J Assist Reprod Genet (2012) 29:293–297
DOI 10.1007/s10815-012-9722-1

GONADAL PHYSIOLOGY AND DISEASE

Challenging cell phone impact on reproduction: A Review

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Received: 23 December 2011 / Accepted: 27 January 2012 / Published online: 16 February 2012

Abstract
Purpose The radiofrequency electromagnetic radiation (RF-EMR) produced by cell phones can enhance the excitability of the brain and has recently been classified as carcinogenic. The suggested use of hands-free kits lowers the exposure to the brain, but it might theoretically increase exposure to the reproductive organs. This report summarizes the potential effects of RF-EMR on reproductive potentials in both males and females.
Methods A critical review of the literature pertaining to the impact of cell phone RF-EMR on reproduction in male and female animals and humans was performed, with a focus on gonad metabolism, apoptosis of reproductive cells, fertility status, and serum reproductive hormones.
Results While some animal and human studies revealed alterations in reproductive physiology in both males and females, others did not report any association. The in vitro and in vivo studies to date are highly diverse, very inconsistent in conduct and, in many cases, report different primary outcomes.
Conclusion The increasing use of cell phone warrants well-designed studies to ascertain the effect of their RF-EMR on reproduction.

Capsule The increasing use of cell phone warrants well-designed studies to ascertain the effect of their radiofrequency electromagnetic radiation on reproduction.

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Keywords Cell phone · Radiofrequency electromagnetic radiation · Reproduction · Pregnancy · Gonad · Sperm · Ovary · Granulosa cell

Cell phones have become an integral part of everyday life. As cell phone use has become more widespread, concerns have mounted regarding the potentially harmful effects of radiofrequency electromagnetic radiation (RF-EMR) from these devices. The World Health Organization (WHO) recently announced that radiation from cell phones can possibly cause brain cancer [1]. According to the WHO's International Agency for Research on Cancer (IARC), RF-EMR fields have been classified as possibly carcinogenic to humans on the basis of an increased risk for brain glioma that some studies have associated with the use of wireless phones [1]. A recent study [2] provided evidence that the human brain is sensitive to the effects of RF-EMR from acute cell phone exposure. The findings of increased metabolism in regions closest to the antenna during acute cell phone exposure suggest that brain absorption of RF-EMR may enhance the excitability of brain tissue. It was concluded that it is important to take pragmatic measures to reduce exposure, such as hands-free devices or texting [1]. The fears from these data might imply that cell phones "in talk mode" should be placed away from the head region and ultimately might spend more time in the trouser, waist or pockets, areas all close to the gonads, while using a hands-free device like Bluetooth. The use of hands-free kits lowers the exposure to the brain, but it might increase exposure to other parts of the body, namely the gonads [3]. Therefore, the alterations caused by RF-EMR on human reproductive organs are plausible.

These recent publications on brain cells triggered a literature search in order to ascertain the effect of cell phone radiation on reproduction in male and female animals and

humans with a special focus on gonad metabolism, apoptosis of reproductive cells, fertility status, and serum hormones. Nevertheless, relevant professional societies, such as the American Society for Reproductive Medicine, the American College of Obstetricians and Gynecologists, and the European Society of Human Reproduction and Embryology, have not expressed a stance regarding cell phone use among infertility patients.

Studies in males

A number of recent reports have suggested a possible link between cell phone use and male infertility [4–12]. The concern has arisen that carrying a cellular phone near the reproductive organs such as the testes may cause dysfunction and particularly a decrease in sperm development and production, and thus decrease fertility in men. A study investigated the effect of free radical formation due to mobile phone exposure and the effect on fertility pattern in male Wistar rats (sham and exposed) [4]. The authors exposed the rats for 2 h a day for 35 days to mobile phone frequency. They found a significant decrease in antioxidant enzymes glutathione (GSH) peroxidase and superoxide dismutase in the exposed rats (compared to unexposed), while there was a significant increase in catalase and malondialdehyde in the exposed group. A significant drop in micronuclei and significant change in sperm cell cycle of G(0)-G(1) and G(2)/M were also noted in the exposed group. Generation of free radicals was significantly increased as well. The authors concluded that there is clear overproduction of reactive oxygen species (ROS) secondary to RF-EMR exposure from commercially available cell phones that might affect the fertilizing potential of spermatozoa [4].

