5 Impact of Radiation on Male Fertility

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Abstract

In today's time, environmental aspects, lifestyle changes, and person's health coalesce to form stupendous impact on the fertility. All of us are knowingly or unknowingly exposed to several types of radiation. These can lead to collection of early and delayed adverse effects of which infertility is one. A spurt in the number of cases of male infertility may be attributed to intense exposure to heat, pesticides, radiations, radioactivity, and other hazardous substances. Radiation both ionizing and non-ionizing can lead to adverse effects on spermatogenesis. Though thermal and non-thermal interactions of radiation with biological tissue can't be ruled out, most studies emphasize on the generation of reactive oxygen species (ROS). In addition, radiation pathophysiology also involves the role of kinases in cellular metabolism, endocrine system, genotoxicity, and genomic instability. In this study, we intend to describe a detailed literature on the impact of ionizing and non-ionizing radiation on male reproductive system and understand its consequences leading to the phenomenon of male infertility.

Keywords

Male fertility · Radiations · ROS

5.1 Introduction

Worldwide, as many as 48.5 million or 15% of couples are affected by infertility. Males are found to be solely responsible for 20–30% of infertility cases and contribute to 50% of cases overall (Agarwal et al. 2015). The various factors which impose male infertility in modern times include environmental factors, lifestyle, biochemical factors, etc. But several studies in recent decades have proved a very huge impact of radiation exposures on reproductive health causing infertility. Strong evidences suggest that long-term exposure to very commonly used household

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devices like mobile phones, Wi-Fi, luminous watches, wireless routers, bluetooth devices, smoke detectors, and laptops can increase the probability of infertility. Besides these, radioactive substances released into the environment from various sources like nuclear power plants also cause increase in such occurrences. Radiation exposures during medical diagnostic and therapeutic procedure can also account for the same. The principal mechanisms include production of reactive oxygen species (ROS) and DNA damage.

Human testes and sperm are overly sensitive to radiation; owing to reasons like the following: (A) testes are located outside the abdominal cavity (Abuelhija et al. 2013) in thin external sac of the skin and is protected by scantier tissue than any other organ (Houston et al. 2006), (B) testicular cells have high proliferation and growth rate (Vogin and Foray 2013), and (C) sperm lack general cellular DNA repair mechanisms and antioxidant pool due to their highly specialized and compact structure. Radiation can be either ionizing or non-ionizing.

5.1.1 Ionizing Radiation

Ionizing radiation (IR) exists as atomic or subatomic particles or a very high-energy electromagnetic waves, all of which can ionize the nucleus of a substance (Ahmad and Agarwal 2017). IR includes X-rays, y-rays, and α-particles.

IRs are more dangerous to living cells as compared to the non-ionizing radiation because the electromagnetic waves of IR contain enough kinetic energy per quantum to break the bonds between molecules causing the ionization of these molecules. This phenomenon leads to initiation and propagation of chemical reactions causing damage to living cells. Since charged particles like electrons, protons, or neutrons are released during this process of radioactive decay, hence any molecule can cause irradiation.

Sources of IR can be natural or artificial. Examples of some natural IR sources include gamma (γ) rays generated during the radioactive decay of uranium, products of radon gas degeneration in the atmosphere, radionuclides of natural origin, and cosmic rays. Sources of artificial IR exposure include therapeutic (diagnostic or medical procedures) like X-rays used in medical diagnostic procedures and radiation therapy (RT), radionuclides present in eating and drinking materials, γ- rays which are generated as derivate in the nuclear industry, and remnant radiations during atmospheric nuclear testing (du Plessis et al. 2014). Occupational hazards during industrial manufacturing or military fallouts can also result in irradiation. Figure 5.1 shows a vicious cycle formed by radiation exposure, cancer development, and its treatment with radiotherapy or chemotherapy and their detrimental effects on male fertility.

