Outlook

Cell phones and male infertility: dissecting the relationship

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Abstract

There has been a tremendous increase in the use of mobile phones in the past decade and concerns are growing about the possible hazardous effects of radio-frequency electromagnetic waves (EMW) emitted by these devices on human health. Preliminary studies, though with limitations in study design, suggest a possible link between cell phone use and infertility. A recent study found that use of cell phones adversely affects the quality of semen by decreasing the sperm counts, motility, viability and morphology. Evidence of detrimental effect of mobile phones on male fertility is still equivocal as studies have revealed a wide spectrum of possible effects ranging from insignificant effects to variable degrees of testicular damage. Although previous studies suggested a role of cell phone use in male infertility, the mode of action of EMW emitted from cell phones on the male reproductive system is still unclear. EMW can affect the reproductive system via an EMW-specific effect, thermal molecular effect or combination of both. Studies performed on human males are scarce and therefore further studies with a careful design are needed to determine the effect of cell phone use on male-fertilizing potential.

Keywords: *cell phone, infertility, radiation, semen, spermatozoa, testicular damage*

Introduction

Cell phones have become indispensable devices in daily life. These phones operate at different frequencies, differing in respect to the frequency usage in different countries and in different continents. Concerns are growing about the possible hazardous effects of radio-frequency (RF) electromagnetic waves (EMW) emitted by these devices on human health. For years the cell phone companies have assured people that cell phones are perfectly safe. However, adverse effects of RF EMW emitted from cell phones on human and animal biological systems have been reported in the literature. Recent studies also suggest that EMW emitted from cell phones can reduce the fertilizing potential of men (Davoudi *et al.*, 2002; Fejes *et al.*, 2005; Kilgallon and Simmons, 2005; Erogul *et al.*, 2006; Agarwal *et al.*, 2007). This review summarizes the type and degree of disturbances in the male reproductive system that have been found to be caused by EMW emitted from cell phones. This in turn may help to demonstrate the need for any protective measures to be taken to prevent or reduce the effect of EMW on the male reproductive system.

Biophysics behind cell phones

Exposure of RF energy depends upon the frequency of the cellular phone used. Most common cell phones (GSM: global system for mobile communication) work at 900–1900 MHz in the USA, whereas in most other parts of world these phones work at 850–1800 MHz frequencies. The higher the frequency, the more energy they carry. Radiant energy is absorbed into human bodies by three main mechanisms: (i) aerial effect: body receives and absorbs the RF signal depending upon size of the body part and wavelength of signal; (ii) coupling of the RF signal with the tissue; and (iii) resonant absorption (D'Andrea *et al.*, 1985). The amount of RF energy absorbed from phones into

local tissues, called the specific absorption rate (SAR), is the most useful quantity for assessing exposure from transmitters located near the body. SAR of cell phones varies from 0.12 to 1.6 watts/kg body weight depending upon the model. In the USA, the upper limit of SAR allowed is 1.6 watts/kg (Federal Communications Commission, 1999).

Effects of radio-frequency waves on human health

Use of cell phones has been demonstrated to cause dose-dependent difficulty in concentration, fatigue and headache (Oftedal *et al.*, 2000), increase in reaction time (Preece *et al.*, 1999), alteration in electroencephalogram pattern and disturbance in sleep (Huber *et al.*, 2000). Cell phone exposure has also shown to increase the resting blood pressure (Braune *et al.*, 1998). Although Fritze *et al.* (1997) found a significant increase in the permeability of blood-brain barrier on exposure to microwaves of SAR 7.5 W/kg, cell phones do not produce such high values of SAR. Likewise, adverse ocular effects were found only at SAR values well above those generated by the cell phones (Elder, 2003). Conflicting studies have been published regarding the effects of RF radiation exposure on melatonin secretion by the pineal gland (Burch *et al.*, 1998; 2002; de Seze *et al.*, 1999). Furthermore, current scientific evidence indicates that RF exposure is unlikely to induce or promote cancers. Most study reports have not supported any increase in the incidence of leukaemia, brain tumour, testicular cancer, genitourinary and breast cancer with exposure to EMW (Moulder *et al.*, 1999; Colonna, 2005).

