenger in living organisms, plays a critical role in the body's antioxidant defense mechanisms against free radicals. Conditions disrupting intracellular GSH levels cause significant changes in cellular metabolism. GSH in the tissues is a determinant of their detoxification capacity, cell redox balance and cell protection. A study suggested an increase in GSH consumption in human ejaculate exposed to RF-RM, and posited that the ROS generated after exposure might be responsible for a low level of sperm (Salama et al., 2010). In brief, an increase in the oxidative stress caused by RF-EMF leads to a decrease in testicular function (Agarwal et al., 2009; Irvine, 1996; Salama et al., 2010; Sepehrmanesh and Davis, 2017). In a study based on a similar hypothesis, Mailankot et al. reported a low GSH concentration in the testes and epididymis, and an increased lipid concentration in 10–12-week Wistar albino rats exposed to 900 and 1800 MHz EMF over 28 days (1 h per day) (Mailankot et al., 2009). An increased level of free radicals in the cells may be induced by lipid peroxidation through oxidative degradation of polyunsaturated fat acids in the cell membranes. Damage to the structure of the lipid matrix of the spermatozoa membrane and axoneme then occurs through lipid peroxidation of sperm. However, rapid loss of intracellular ATP is related to a decrease in sperm viability and increased structural defects, and spermatogenesis can thus be inhibited (Ceribasi et al., 2012; Turk et al., 2008).

Recent studies have investigated the potential effects of EMF on sperm quality (Fejes et al., 2005; Kilgallon and Simmons, 2005; Turk et al., 2008). In this context, Kilgallon et al. suggested that keeping mobile phones close to the testicles has a significant adverse effect on concentrations and percentages of mobile sperm (Kilgallon and

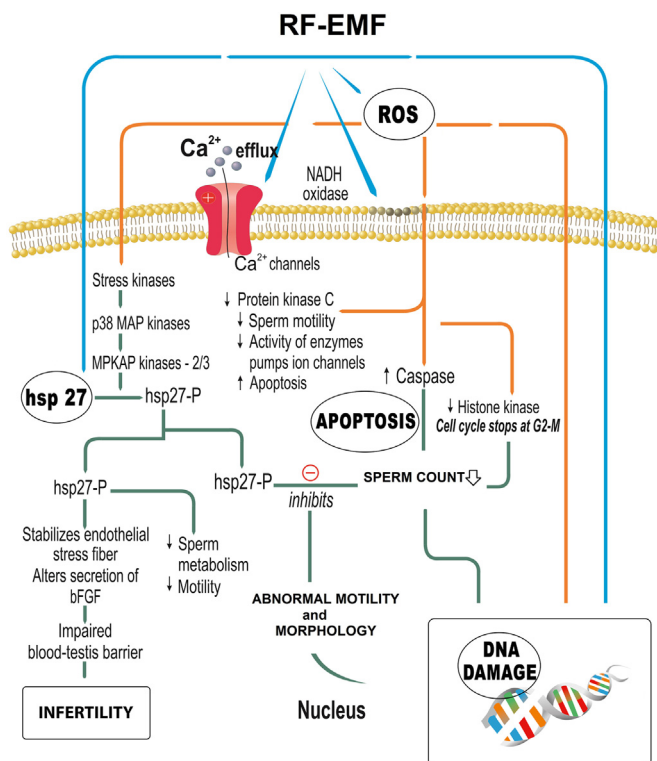


Fig. 2. Exposure to RF-EMF causes an alteration in calcium efflux and a decrease in the activity of protein kinase. The figure shows a schematic representation of biological effects associated with male infertility. hsp: heat shock protein, bFGF: basic fibroblast growth factor, MAP: mitogen-activated protein (adapted from Desai et al., 2009b; Hamada et al., 2011).