Two studies on adult male rabbits evaluated the effect of RF-EMR emitted from a mobile phone on fructose and citrate levels from weekly collected semen samples [5, 6]. Mobile phone standby mode was positioned adjacent to the rabbits' genitalia for 8 h daily for 12 weeks. In addition to fructose and citrate, they evaluated sperm motility and viability, serum testosterone levels, histological sections from the prostatic complex, ampulla, and vesicular gland. Compared to the unexposed group, there was a significant drop in both fructose levels and number of motile sperms in the exposed group at the 10th week of exposure. There was also a significant drop in the sperm concentration in the exposed group at week 8 and a drop in sperm motility at week 10, and a significant decrease in the diameter of seminiferous tubules. There were no changes in citrate levels [5, 6].

Male mice exposed to RF-EMR from mobile phone base stations at a workplace complex and residential quarters had significantly and in dose-dependent manner more sperm head abnormalities (knobbed hook, pin-head and banana-shaped sperm head) compared to unexposed animals (40% versus 2%, respectively) [7]. The study implicated that living in close proximity to mobile base stations might have an adverse outcome on male reproductive health [7]. Male albino Wistar rats (10–12 weeks old) were exposed to RF-EMR from an active mobile phone for 1 h continuously per day for 28 days [8]. No significant difference was observed in total sperm count between controls (exposed to a mobile phone without a battery for the same period) and RF-EMR exposed groups. However, rats exposed to RF-EMR exhibited a significantly reduced percentage of motile sperm. Moreover, RF-EMR exposure resulted in a significant increase in lipid peroxidation and low GSH content in the testis and epididymis [8]. A significant decrease in protein kinase C and total sperm count, along with increased apoptosis, were observed in male Wistar rats exposed to mobile phone frequencies (2 h/day×35 days) [9]. The results suggest that a reduction in protein kinase activity may be related to overproduction of ROS under microwave field exposure. Decrease in sperm count and an increase in apoptosis may be a causative factor due to mobile radiation exposure leading to infertility [9].

A pilot study in humans evaluated the effect of cellular phone RF-EMR during talk mode on unprocessed (neat) ejaculated human semen from normal healthy donors (n=23) and infertile patients (n=9) [10]. Each semen sample was divided into two: one part was exposed to cellular phone radiation (in talk mode) for 1 h, and the second unexposed part served as control. Samples exposed to RF-EMR showed a significant decrease in sperm motility and viability, increase in ROS level, and decrease in total antioxidant capacity (TAC) score. Levels of TAC and DNA damage showed no significant differences between the exposed and unexposed group. These results reveal that RF-EMR emitted from cell phones may lead to oxidative stress in human semen [10]. Another study evaluated serum free testosterone (T), follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) in humans [11]. In the exposed participants, 68% of the spermatozoa featured a pathological morphology, compared to only 58% in the unexposed subjects. Participants with cell phone usage showed significantly higher T and lower LH levels than those who did not use cell phones. No significant difference between the two groups was observed regarding FSH and PRL values. These results showed that cell phone use might negatively affect sperm quality in men [11]. To investigate the effect of RF-EMR generated by mobile phones on serum T levels in Wistar albino rats, a total of 34 male albino rats were studied [12]. Exposure to mobile phone radiation for 60 min/day for the total period of 3 months significantly reduced serum T level (p=0.028) in Wistar albino rats compared to their matched unexposed control. These results

indicate that long-term exposure to mobile phone radiation might lead to reduction in serum T levels [12].