Cell phone use and decrease in semen quality

Infertility affects approximately 15% of couples of reproductive age, with nearly half of these cases resulting from male factor infertility (Thonneau *et al.*, 1991; Sharlip *et al.*, 2002). A number of reports, though with limitations in study design, suggest a possible link between cell phone use and infertility. Our recent study (Agarwal *et al.*, 2007) involving 361 men attending an infertility clinic suggested that use of cell phones adversely affects the quality of semen by decreasing the sperm counts, motility, viability and morphology, which might contribute to male infertility. The above four sperm parameters were lower in the study population who used cell phones for longer duration. The effect of cell phone use on sperm parameters did not depend on the initial semen quality of the subjects when the patients were further examined, based on their sperm count, whether they were either normozoospermic (≥20 million spermatozoa/ml) or oligozoospermic (<20 million/ml) (Agarwal *et al.*, 2007).

In a study done by Fejes *et al.* (2005) on 371 men undergoing infertility evaluations, the duration of possession and the daily transmission time of cell phones correlated negatively with the proportion of rapidly progressive motile spermatozoa, suggesting that prolonged use of cell phones might have negative effects on the sperm motility. Davoudi *et al.* (2002), in a small prospective study involving 13 men with normal semen analysis, also found that using GSM phones for 6 h a day for 5 days decreased the rapid progressive motility of spermatozoa. Similarly, Erogul *et al.* (2006) found a decrease in sperm motility in semen samples of 27 men exposed to 900 MHz cell phone for 5 min. In a recent study, keeping cell phones close to the waist has been found to decrease sperm concentration as compared with men not using cell phones at all or storing it elsewhere (Kilgallon and Simmons, 2005). In spite of their consistent results, all these past studies had some serious limitations, such as the exclusion of covariates including life style issues, occupational history and RF exposure from other sources such as radio towers, personal digital assistants (PDA), Bluetooth devices and computers.

Pathophysiology of EMW-induced damage to the male reproductive system

Although previous studies suggested a role for cell phone use in male infertility, the mode of action of EMW emitted from cell phones on the male reproductive system is still unclear. At high intensities, RF radiation has heating properties leading to thermal effects. An increase in tissue or body temperature on exposure to EMW may cause reversible disruption of spermatogenesis (Kandeel and Swerdloff, 1988; Saunders *et al.*, 1991; Jung and Schill, 2000). EMW can also affect reproductive function via an EMW-specific effect ('microwave' effect produced by an increase in tissue temperature less than its normal temperature fluctuation) or its combination with the thermal molecular effect (Blackwell, 1979). Wang *et al.* (2003) suggested, in their study on mice, that Leydig cells are among the most susceptible cells to EMW and injury to these cells may affect spermatogenesis. Dasdag *et al.* (1999, 2003) observed a decrease in mean seminiferous tubular diameter in rats by exposing them to 890–915 MHz cell phone, 3 min daily for 30 days; however they could not replicate their results in a subsequent study. Ozguner *et al.* (2005) demonstrated a decrease in seminiferous tubular diameter and epithelium thickness after applying a radio-frequency generator of 869–894 MHz. However, a recent study by Ribeiro *et al.* (2007) could not find any significant adverse effect of cellular phones (1835–1850 MHz) on rat testis. De Seze *et al.* (1999) studied the change in the concentrations of anterior pituitary hormones including FSH and LH in 21 healthy male volunteers after applying 900 MHz RF radiation exposure emitted from a cell phone for 2 h a day, 5 days a week for 1 month and found no effect. However, the duration of RF radiation exposure in their study might not be sufficient to produce any significant effect.