Simmons, 2005). In addition, a study of 271 healthy males by Fejes et al. (2005) demonstrated no significant effect of communication signals in standby mode on spermatozoa. The authors therefore concluded that long-term mobile phone use may affect sperm motility. Although the general motility of sperm did not change, the moderate decrease observed in grade A motility and the moderate increase observed in grade B motility may be a result of the EMF emitted from mobile phones (Fejes et al., 2005). Additionally, Sun et al. (2005) demonstrated that the EMF emitted from computers did not alter sperm quality (Sun et al., 2005). Eroglu et al. (2006) reported that exposure to EMF causes a decrease in sperm motility. Semen analysis in the exposure group and control group showed significant alterations in sperm motility. (Eroglu et al., 2006). Similarly, Imai et al. (2011) examined the effects of EMF on offspring male rats. No differences were determined in terms of testis weight between the control group and rats exposed to 1.95 GHz (SAR 0.4–0.08 W/kg). In addition, no abnormalities were observed in terms of sperm motility and morphology or the histological appearance of seminiferous tubules (Imai et al., 2011). Agarwal et al. (2008) showed that EMF emitted by mobile phones at an 850 MHz frequency (maximum power ≤ 1 W, SAR 1.46 W/kg) caused oxidative stress in semen and reduced spermatozoa motility and viability. Based on *in vitro* data, they concluded that carrying mobile phones in pockets causes deterioration in sperm quality due to exposure to oxidative stress (Agarwal et al., 2008a). Another retrospective study of 304 men by Wdowiak et al. (2007) observed a decline in reproductive age and a decrease in sperm cell levels due to mobile phone use. In that study, while 65.7% of patients without mobile phones had prospective motile sperm rates exceeding 50%, the figure was only 17% for subjects who had been using mobile phones for more than 2 years (Wdowiak et al., 2007). Recently, Oyewopo et al. (2017) concluded that impaired spermatogenic function may be associated with increased oxidative stress. This stress can be detected by elevated levels of malondialdehyde (MDA) in the circulation after exposure to mobile phone-derived EMF-RF for 2–3 h (Oyewopo et al., 2017). This finding supports the idea that increased MDA concentrations damage the cell plasma membrane by inducing lipid peroxidation in the sperm membrane, and that this then results in cell death. In this case, sperm motility and viability also reduce the capacity of spermatozoa to undergo acrosomal reaction and fertilization (Eskicak et al., 2006; Oyewopo et al., 2017).

2.2. The role of EMF in the apoptotic process underlying infertility

Male infertility is a growing problem worldwide. In this context, the assessment of possible side-effects of new technologies is a matter of critical importance (Yan et al., 2007). Because they play a key role in sperm differentiation and maturation, alterations in the function of caspases can be an important contributor to or cause of infertility (Fig. 2). Caspase-3 is detected in both the perinuclear field and in the cytoplasm of germ cells. Conflicting studies exist with respect to the relationship between EMF and caspase. Some studies have shown that exposure to EMF radiation for 45 days (1 h per day) does not sufficiently induce apoptosis in rat testis tissue (Paasch et al., 2004; Said et al., 2004). Lee et al. (2010) performed a histological examination of the stages of spermatogenesis, germ cell numbers and apoptotic cells emerging in the rat testis exposed to EMF at 848.5 MHz (2.0 W/kg) for 12 weeks. Testicular levels of Bcl-2, p21, p53 and caspase-3 were measured. However, no significant effect on rat spermatogenesis was observed following subchronic exposure to 848.5-MHz EMF (Lee et al., 2010). Apoptosis plays a crucial role in regulating the numbers of germ cells performing proliferation. However, some factors such as radiation exposure and H₂O₂ availability may increase the rate of apoptosis (Agarwal et al., 2011). In contrast to these negative studies, Kesari and Behari (2012) reported that exposure to RF radiation at 900 MHz from a mobile phone caused apoptosis leading to an increase in caspase-3 activity in sperm cells during spermiogenesis and sperm maturation, thus affecting reproductive physiology (Kesari and Behari, 2012). Yilmaz

et al. (2008) examined Bcl-2 levels in the rat testis exposed to EMF for 1 month (20 min a day) and demonstrated using immunohistochemical analysis that mobile phones did not alter anti-apoptotic protein levels in the rat testis (Yilmaz et al., 2008). Azadi Oskouyi et al. (2015) showed that EMF induce apoptosis in epithelial cells and reduce the diameter and height of epithelial cells in the epididymis. This decrease may be due to a reduction in metabolic activity in cells and in nuclear activity (Azadi Oskouyi et al., 2015).

