Review Article

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Effect of radiofrequency radiation on reproductive health

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The development of cellular phone system has greatly increased the extent and magnitude of radiofrequency radiation (RFR) exposure. The RFR emitted from mobile phone and mobile phone base stations exerts thermal and non-thermal effects. The short-term and long-term exposure to RFR may have adverse effect on humans as well as animals. Most laboratory studies have indicated a direct link between exposure to RFR and adverse biological effects. Several *in vitro* studies have reported that RFR induces various types of cancer and DNA or chromosomal damage. On the other hand, some animal studies have not reported adverse effects of this radiation. The present review summarizes information available on the possible effects of RFR on the reproductive health.

Key words Biological effect - electromagnetic field - mobile phone - mobile phone base station - radiofrequency radiation - thermal and non-thermal effects

Introduction

The radiofrequency radiation (RFR) is a component of electromagnetic energy covering the frequency range of 3 KHz-300 GHz[1]. Cellular phones were introduced during the 1990s, and today there are more than millions of cell phone users in the country[2]. The explosive expansion of cell phone system has greatly enhanced the level and magnitude of RFR exposure. There is potential exposure in the surrounding areas of the fixed broadcast facilities situated in residential areas, schools, *etc*. With the increased use of cell phones, the levels of radiations and exposure of the population have consequently amplified drastically[2].

The RFR is of short term and repeated nature at a comparatively high intensity when emitted from cell phones, whereas RFR of cell phone base stations is of long duration but with a very low intensity. The biological effects of low-frequency (<100 Hz) radiations are well recognized and reported to cause adverse effect on health via either thermal or non-thermal effect. Thermal effects occur due to holding cell phones near to the body, whereas non-thermal effects are from both cell phones and cell phone base station[2].

RFRs have adequate energy to create thermal effect in living cells and tissues. RFR may be absorbed at the

molecular level producing an alteration of dielectric properties of molecules[2]. Molecular dielectric properties are responsible for the magnitude of heat. Therefore, electromagnetic field (EMF) can generate heat. A thermal response can be altering many biochemical and physiological pathways in living organisms. It has been reported that a specific absorption rate (SAR) of more than 4 W/kg may enhance temperature around 1°C, under moderate condition, and the SAR of RFR is a time-dependent factor[2].

Biological effects from RFR exposure also occur where thermal mechanism may not be possible or inadequate to account for these effects. These are referred to as non-thermal (athermal) effects. RFR could be absorbed at the surface of tissue at molecular level producing various molecular transformations and alterations[1]. Long-term exposure to RFR-EMF could induce a variety of effects in the cellular response[2]. A possible mechanism of non-thermal effects of RFR-EMF on living organisms is by producing reactive oxygen species (ROS) and activation of ion channels of membrane. The ROS and ions can activate cell receptors and cell signalling cascade, which induces secondary messenger system[3]. Any alteration in cell receptor and signalling mechanism can upregulate and downregulate the gene expression, peptide synthesis, protein formation and enzyme activity (protein function). Cleary *et al*[4,5] have reported that continuous exposure of RFR increases cell proliferation including human peripheral lymphocytes. RFR downregulates gap-junctional intracellular signalling which plays an important role in cell growth and cell differentiation[6]. Furthermore, RFR has also been reported to decrease the rates of channel protein formation and frequency of single-channel opening and enhance the rates of rapid burst[7]. Paulraj and Behari[8] observed an increase in calcium-dependent protein kinase C in rat brain, suggesting that it could affect membrane-bound enzymes linked with cell proliferation and signalling.

The main difficulty to understand the biological effects of low-frequency radiation is due to different exposure parameters and complex interactions as well as the variation in body structure and environment. Environmental factors such as temperature, air velocity, humidity and body insulation may also play an important role in biological effects. Therefore, safety of humans from EMF exposure both at home and workplace has become an important issue. Many scientific bodies conducted researches on this issue and developed guidelines for safe EMF exposure levels[2]. The International Commission on Non Ionizing Radiation Protection (ICNIRP), Institute of Electrical and Electronics Engineers (IEEE) and Federal Communications Commission (FCC) have developed safety guidelines for RFR-EMF exposure and decided maximum permissible limits in terms of power density, electric field and SAR at both general- and occupational-level exposure[1]. In addition to these exposure limits, many developed countries have their own health-based precautionary guidelines for RFR-EMF exposure[1]. As the usage of cell phones has increased, there is an urgent need to pay attention to the impact of RFR on human health. The maximum permissible exposure limits may vary widely. The existing data on the effects of cell phone radiation are inconclusive, currently under debate and still are a controversial issue[2]. However, the existing literature on the effect of non-ionizing radiation-EMF indicates the biological effects and adverse health effects[2]. In the present review, we summarize the available evidences and critically assess the investigations as to their ability to support or dismiss a potential effect of RFR exposure on reproductive health that might be helpful for the creation of new precautionary guidelines for the exposure limit.