5.1.2 Non-ionizing Radiation

These can be broadly classified into two types: (A) ELF-EMF – extremely low-frequency (ELF) electromagnetic fields (EMF) or power line (60 Hz) – and (B) RF-EMF, radiofrequency electromagnetic fields which are produced by wireless radio wave/microwave products. Non-ionizing radiation emitted as ELF-EMF are considered as non-thermal and do not cause serious irradiation in the living systems and hence are not considered as a potential health hazard in general. The higher energy radiations of the electromagnetic spectrum like radio frequencies (RF), microwaves, lasers, infrared, visible spectrum, and ultraviolet rays (from lowest to highest frequency), however, contain energy which can cause molecular excitation (changes in rotational, vibrational, or electronic structure of atoms and molecules) causing excitation of electrons from lower to higher energy states through the matter it passes. In the biological systems, these radiations can produce several thermal/non-thermal effects (depending on frequency and power level) which can range from burns, photochemical reactions, and accelerated radical reactions such as photochemical aging to non-thermal biological damages, similar to ionizing radiations. Although long-term exposure leads to the effects similar to IR (Lancranjan et al. 1975).

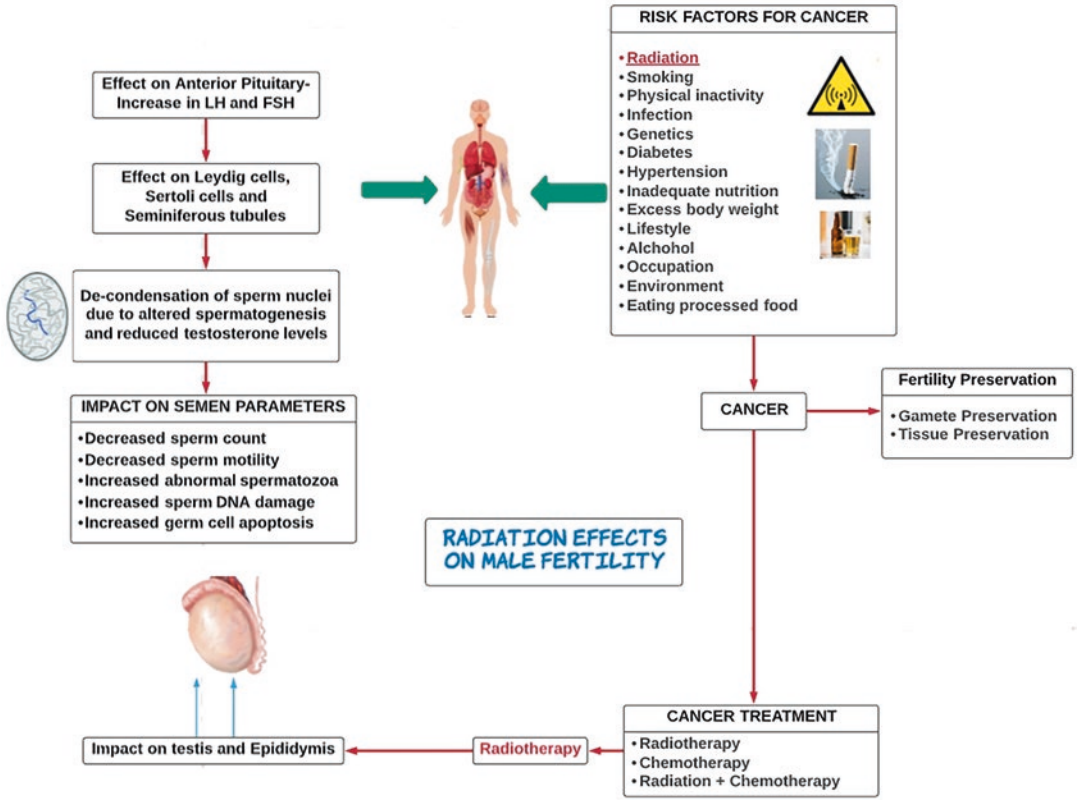

Fig. 5.1 Different sources and impact of radiation exposure on male fertility (Reproduced from Ahmad and Agarwal 2017)

5.2 Ionizing Radiation and Spermatogenesis

As mentioned earlier, human testis is very sensitive to radiation and even a low-dose exposure can impair spermatogenesis. Rowely et al. showed that an exposure of 1 Gy radiation for 14 days can result in significantly reduced number of spermatocytes (Rowley et al. 1974). However, the degree and persistence of damage in the gonads depend upon variable factors like dose, target volume, fraction size of radiation, and also the architecture and reserve capacity of specific target cell population (De Felice et al. 2016). When specifying the effect of radiation, two cell populations should be assumed as stated in the Oakberg-Hukins model of stem cell renewal and the Clermont and Bouton's two stem cell model:

(i) Stem cell spermatogonia: Occur as single isolated cells and are responsible for the repopulation of the germinal epithelium after radiation exposure
(ii) Differentiating spermatogonia: Occur in groups and signify the initial step in spermatogenesis (De Felice et al. 2019)

Stem cell spermatogonia are in continuous long cycle and hence are more resistant to radiation than the differentiating spermatogonia. These differentiating cells are randomly distributed over the tubules. After the RT or exposure, the fraction of re-populated seminiferous tubules is indicated by the re-population index (RI). This RI is directly proportional to the number of surviving stem cells (UNSCEAR 2008).