2.3. The role of EMF in the hormonal regulation of spermatogenesis: cellular mechanisms

Several hormones are necessary for the regulation of the reproductive organs. Circulating hormones containing follicle-stimulating hormone (FSH), luteinizing hormone (LH), activin B, inhibitor B, testosterone and prolactin (PRL) regulate the first wave of spermatogenesis (Barakat et al., 2008). In this context, Sepehrmanesh et al. (2014) investigated whether levels of serum testosterone, inhibin B, and prolactin, activin B, FSH and LH in adult male *Sprague dawley* rats would change following continuous exposure to 900-MHz EMF. They reported that exposure to 900-MHz RF-EMF for 30 days increased activin B, FSH, LH, and PRL levels and reduced serum inhibin B and testosterone levels in male rats. Although the physiological importance of these changes is still unclear, the authors suggested that EMF may cause significant negative effects on the male reproductive system (Sepehrmanesh et al., 2014). Further studies are needed to elucidate possible mechanisms.

Testosterone is a hormone primarily responsible for sperm production and growth. Testosterone synthesis is controlled by secretion of LH and FSH from the anterior pituitary gland in response to hypothalamic gonadotropin-releasing hormone (GnRH) release. Leydig cells induce a high intratesticular testosterone level that directly affects spermatogonia and primary spermatocytes and promotes meiotic division. The effects of mobile phone EMF on testicular steroidogenesis have been evaluated in this context (De Rosa et al., 2003). Wang et al. (2003) suggested that Leydig cells, which affect spermatogenesis, are the cells that are most sensitive to damage from EMF (Wang et al., 2003). Oxidative stress and alterations in the protein kinase enzyme complex in Leydig cells and seminiferous tubules may explain the EMF induced impairment in the functional structure of Leydig cells (Nikula et al., 1987). In addition, EMF has been shown not only to alter serum testosterone, but also to affect P450_{sc} mRNA expression in the testis in steroidogenesis (Zhou et al., 2005).

Forgacs et al. (2006) observed a decrease in serum testosterone level but no histopathological change in Leydig cells following 1800 MHz of GSM-like EMF. They concluded that Leydig cells are not the primary target of short-term exposure to EMF and that additional study was required to determine factors affecting testosterone production (Forgacs et al., 2006). Salama et al. (2009) examined androgen-dependent secretory activity in rabbits exposed to EMF and detected a dose-related decrease in seminal plasma fructose. However, no change was observed in serum testosterone levels in the EMF-exposed groups. Changes in testosterone receptors and enhanced oxidative stress in accessory glands have also been reported to occur in human males (Salama et al., 2009). In contrast, others report that short-term EMF exposures have no observable effect on the pituitary gland or the production of gonadotropins both humans and animals exposed to EMF. Thus, De Seze et al. (1998) evaluated the concentrations of gonadotropin in 21 healthy men exposed to 900 MHz RF for 1 month (2 h per day, 5 days weekly) and observed no effect (de Seze et al., 1998).

Chronic exposure to the EMF emitted from mobile phones causes deteriorations in testicular functions and decreased gonadotropic hormone levels linked with increased oxidative stress (Oyewopo et al., 2017). Gutschi et al. (2011) investigated 2110 men attending an Austrian infertility clinic between 1993 and 2007 and evaluated the serum levels of fertility-related hormones (FSH, LH, testosterone, and PRL). They concluded that mobile phones affect sperm quality and impair

male fertility (Gutschi et al., 2011). Another study investigated the effects of EMF exposure on plasma hormonal biomarkers and observed a lower testosterone level in the group exposed to EMF compared to the control group. The authors concluded that chronic EMF exposure may reduce levels of plasma testosterone and the ratio of testosterone/estradiol in males (Wang et al., 2016). Many animal studies have also reported that exposure to EMF can reduce serum or plasma testosterone (Kesari and Behari, 2012; Ozguner et al., 2005; Shahin et al., 2014). For instance, decreased testosterone levels may lead to EMF-induced damage in Leydig cells (Sepehrimanesh et al., 2014).