Exposure to RF electromagnetic radiation and mild scrotal heating can induce DNA damage in mammalian spermatozoa, although the underlying mechanisms are unclear. Several investigators have demonstrated an increase in DNA fragmentation in a variety of human and animal cells (Lai and Singh, 1996; Diem *et al.*, 2005; Stronati *et al.*, 2006; Panagopoulos *et al.*, 2007). Lai and Singh first reported DNA strand breaks from low intensity microwave RF radiation in rat brain cells. In their study, 2 h exposure to 2450 MHz continuous and pulsed RF radiation produced a dose-dependent increase in DNA single- and double-strand breaks (Lai and Singh, 1996). More recently, Aitken *et al.* (2005) found significant damage to mitochondrial and nuclear genome in epididymal spermatozoa of mice with RF EMW, 900 MHz, 12 h a day for 7 days. Spermatozoa are

extremely vulnerable to induction of DNA damage as they lose their cytoplasm, which contains anti-oxidant enzymes, and their capacity for DNA repair after spermiation. They are also differentiated to the point that they can no longer undergo apoptosis in response to any severe genetic damage (Aitken *et al.*, 2005). The induction of DNA damage in spermatozoa has been associated with male infertility, early pregnancy loss and morbidity in the offspring, including childhood cancer (Aitken, 1999). Although currently no human studies are available demonstrating DNA damage in sperm cells by RF radiation exposure, EMW have been shown to affect sperm motility (Davoudi *et al.*, 2002; Fejes *et al.*, 2005; Erogul *et al.*, 2006), and it is known that a negative correlation exists between sperm motility and sperm chromatin damage (Giwercman *et al.*, 2003). **Figure 1** depicts several proposed mechanisms of damage to spermatozoa by cell phone radiation based on the preliminary findings in the studies discussed above.

Spermatozoa are known to be susceptible to damage induced by oxidative stress; however whether RF radiation is capable of inducing oxidative stress is still debatable. Musaev *et al.* (2005) found that high-intensity microwave exposure stimulates lipid peroxidation in the hypothalamus of rats. However, Hook *et al.* (2004) did not find any alteration in the concentration of intracellular oxidants, glutathione concentration and antioxidant defences in interferon-γ and lipopolysaccharide-stimulated cells on exposure to RF radiation fields. Conflicting studies have also been published regarding the effect of EMW exposure on the secretion of an antioxidant melatonin (de Seze *et al.*, 1999; Gavella and Lipovac, 2000; Burch *et al.*, 2002).

Studies analysing the effects of RF radiation on apoptosis have failed to find any significant effect. An exposure of 1800 MHz signal for 12 h failed to induce apoptosis in human Mono Mac 6 cells (Lantow *et al.*, 2006). Similarly no evidence of apoptosis has been detected after exposing human leukaemia cells *in vitro* to RF waves 25 times higher than the reference levels set by the International Commission on Non-Ionizing Radiation Protection (Port *et al.*, 2003). The effects of RF radiation on human sperm cell apoptosis have not yet been evaluated.

Future research

In spite of the extensive research, evidence for a detrimental effect of cell phones on male fertility is still equivocal as all the previous studies have revealed a wide spectrum of possible effects, ranging from insignificant effects to variable degrees of testicular damage. Furthermore, it is impractical to compare rat model to humans (Cairnie and Harding, 1981). The inconclusive findings have started an intense debate on whether the spermatogenesis, sperm quality and sperm-fertilizing potential are affected by the use of cell phones or not. Given the vulnerability of spermatozoa to RF damage, and the clinical significance of this damage in terms of fertility, pregnancy and childhood health, human studies with a careful design are urgently needed to investigate the impact of RF waves from cell phones on testicular tissue and male germ line. Research is being conducted in our centre utilizing better study designs (by eliminating possible bias due to patient demographics, lifestyle issues and environment) in order to verify the results of earlier investigators and explore the pathophysiology of damage caused by EMW emitted from cell phones on the male reproductive system.