Although IR kills the cells immediately by necrosis and/or apoptosis during their prolifera-

tion, the decline in spermatogonial numbers to lower level does not happen at once but instead occurs in a progressive manner. The effects of radiation do not manifest until 18 weeks of irradiation when azoospermia is observed (Paulsen 1973). The exact reasons for this gradual decline are unknown, but it is conjectured that the expression of lethal damage by some of the non-cycling spermatogonia occurs only when they proceed into the cell cycle. The differentiation steps of spermatogonia into the spermatocytes are affected and get reduced. IR impairs spermatogenesis, spermatogonia being more radiosensitive than spermatocytes or spermatids. Radiation exposure leads to low sperm counts, decreased sperm motility, and increased rate of chromosomal abnormalities in some men. Sperm production is observed to remain >50% above control values during the first 50–60 days after low doses of irradiation (15–200 cGy). Also, multiple increments of a single dose of radiation lead to a dose-dependent reduction in semen volume and sperm count. It is evidenced that the time for spermatogenesis and semen volume to recover is directly proportional to the dose applied. This amounts to roughly 9–18 months for a radiation dose less than 1 Gy, 30 months for an exposure of 2–3 Gy, and 5 or more years after 4–6 Gy dose exposure (Ogilvy-Stuart and Shalet 1993).

5.3 Non-ionizing Radiation and Spermatogenesis

Non-ionizing radiation is of particular concern these days as the source of the radiations include commonly used devices like Wi-Fi, laptop, and cell phones in addition to base transceiver station (BTS) high-power electric lines. Continued exposure to low-frequency electromagnetic radiation (EMR) stimulates occurrences of damaged chromosomes and genomic instability and could potentially result in cancer development (Martin et al. 1986).

EMR impacts on different human organs but male testis is found to be most sensitive. The law of Bergonie and Tribondeau states "the radiosensitivity of tissue is directly proportional to its reproductive capacity and inversely proportional to the degree of differentiation of its cells." Accordingly, the spermatogonial stem cells with high mitotic activity tend to be more radio-sensitive than mature cells of testes (Vogin and Foray et al. 2013). EMR can significantly reduce sperm function like motility and vitality and may also impair DNA integrity (Fejes et al. 2005). Males experiencing subfertility, e.g., asthenozoospermia and oligozoospermia, show particular vulnerability to RF-EMR. It was found that such patients exhibit a marked decline in sperm motility following an exposure of their semen sample to a cellular device for just 60 minutes (Zalata et al. 2015).

5.4 Pathophysiology

Though the exact underlying mechanism is not completely known, some important mechanisms causing radiation-led DNA damage are discussed. It is believed to cause direct damage if the energy level is sufficient to break the intermolecular chemical bonds as commonly seen with ionizing radiation or cause the intracellular effects indirectly as seen mostly in non-ionizing radiation. The generation of free radicals is the commanding phenomenon among all the indirect methods.

Ionizing radiation directly attacks DNA structure by inducing DNA breaks, particularly double-stranded breaks (DSB). However, some other effects in DNA damage like generation of a basic sites and single-strand breaks (SSB) and oxidation of proteins and lipids can also occur. These effects occur as secondary complications through generation of ROS (Borrego-Soto et al. 2015).

Non-ionizing radiation interferes with the oxidative repair mechanisms within the cells resulting in an override of ROS concentration generating oxidative stress and damage to cellular components including DNA and also to cellular processes finally leading to cancer (Havas 2017).

5.4.1 Generation of Oxidative Stress

RF-EMR is well known to have the capacity to induce oxidative stress characterized by excessive generation of ROS. This increase of free radical in the cell occurs principally by Fenton reaction (Lai and Singh 2004). The reaction proceeds by the conversion of hydrogen peroxide, an oxidative respiratory product generated in the mitochondria, to free hydroxyl molecules via catalysis with iron (Bandyopadhyay et al. 1999).