In addition to a number of studies showing that EMF may have harmful effects on sperm function, there have also been many reports indicating that such radiation can also affect the testicles. Exposure of male rats to EMF twice daily for 60 min may lead to dilation of seminiferous tubules (Al-Damegh, 2012). Dasdag et al. (1999) reported thinning of the seminiferous tubules as a reaction to exposure to mobile phone for 1 month (2 h a day). In a subsequent study, they also reported that daily exposure to 20-min EMF for 1 month does not result in any changes in testicular structure (Dasdag et al., 2003). In addition to the potential effects on the diameter of seminiferous tubules, chronic exposure (3 h a day for a year) to EMF causes a decrease in tunica albuginea thickness in the rat testis (Tas et al., 2014).

3. The metabolomic effects of EMF on the female reproductive system

The female reproductive organs have critical functions for the survival of the species. Damage to female reproductive tissue or processes from both low frequency EMF as well as higher frequency RF due to the widespread use of mobile phones (Nazioglu et al., 2013) may increase the risk for infertility or contribute to abnormal fetal growth (Fig. 4) (Pouletier de Gannes et al., 2013). Data obtained from both animal and human studies of EMF have shown adverse effects on granulosa cells, numbers of ovarian follicles, endometrial tissue, oocyte and embryo quality, and even changes in fetal heart physiology during pregnancy (Batellier et al., 2008; Diem et al., 2005; Merhi, 2012). Male offspring exposed prenatally to EMF develop a range of deficiencies in Leydig cells as well as reduced levels of testosterone and have also been

associated with increased behavioral anomalies (Aldad et al., 2012).

3.1. Morphological alterations in female infertility caused by mobile phone use

A considerable number of studies have investigated the impacts of EMF on the ovaries. Roushangar and Rad (2007) studied the effect of low frequency EMF on follicle development in the rat ovary. Their results indicated thinner nuclei of oocytes and zona pellucida in an EMF-exposed group compared to a matched control group. Apoptotic bodies were more common in EMF-exposed rats than controls (Roushangar and Rad, 2007). Morphological alterations observed in the oocytes indicate the cytotoxic effect of EMF. Researchers have suggested that EMF exposure may disturb normal folliculogenesis. Roshanger et al. (2014) studied the effects of exposure to low frequency EMF on oocyte differentiation and follicle growth. They concluded that EMF exposure during the growth period may affect both oocyte differentiation and folliculogenesis, and that it may decrease fertility by reducing ovary reservoirs (Roshanger et al., 2014). Türedi et al. (2016) reported degeneration in granulosa cells and vacuolization of granulosa cells towards the antrum of ovarian tissue in rats exposed to 900 MHz EMF during the prenatal period (Türedi et al., 2016). Similarly, several studies have indicated that histo-morphological evidence of the apoptotic process in the granulosa cells and the ovary is supported by degenerative findings, such as chromatin changes, cytoplasmic vacuolization, inflation, nuclear concentration and nuclear destruction (Boone et al., 1997; Hughes and Gorospe, 1991). Oral et al. (2006) examined oxidative stress and the apoptotic process in endometrial tissue following the RF-EMF exposure for 30 days (30 min per day). They used immunohistochemical methods to investigate Bcl-2, caspase-3, caspase-8, Bax and MDA in order to evaluate the lipid peroxidation as an indicator of endometrial disorder induced by oxidative stress. The authors underlined that 900 MHz EMF caused oxidative stress and endometrial apoptosis (Oral et al., 2006).