On the other hand, other animal and human studies did not find any difference in the alterations caused by RF-EMR on male fertility potential. Results of a study [13] performed on Sprague–Dawley rats (5-week old animals) with whole body exposure to mobile multimedia access for 5 h per day, 7 days a week for 5 weeks showed no difference in weights of the testis, epididymis, seminal vesicles, and prostate among the exposed group compared to unexposed controls. The number of sperm in the testis and epididymis was not changed in the RF-EMR exposed group, and there were no alterations in the sperm motility, morphology, or the histological appearance of seminiferous tubules, including the stage of the spermatogenic cycle. This study revealed no testicular toxicity due to exposure to RF-EMR [13]. The effect of radiation on induction of apoptosis-related properties in human spermatozoa was evaluated. Flow cytometry studies were used to examine caspase 3 activity, externalization of phosphatidylserine, induction of DNA strand breaks, and generation of ROS in ejaculated, density-purified, highly motile human spermatozoa exposed to mobile phone radiation. It was found that mobile phone radiation had no effect on any of these sperm parameters [14]. This suggests that the impairment of fertility reported in some studies may not be caused by the induction of apoptosis in spermatozoa. The histological changes by RF-EMR fields on rat testis, specifically with respect to sensitive processes such as spermatogenesis, have been also evaluated [15]. Male rats were exposed to RF-EMR for 12 weeks (two 45-min exposure periods, separated by a 15-min interval). Sperm counts in the cauda epididymis, malondialdehyde concentrations in the testes and epididymis, frequency of spermatogenesis stages, germ cell counts, and appearance of apoptotic cells in the testes were assessed. PARP, p53, bcl-2, caspase 3 and p21 immunoblotting of the testes in RF-EMR exposed and unexposed animals were also evaluated. RF-EMR did not have any observable adverse effects on rat spermatogenesis in this study [15].

A study in humans did not reveal an adverse outcome by RF-EMR on male serum reproductive hormones [16]. Twenty healthy male volunteers aged 19 to 40 were studied. Each subject was exposed to RF-EMR radiation through the use of a cellular phone 2 h/day, 5 days/week, for 1 month. They measured serum (for adrenocorticotropin, thyrotropin, growth hormone, PRL, LH, and FSH concentrations) in nine weekly blood samples obtained starting 3 weeks before the commencement of the exposure and ending 2 weeks after exposure. Within each individual, the preexposure hormone concentration was used as a control. One month of intermittent exposure to cell phone RF-EMR did not induce a long-lasting or cumulative effect on the hormone secretion rate of the anterior pituitary gland in humans [16].

Finally, whether keeping the cell phone in areas close to gonads in active mode will negatively affect spermatozoa and impair male human fertility needs to be determined. Additionally, it needs to be determined whether men of reproductive age who engage in high levels of mobile phone use should not keep their phones in receiving mode below waist level.

Studies in females

Data in animals and humans might indicate an adverse impact caused by RF-EMR on granulosa cells, ovarian follicle numbers, endometrial tissue, quality of oocytes and embryos and even alterations on fetal heart physiology during pregnancy. Diem et al [17] evaluated the effect of intermittent and continuous RF-EMR used in mobile phones on DNA strand breaks in vitro on cultured rat granulosa cells. RF-EMR exposure induced DNA single- and double-strand breaks after 16 h exposure (intermittent 5 min on/10 min off or continuous wave) and after different mobile phone modulations [17]. Batellier et al [18] assessed the effect of RF-EMR exposure on fertile chicken eggs by repeatedly calling a 10-digit number at 3-min intervals over the entire period of incubation. One batch of 60 eggs was exposed to the immediate environment of a cell phone in the "call" position (exposed group), while another batch of 60 eggs was exposed to a similar cell phone in the "off" position (sham group). A significantly higher percentage of embryo mortality was observed in the exposed group compared to the sham group. Significant embryo mortality in the exposed group occurred mainly between days 9 and 12 of incubation [18]. Zareen et al [19] studied the effect of RF-EMR on survival and general growth and development of chick embryos using different doses of RF-EMR. A mobile phone was placed in the incubator in the center of fertilized eggs in "silent ringing" or "active ringing" mode. After incubation for 10 or 15 days, the developmental milestones of the surviving embryos were compared to embryos of unexposed control group. RF-EMR exposure significantly decreased the survival of chick embryos, indicating embryo growth retardation [19].