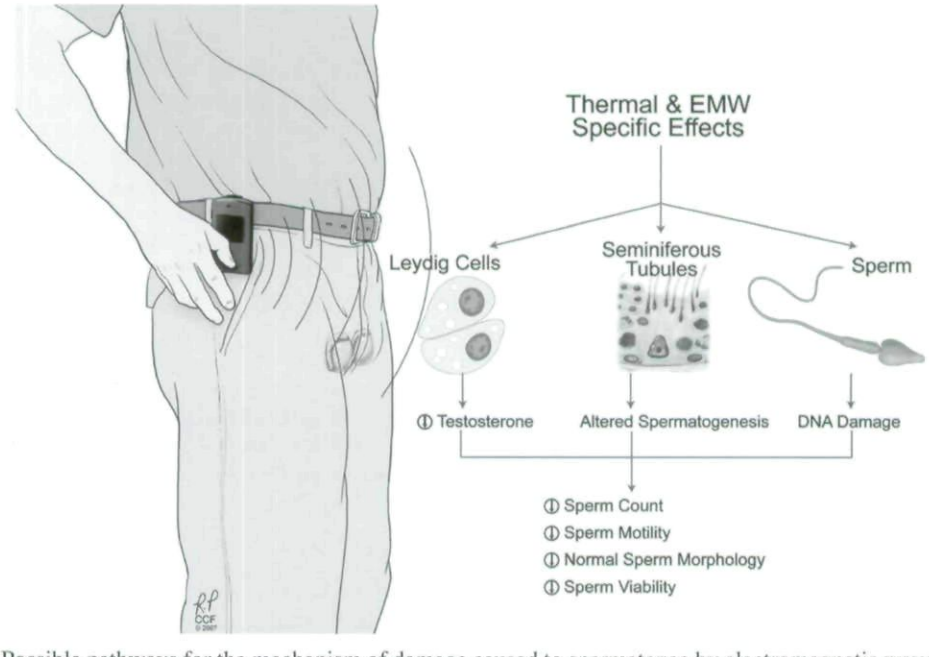

Figure 1. Possible pathways for the mechanism of damage caused to spermatozoa by electromagnetic waves (EMW) emitted from cell phones.

Conclusion

The question as to whether cell phone radiation causes any adverse effects on human fertilization potential has raised a significant public concern. Various preliminary studies, though with limitations, have suggested a use-dependent decrease in seminal quality and testicular tissue damage in men using cell phones. However, the mode of this damage to male reproductive system by EMW is still unclear.

In contrast to the scientific discussion, public discussion is not only driven by facts but also by anxiety, emotions and economic and political interests. To deal with the uncertainty regarding this issue, it is generally agreed upon that further high-quality research is needed.

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Stem cells derived from parthenogenetic human embryos

Activation of human eggs parthenogenetically has recently been offered as another means of avoiding the use of embryos to prepare human stem cells. Curiously, it was published soon after an article describing the formation of parthenogenetic mice and sharks (Edwards, 2007). The work on parthenogenesis and stem cells was carried out by Elena Ravazova and Jeffery Janus of Lifeline Cell Technology, Maryland, USA. The eggs were activated chemically and many died very early although some developed to blastocysts as a source of stem cells, some of which grew for 10 months *in vitro* and were capable of producing cells typical of the three germ layers. According to Cyranoski (2007), these cells would not induce an immune response in the embryo donors and perhaps in many women recipients, but this must be a matter for enquiry and may be assisted by making banks of known stem cells.

Some indications of possible results are worrying as shown when cells from normal and parthenogenetic mice were mixed to form a chimaera in which tissues grew poorly. Safety trials in mice are proposed for early 2008 with the intention of producing retinal cells, and will be followed by human trials later in the year. So far, six stem cell lines have been produced from 46 eggs collected from five women, who were recruited in Russia as they were undergoing IVF. These donors received no payments although some of their costs for IVF were covered.

Previously, a group of embryologists in Milan claimed to have prepared parthenogenetic stem cells in 2006 but their data is still unpublished (Cyranoski, 2007). Even earlier, Pincus and Shapiro (1940) claimed to have produced parthenogenetic rabbit blastocysts, and Kaufman (1983) produced parthenogenetic mouse embryos that reached the 20-somite stage. A method aimed at overcoming epigenetic problems in early mouse embryos was reported by Kono *et al.* (2004) who correctly inserted IGF2 into the nucleus of mouse oocytes. Of the resulting embryos, 80% reached the blastocyst stage, with 10 live and nine dead offspring being born. Data such as these send a warning signal to proponents of parthenogenetic stem cells.

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