Sangun et al. (2015) investigated the effects of long-term 2450 MHz EMF exposure on pubertal development and growth of female *Wistar albino* rats. They concluded that prenatal exposure to 2450 MHz EMF caused delayed puberty and restriction in postnatal growth (Sangun et al., 2015). In contrast, Pouletier de Gannes et al. (2013) reported that exposure to Wi-Fi for 1 h per day (6 days/week) for 3 weeks of gestation had no gross adverse effects on the reproductive organs and fertility in either male or female rats (Pouletier de Gannes et al., 2013). Oral et al. (2006) suggested that exposure to 900 MHz EMF has a significant effect on the rat endometrium and that the production of ROS is related to experimental conditions. In that context, an increase in the MDA levels as an indicator in the increased ROS production has been reported. An association between the lipid peroxidation and EMF-induced damage may reflect the pathological mechanism resulting from exposure (Oral et al., 2006). For these as with all studies the lack of standardization of exposure metrics hampers the interpretation of the findings.

3.2. The effects of EMF exposure on oogenesis

Margaritis et al. (2014) evaluated the effects of exposure to GSM-like 900 MHz EMF on apoptosis of the follicles in oogenesis in *Drosophila virilis* and *Drosophila melanogaster*. Their findings revealed that 900 and 1800 MHz EMF led to a significant reduction in fertility in *D. virilis*. A decrease of 30% was observed in the group exposed to 900 MHz EMF, while a decrease of 20% was observed in the group exposed to 900 MHz EMF (Margaritis et al., 2014). Notably, exposure to the EMF emitted by GSM for 2 min/a day causes a decrease in the reproductive capacity of *D. melanogaster* during adulthood (Panagopoulos et al., 2004). Similarly, Panagopoulos (2012) investigated *D. melanogaster* exposed to GSM radiation and reported that mobile phones caused delayed ovarian development because of DNA damage resulting in apoptosis in the

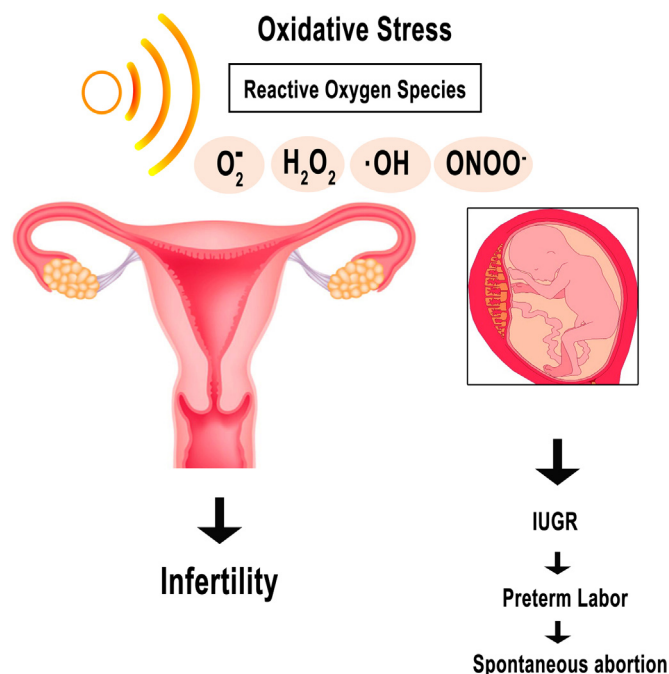


Fig. 4. The effect of EMF on female reproduction and fetal development. IUGR: Intrauterine growth restriction (Agarwal et al., 2012).