The effect of RF-EMR of cellular phones in rat ovaries was also investigated. In one study [20], 82 female pups (21 day old rats) were used. Pregnant rats in the study group (n=43) were exposed to mobile phones that were placed beneath the cages during the whole period of pregnancy. A mobile phone in a standby position for 11 h and 45 min was turned on to speech position for 15 min every 12 h. On the 21st day after the delivery, the female rat pups were killed and the right ovaries were removed to assess the number of follicles. They found that the number of follicles was lower than that in the control unexposed group (n=39), suggesting a toxic effect of RF-EMR in utero on pup ovaries [20].

A study examined oxidative stress and apoptosis induced by RF-EMR on rat endometrial tissue exposed for 30 min/day for 30 days to RF-EMR. In this study, Oral et al [21] measured malondialdehyde (an index of lipid peroxidation) as a marker of oxidative stress-induced endometrial impairment and they also assessed Bcl-2, Bax, caspase-3, and caspase-8 by immunohistochemistry (as markers for apoptosis). Their results indicated that mobile phones may cause endometrial apoptosis and oxidative stress [21]. Another study evaluated fetal and neonatal heart rate and cardiac output, following acute maternal exposure to RF-EMR emitted by mobile phones [22]. Ninety women with uncomplicated pregnancies (aged 18–33 years), and 30 full-term healthy newborn infants were included. The pregnant mothers were exposed to RF-EMR emitted by mobile phones while on dialing mode for 10 min during pregnancy and after birth. They found that exposure of pregnant women to mobile phone significantly increased fetal and neonatal heart rate, and significantly decreased fetal cardiac output [22].

On the other hand, some data negate any relationship between cell phone RF-EMR and reproductive outcome. For instance, a study by Ogawa et al [23] evaluated whether gestational exposure to RF-EMR can affect embryogenesis in rats. At gestational day 20, all dams were killed and fetuses were taken out by cesarean section. There were no differences in maternal body weight gain. No adverse effects of RF-EMR exposure were observed on any reproductive and embryotoxic parameters such as number of live, dead or resorbed embryos; placental weights; sex ratios; weights; or external, visceral or skeletal abnormalities of live fetuses [23]. Another study on 40 women undergoing non-stress test was performed to determine the effect of RF-EMR produced by cellular phones on baseline fetal heart rate, acceleration and deceleration [24]. Non-stress test was obtained while the subjects were holding the cell phone on standby mode and on dialing mode, each for 5 min. Similar recordings were taken while there were no phone around for 10 min. RF-EMR did not cause any demonstrable effect on fetal heart rate acceleration and deceleration [24].

The studies to date are highly diverse, very inconsistent in conduct and, in many cases, report different specific outcomes. The most important outcome would be to demonstrate an increase in infertility among heavy cell phone users compared to those with little or no cell phone use. At least for animal and tissue studies, mechanisms to precisely and specifically deliver controlled radiofrequency energy at specified time periods and intensities across the full range of the radiofrequency band reserved for cell phone use is available. Performance of studies in humans using these very specific and available techniques will at least be required before we are able to unlock the uncertainty as to whether cell phone use