Radiofrequency radiation and reproductive health: *In vitro* studies

Several *in vitro* studies have been conducted to find out the impact of RFR-EMF on the parameters of reproductive health. The semen sample of a healthy person was exposed to 850 MHz frequency with controlled maximum power <1 W and SAR 1.46 W/kg for 60 min at a distance of 2.5 cm of antenna from the sample. The obtained data showed that sperm motility and sperm viability were significantly lower in the exposed group. The level of ROS was markedly higher in the exposed group as compared to that of the unexposed group[9,10]. This was also supported by Yan *et al*[11] who reported that 900 MHz frequency from mobile phone at 2 W/kg for one hour decreased sperm-fertilizing ability. Exposure to 2.45 GHz radiation led to decline in progressive sperm-fertilizing ability and enhanced DNA fragmentation in human sperm in an *in vitro* study[12]. Exposure of cell lines of neuroblastoma cells, fibroblasts, rat granulosa cells and spermatogenic cells to 900-2400 MHz at SAR ≤2 W/kg caused significant DNA damage, changes in protein folding, increased level of stress protein (hsp 70) and induced apoptosis[13-19]. Others also reported DNA breakage

in cauda epididymal spermatozoa and embryonic stem cells in mice when exposed to RF EMF of 900 MHz and 1.7 GHz[9,20]. Bernabò *et al*[21] reported that 1 mT EMF decreased sperm function. A 50 Hz super low frequency (SLF)-EMF has been reported to change sperm motility and decrease their viability in rabbits[22].

Radiofrequency radiation and reproductive health: *In vivo* studies on animals

To find out the link between RFR and reproductive health, different animal models as well as different parameters have been studied.

Effect of RFR on the morphology and function of reproductive organs

The RFR-EMF has shown adverse effect on the morphology and functions of reproductive organs. Exposure to RF-EMF is shown to increase testicular proteins in Sprague-Dawley rats, which is related to carcinogenic risk including reproductive damage[23]. Exposure of 2.4 GHz RF emitted from Wi-Fi also affects reproductive parameters of male rats[24]. In another study, Sprague-Dawley male rats (adults) were exposed to 900 MHz EMF for 30 min/day, 5 days/week for five weeks. The effect of EMF was investigated on testes weight, testicular biopsy score count and percentage of interstitial tissue out of the entire testicular tissue, sperm count and apoptosis. No significant change was found in testes weight and testicular biopsy score count. However, seminiferous tubule diameter, mean height of germinal epithelium and serum total testosterone levels were reduced in the EMF-exposed group[25,26]. The acute EMF exposure also showed an increase in testicular temperature[14,27,28]. Mice exposed to 2.45 and 1.7 GHz EMF showed changes in the histology of seminiferous tubular epithelium and deranged parameters of semen[29]. A significant alteration in seminiferous tubules and increase in the death rate of germ cells in testes were also found when mice were exposed to 60 Hz EMF at 0.5 mT[30]. Similarly, in mice, 60 Hz EMFs of 14 and 200 μT stimulated spermatogenic cell apoptosis[16]. In Wistar rats, 2.45 GHz stimulated a decrease in Leydig cell number and an increase in apoptosis-positive cell number in the seminiferous tubules[31]. In contrast, Imai *et al*[32] reported significant increase in sperm count, without abnormalities of sperm motility or morphology at similar exposure level. Other published data showed a decrease in the diameter of seminiferous tubules and epithelial thickness[14,25,33-35]. In some studies, no histological changes were found in the animal testicular tissues after exposure to radiation emitted from cell phones[34,36,37]. Guney *et al*[38] reported that enhanced oxidative stress (OS) by a 900 MHz EMF led to endometrial histopathology impairment in rats. Oxidative endometrial damage plays an important role in endometrial impairment at biochemical and histological levels, leading to endometrial histopathologic impairment in rats[39,40]. A decrease in the number of seminiferous tubules, Leydig cells and height of seminiferous epithelium was reported after exposure of rats to 60 Hz, 1 mT SLF-EMF from gestation day 13 to post-natal day 21[41].