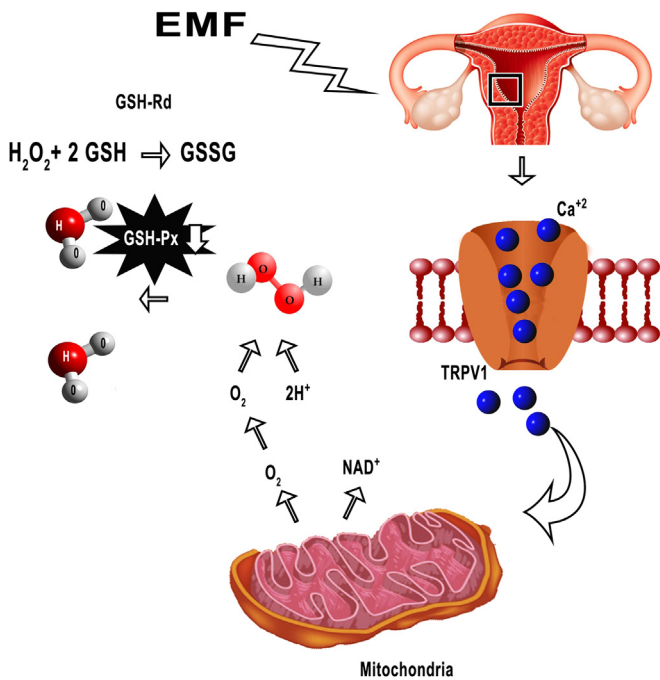


Fig. 5. The role of TRPV1-mediated Ca^{+2} channels in oxidative stress -induced damage in the rat uterus exposed to long-term EMF during pregnancy. The figure also shows the production of superoxide (O_2^-) and hydrogen peroxide (H_2O_2). Glutathione peroxidase (GSH-Px) catalyzes the reduction of H_2O_2 to H_2O (modified from [Yüksel et al., 2016](#)).

ovary. There are some similarities in EMF-induced fertility disorders between insects and mammals in terms of induction of apoptosis ([Panagopoulos, 2012](#)). Previous studies have shown that antioxidant biochemical changes may occur due to long-term EMF exposure ([Agarwal et al., 2009](#)). [Yüksel et al. \(2016\)](#) investigated the effects of 900, 1800 and 2450 MHz EMF emitted by mobile phones and Wi-Fi on the uterus in pregnant rats and their offspring by evaluating levels of

plasma hormones and the oxidative stress parameters ([Yüksel et al., 2016](#)). Additionally, EMF-induced damage may occur through the consumption of non-enzymatic antioxidants and enzymatic antioxidants ([Naziroglu et al., 2013](#); [Ozorak et al., 2013](#)). GSH-Px is the thiol antioxidant enzyme in mammalian cells and protects cytosolic lipids, proteins and nucleic acids as a response to oxidative damage ([Anderson, 1998](#); [Naziroglu, 2009](#)). [Yüksel et al. \(2016\)](#) observed decreased levels of prolactin, estrogen and progesterone in pregnant rats exposed to 900, 1800 and 2450 MHz EMF and their offspring. They also noted that lipid peroxidation in the rat uterus, was linked with a decline in GSH-Px, the key antioxidant enzyme, in EMF. However, no changes were observed in the rat developmental period. These findings suggest that the antioxidant response of GSH can be upregulated through the enzymatic activity of GSH-Px ([Fig. 5](#)) ([Yüksel et al., 2016](#)).

4. The effects of mobile phone use on fertilization and pregnancy

Reproductive cells seem to be more sensitive to both ionizing and non-ionizing radiation than other cells because they undergo rapid rates of growth during meiosis and mitosis. The faster that cells grow the greater their chance of incorporating errors during the synthesis of various biomolecules ([Panagopoulos, 2012](#)). EMF induces the generation of ROS in various animal and human tissues ([Kismali et al., 2012](#); [Ozorak et al., 2013](#); [Seite et al., 2004](#)).

When the water present in approximately 70–80% of cells is exposed to EMF, decomposition can occur. The body's electrical conductivity increases due to increased water consumption, and amniotic fluids during pregnancy can also result in greater sensitivity to EMF. ([Kismali et al., 2012](#); [Obolenskaya et al., 2010](#)).