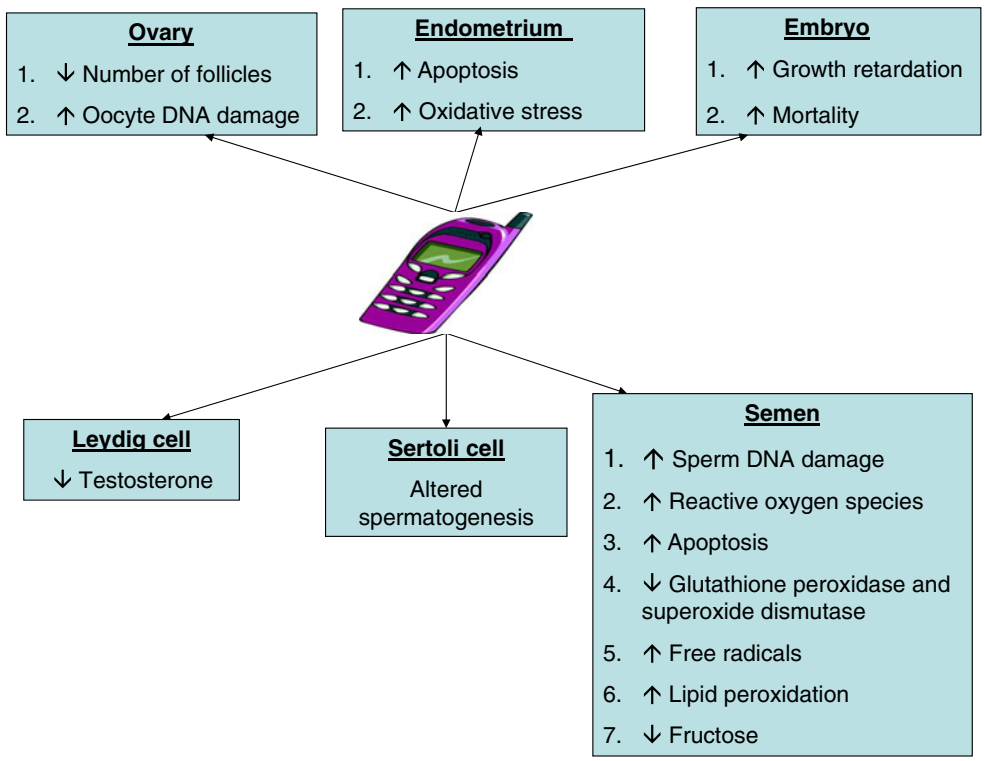

Fig. 1 Potential effects of cell phone radiofrequency electromagnetic radiation on male and female reproduction in animals and humans

does or does not negatively impact reproductive physiology in such a way that it might increase the risk of infertility.

Conclusion

The research on the health effects of RF-EMR has lagged behind the rapid growth in the use of communication technologies, mainly mobile phones and smartphones. Smartphones now account for more than one-quarter of the U.S. cell phone market, and for the past 2 years customers in that market have sent more text messages than made calls [25]; the effect of RF-EMR exposure from text messaging to body organs remains understudied. Most of the studies to date assessing the effect of RF-EMR on reproduction are performed in animals. Data in humans have been criticized to be subject to recall bias; nevertheless, cohort studies are scarce, as most of the published literature relied on case–control and time-trend studies. Additionally, the lack of control groups in human studies (men or women who do not use cell phones) is obvious. In vitro studies on human sperms or granulosa cells might not be a good representative of the effect of RF-EMR because in real life the device and the reproductive organs are separated by multiple tissue layers. Therefore, designing experimental conditions to mimic real lifelike cell phone exposure might be the next step in answering unknown clinical questions. Additionally, isolating cell phone RF-EMR from other environmental factors (including the ones that emit radiations that might constitute potential confounders) might be a challenge for ideal study design. The effect of RF-EMR from commercially available cell phones on reproductive potential is summarized (see Fig. 1). The potential alterations reported to date in animal and human models will always be a challenge to infertility doctors and their patients.

Conflict of interest None

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