Fenton reaction can be summarized as follows:

(i) The interaction of Fe^{++} salt with hydrogen peroxide results in the generation of free hydroxyl ions (OH).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^+ + OH^-$$

(ii) Any trace iron (Fe^{3+}) present further reacts with hydrogen peroxide forming hydrogen ion and superoxide given by the formula

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + O_2^- + H^+$$

(iii) Thereafter hydrogen peroxide interacts with superoxide ion leading to formation of OH.

$$O_2^- + H_2O_2 \rightarrow OH^- + OH^- + O_2$$

ROS cause cell injury and damage in three ways:

- Lipid peroxidation of membranes
- Oxidative damage of proteins
- DNA damage

ROS react with the double bond of free fatty acids of membrane lipids causing lipid peroxidation of plasma and organellar membranes, such as free hydroxyl molecules. This produces peroxides which are unstable and highly reactive. A chain reaction starts producing large amount of these products which cause extensive membrane damage. Oxidative damage of proteins are caused by ROS by oxidation of amino acid chains. This leads to damage in the active sites of enzymes, increased proteasomal degradation of misfolded proteins, and destroys formation of structural proteins. The formation of DNA adducts, breakage of single or double strands of DNA, and cross-linking of DNA eventually cause extensive DNA damage.

The unique, compact, and highly specialized structure of spermatozoa makes it more vulnerable to oxidative stress. Characteristically as sperm have low cytoplasmic volume, they possess limited protective antioxidant capacity than the other somatic cells. They also have relatively large substrate for free radical attack like DNA, thiol-rich proteins, and polyunsaturated fatty acids (PUFAs) (Aitken et al. 2012a). PUFAs are necessary for generating membrane fluidity which is essential for supporting both motility and fertilization.

Stress generators such as RF-EMR exposure to spermatozoa causes increased production of superoxide radical of mitochondrial and cytosolic origin (Agarwal et al. 2009; De Iuliiset al. 2009). This causes the peroxidation of PUFA and membrane lipids and elicits formation of electrophilic aldehyde like malondialdehyde, 4-hydroxynonenal (4HNE), and acrolein. These compounds further cause alkylation of sperm axonemal proteins particularly dynein heavy chain that is responsible to regulate sperm motility (Baker et al. 2015; Moazamian et al. 2015) and hence hamper sperm motility. 4HNE perpetuates a state of oxidative stress causing overproduction of mitochondrial superoxide radicals by adducting protein of electron transport chain (ETC) particularly succinate dehydrogenase (Aitken et al. 2012b). Hence a cascade of events shown in Fig. 5.2 following ROS attack on sperm substrates creates an override and imbalance in the cellular ROS concentration which finally leads to oxidative damage of DNA as the toxic hydrogen peroxide produced during the course moves to the sperm head and targets the guanine residues of the DNA.

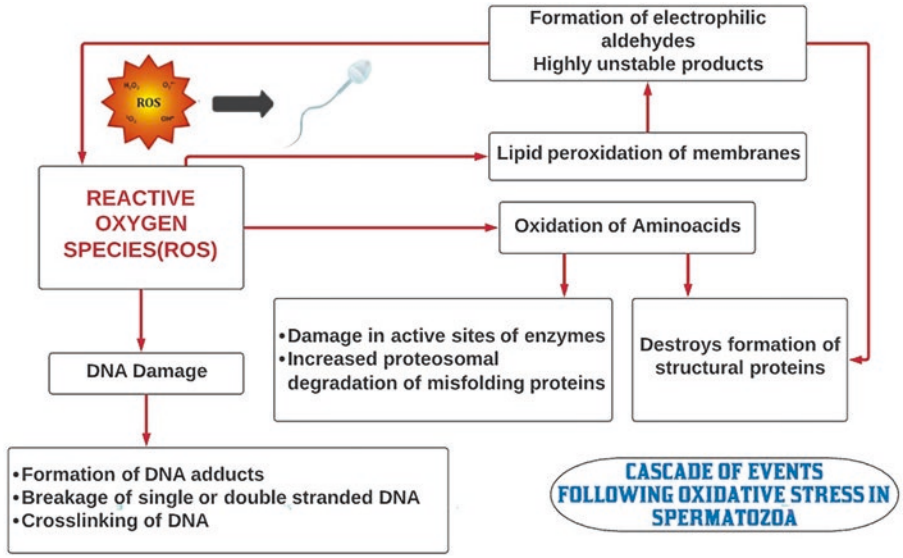

Fig. 5.2 Sequential molecular impacts of oxidative stress within the spermatozoon

5.4.2 Thermal Effect

The absorbed EMR when converted to heat causes thermal effect. Biological systems are affected by thermal effect when the heat generated exceeds 100 mW/ cm^2 (Habash 2011). While blood cells are capable of dissipating any excess heat, the sensitive organs like the eye, cornea, and testis do not have any temperature regulation mechanism.