Effect of radiofrequency radiation on hormonal profile

Reproductive endocrinology plays a vital role in controlling the following two important functions of testes: spermatogenesis and steroidogenesis. In the hypothalamus, melatonin regulates the pulse of luteinizing hormone (LH)-releasing hormone, influencing follicle-stimulating hormone (FSH) and LH secretion. This alters the gonadal sex steroid production and changes in reproductive cycle[42]. The circulating level of melatonin was decreased in rats and hamsters exposed to 50 Hz EMF for six weeks[43,44]. In another experiment, mice were exposed to electromagnetic pulse irradiation five times within two minutes and it was observed that serum testosterone level was significantly dropped and there was no difference in serum LH and oestradiol (E2) level as compared to that in sham-operated animals. The decrease in the level of testosterone shows the effect of EMF on Leydig cells and susceptibility to EMP irradiation, which causes injury in the structure and function of Leydig cells in mice[45,46]. The mRNA expression for P450 cholesterol side chain lyase in Leydig cells was also altered after EMF exposure[47]. In another study, the level of seminal plasma fructose declined significantly in rabbits exposed to radiation emitted from cell phones for 10 weeks; however, there was no change in serum testosterone levels between the study groups[33]. Oyewopo *et al*[48] reported that the levels of FSH, LH and testosterone significantly decreased in adult male Wistar rats when exposed to radiation emitted by cell phones in comparison with that in control group.

Effect of radiofrequency radiation on oestorus cycle

Female mice after weaning exposed to electromagnetic radiation for six weeks showed extended oestrous cycle[49]. Similarly, dairy cows exposed to 60 Hz 30 μT EMF for 16 h/day showed

extended oestrous cycle[50]. Extended oestrous cycle can slow down ovulation in females during the fertile period of their life and hence decreases the probability of fecundity. Follicle cultures of mouse exposed to 33 Hz SLF-EMF at five-day intervals showed defects in follicle growth, whereas mouse exposed to 50 Hz EMF did not show any effect on growth. SLF-EMF exposure to 33 or 50 Hz for three days has been reported to inhibit the formation of antrum in cultured follicles *in vitro*[17]. The data suggested that ovarian steroid-regulated oestrous cycle could be more sensitive when exposed to EMF as compared to foetal development and foeto-maternal interaction. However, 10 kHz, 0.2 mT sine wave EMF in female rats did not show any effect on oestrous cycles[51], suggesting that EMFs' effect on oestrous cycle might depend on frequency, energy and animal species. In a study on adult Wistar female rats, continuous exposure to 50 Hz SLF-EMF for three months resulted in significant decrease in plasma catalase activities, but there was no effect on progesterone level, oestrous cycle and weight of uterus and ovaries[52]. On the contrary, EMF exposure to ovariectomized female Sprague-Dawley rats for four hours per day for three days at 1439 MHz showed no differences in uterine wet mass or serum E2 level[53]. Oral *et al*[54] reported that OS and endometrial apoptosis increased in female rats exposed to 900 MHz EMF for 30 min/day for 30 days.

Effect of radiofrequency radiation on oxidative stress

Several studies have reported that exposure to RFR enhances the formation of ROS. Extremely low-frequency RFR exposure resulted in an increase in testicular tissue malondialdehyde and nitric oxide levels and caused a decrease in glutathione (antioxidant) levels in male Wistar rats[55]. Kesari and Behari[56] used male Wistar rats, aged 60-70 days old, exposed to 2.45 GHz microwave radiation and cell phone radiation, at SAR 0.9 W/kg in a Plexiglas® cage for 2 hours/day for 35 days. They found that cell phone exposure led to a build-up of free radicals and ROS levels in sperm which in turn resulted in the generation of OS in the testicular tissue. They also reported an enhanced ROS level in the semen when rats were exposed to mobile phone radiation as compared with sham-operated animals[57,58]. The same group also reported that exposure to electromagnetic radiation directly from cell phone 2 h/day ×35 days at 0.9 W/kg SAR showed decreased total sperm count and an increased mean percentage of apoptotic cells in rats[59].