[Chen et al. \(2017\)](#) studied the effects of EMF emitted by simulated mobile phone use on fertilization and embryo development. They reported that 935 MHz EMF in medium and high-density can reduce fertilization rates and blastulation in mice, thus lowering the probability of embryo implantation. Alanine, glycine, glutamic acid and glutamine promote embryo development during the cleavage stages ([Chen et al., 2017](#)). Heynick and Merritt reported that RF may interact with the embryo or fetus during pregnancy and cause developmental

Table 1
Summary of the metabolomics effects of mobile phones on reproductivity.

Frequency	Study type	Dose/time	Conclusion/mechanism	References
900 MHz 1800 MHz 2450 MHz	Rats	60 min/day	EMF-induced oxidative stress increased in the development of offspring when the maternal uterus was exposed tho EMF.	(Yüksel et al., 2016)
2450 MHz	Rats	60 days daily 2 h	2450 MHz EMF exposure leads to apoptosis by increasing caspase-3 activity in the rat sperm during spermiogenesis and affects sperm maturation	(Kumar et al., 2011)
850 MHz	Human	60 min/day	RF-EMF emitted by mobile phones may cause oxidative stress in human semen and affect sperm mobility and viability.	(Agarwal et al., 2009)
900 MHz	Rats	35 days Daily 2 h	Following EMF exposure, an increase in CAT activity and a decrease in GPx, SOD activity may cause oxidative stress and enhance the possibility of infertility.	(Kesari et al., 2011)
900 MHz	Rats	1 month 7days/week 20 min/day	No effect was observed in the testis following 20 min exposure to EMF emitted by mobile phones.	(Dasdag et al., 2003)
1900 MHz (800 MHz digital and 800 MHz analog)	Rats	18 week 6 h/day	Long-term exposure to EMF may cause a decrease in sperm motility.	(Kang et al., 2010)
900 MHz	Rats	4 weeks 5 days /week 30 min/day	Long-term EMF exposure may affect the hormonal regulation of spermiogenesis	(Ozguner et al., 2005)
800 MHz	Rabbits	12 weeks 8 h/day	When mobile phones are kept in standby mode, EMF may cause deteriorations in testicular morphology and functions in the adult rabbit.	(Salama et al., 2010)
900/ 1800 MHz	Rats	28 days 1 h/day	Exposure to RF-EMF leads to an increase in lipid peroxidation and low GSH levels in the epididymis and testis.	(Mailankot et al., 2009)
900 MHz	<i>Drosophila melanogaster</i>	5 days 6 min/day	Exposure to continuous 900 MHz EMF leads to actin-cytoskeleton disorganization resulting in cell death during early and mid-oogenesis.	(Panagopoulos et al., 2004)
2450 MHz	Rats	21 days 1 h/day	EMF exposure caused an increase in total antioxidant status and oxidative stress index. More apoptotic cells were observed in prenatal rats exposed to EMF.	(Sangun et al., 2015)

abnormalities. It has also been suggested that EMF exposure can result in fetal death or mutations (Heynick and Merritt, 2003) along with attention deficit disorders in offspring (Aldad et al., 2012).

In conclusion, EMF emitted by mobile phones has a number of well-documented adverse metabolomic effects on the male and female reproductive systems and can lead to infertility by increasing ROS production and reducing GSH and other antioxidants. The primary target of the EMF emitted by mobile phones may be the cell membrane (Pall in press, this volume). This then results in accelerated activity of membrane NADH oxidase and, consequently, greater rates of ROS formation that cannot be easily conjugated or detoxified. Although many studies have reported morphological and functional deteriorations in testis and ovary following EMF exposures, as well both structural and functional deficits in reproductive health, the underlying mechanisms have not been fully elucidated. To assist in further clarification of these processes and mechanisms, Table 1 summarizes key studies on the metabolomic effects of EMF on reproductive systems. Future studies will benefit greatly from standardized exposure protocols and evaluations of key metabolomic indicators.

Conflict the interest

The authors declare that they have no conflict of interest.

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