Radiofrequency radiation-induced DNA damage and micronuclei formation

The effects of RFR-EMF on DNA damage have been investigated and demonstrated in several studies carried out in different tissues[60-64]. A DNA segment rearrangement and breakage is reported in mouse testis when exposed to RF-EMF of 2450 MHz[63]. Furthermore, exposure to RF-EMF of 900 MHz and 1.7 GHz has been reported to induce DNA damage in cauda epididymal spermatozoa and embryonic stem cells in mice[64,65]. De Iuliis *et al*[66] found that exposure to RF-EM wave significantly damaged sperm DNA. In mice, exposure to RF-EMW at 900 MHz for 12 h/day×7 days significantly damaged mitochondrial and nuclear genome in epididymal spermatozoa[64]. Gollapudi and McFadden[67] reported harmful effects of SAR of 0.9 W/kg emitted from cell phone on DNA and chromatin. Kesari *et al*[58] reported a significant increase in micronucleated polychromatic erythrocytes (PCEs) in mobile phone-exposed Wistar rats, whereas a decrease in the ratio of PCE and normochromatic erythrocyte in blood cells exposed by radiation emitted from mobile phone. The micronuclei levels in bone marrow cultures increased when exposed to mobile phone frequency for 35 days at 0.9 W/kg SAR[58].

Effect of radiofrequency radiation on embryo development

Ovulated and mated female mice exposed to 50 Hz EMF for four hours per day, six days a week, for two weeks, showed decreased number of blastocysts with increase in DNA fragmentation[68]. These findings indicated that EMF exposure in the pre-implantation stage may have negative effects on embryonic development[68]. Furthermore, SLF-EMFs of 50 Hz, 0.75 mT EMF exposure for four hours before ovulation delayed the cleavage of fertilized eggs in swine, suggesting a negative effect of SLF radiation on early embryonic development[21]. Exposure of pregnant mice to a 50 Hz, 20 mT EMF during gestation days 0 to 17 did not show any remarkable changes in embryonic survival, sex ratio and embryonic malformation; however, significant increase in the height and body weight of offspring was reported[28]. In contrast, exposure to a 50 Hz sine wave EMF at 5.0 mT for nine and two weeks, respectively, before copulation was not able to exert any changes in the fertility of both gamete and foetal development[69]. During pregnancy, mice exposed to a 20 kHz sawtooth EMF at 6.5 μT for eight hours per day showed increased abnormalities in foetus[16].

Epidemiological studies

Several researchers reported a link between cell phone usage and changes in sperm count, motility, normal morphology and viability[70]. A study on foetal and neonatal cardiac output (COP) and heart rate (HR) following acute maternal exposure to radiation emitted by cell phone reported significant changes in HR and COP[71]. An increase in the HR of foetus and neonates and decrease in stroke volume and COP were found prior to and later than mobile phone use[71]. A retrospective study on 371 men of reproductive age reported negative effects of prolonged use of mobile phone on sperm motility[72]. Wdowiak *et al*[73] also conducted a retrospective study on 304 men of reproductive age and found a correlation between time-dependent cell phone use and decreased normal forward progressive motility of sperm. Wdowiak *et al*[73] also observed that decrease in normal sperm morphology and count was linked with the duration of exposure to radiation emitted by GSM cell. An observational study by Agarwal *et al*[74] on 361 men showed marked variation in the normal morphology of sperm between low- and high-usage groups. Moreover, the author also found significant difference in sperm motility and viability between the groups[74]. Another observational study on 231 men showed low sperm count in heavy cell phone users[72]. Andersen *et al*[75] studied 708 men and obtained data of semen quality, testicle size and reproductive hormones. They reported that sperm count was positively correlated with testicular size and minor difference in FSH, while there was no difference in the concentration of reproductive hormones.

Conclusion

Available data indicate that exposure to EMF can cause adverse health effects. It is also reported that biological effects may occur at very low levels of exposure. The RFR effect can be more intensified based on the range and duration of the exposure. The RFR can also exert adverse effects in the first few minutes. Persistent exposures of EMF radiation can result in health hazards because these radiations interfere with normal physiological and biological function of the body. EMF works as an environmental pollutant and has undesirable health effects on animals and humans. Several developed countries have already established health-based guidelines for exposure level for their countries. India has also developed health-based guidelines for exposure level of RFR from cell phones and cell phone base stations, but given the difference in environmental conditions, and lower muscle contents, bone mineral density, fat content, *etc*., of Indians than the people of developed nations, there is a need to have a mid-course correction in the existing exposure limit of RFR in the country.

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