Few studies have shown that use of laptop and exposure to low-frequency EMR may increase the temperature in the testis leading to impaired DNA integrity and apoptosis of germ cells (Durairajanayagam et al. 2015). Apart from several other lifestyle factors, use of cell phones has been vastly studied to induce DNA damage. It has been reported that if cell phone is kept in trouser pocket for a long time, it can cause DNA strand break in the sperm cells after exposure of only 2 hours/day for 60 days. The duration and power density of the exposure was found to be directly proportional to the magnitude of effect (Kumar et al. 2014). During the processing of repair mechanisms activated by radiation damage, heat is seemingly known to increase the levels of single stranded breaks (SSBs) and double stranded breaks (DSBs) of DNA by impairing the repair of corrupted bases.

Microwaves also operate by rotating the polar molecules assisted by generation of electromagnetic fields leading to hazardous effects on germ cells. Meena et al. have reported a significant increase in sperm DNA damage after a whole body microwave exposure of 2.45 GHz for 2 hours per day for 45 days. This was visually evaluated by a single cell gel electrophoresis also known as Comet assay. The undamaged DNA nucleotide was referred to as head, while trailing damaged DNA streak was referred to as tail. An increasing tail length and tail movement was demonstrated (Meena et al. 2014).

Studies have highlighted that the exposure to microwave EMR significantly suppresses histone kinase activity in the sperm as compared to the non-exposed counterparts (Kesari et al. 2011). During spermiogenesis, the germ cells undergo a distinct morphological change where to ease the chromatin compaction, the core histones are replaced by protamines. Defects in either the replacement or the modification of histones might cause male infertility with azoospermia,

oligozoospermia, or teratozoospermia. In the differentiating cells, a decrease in histone H1 activity, just before their entry into the M-phase from G2-phase, suggest the role of Cd2/CdK2 in regulating this phenomenon (Agarwal et al. 2009). Some studies have reported that depletion in the activity of both histone kinase and protein kinase may serve as enzymatic markers of microwave EMF's ability to affect spermatogenesis and sperm cell cycle (Shokri et al. 2015).

5.4.3 Calcium Ion Concentration

Calcium ion concentration affects vital events of fertilization and activities of sperm. The processes of sperm motility, chemotaxis, capacitation, and acrosomal reaction within the female reproductive tract are highly regulated by the calcium ions (Beigi Harchegani et al. 2019) together with many other factors. Seminiferous tubules and Leydig cells have pyruvate kinase enzyme complex (PKC) which modulate the ion conductance via calcium-dependent phosphorylation of membrane and ion exchange proteins. PKC, cAMP, and variations in calcium ion concentration have important function and affects sperm motility (Kimura et al. 1984). The coordinated sperm tail action requires energy obtained from ATP and signaling via cAMP and Ca^{2+} from the surroundings (Yan 2009). Hence factually reduced fertilization and male infertility can be coherently associated with deficiency in calcium ions and also disturbance in energy supply or signal transduction (Beigi Harchegani et al. 2019).

Animal studies conducted by Wang et al. proved significant disturbances in calcium ion homeostasis together with activation of endoplasmic reticulum stress (ERS) and apoptotic signaling molecules in the testicular cells of mice irradiated with low-dose radiation (LDR) ranging in 25–200 mGy. They proved a time- and dose-dependent decrease in Ca^{2+} ions and Ca^{2+}- ATPase activity and a similar increase in the ERS molecular markers and apoptotic signaling markers (Wang et al. 2013).

5.4.4 Endocrine Effects

Leydig cells are among the most susceptible cells to EMR. Radiation may disrupt Leydig cell population and thereby affect spermatogenesis. Leydig cells produce testosterone, and hence a decline in testosterone levels is observed. There may also be elevated luteinizing hormone (LH) levels along with reduced or even normal testosterone levels (Tsatsoulis et al. 1990). Meo and Al-Drees have proposed that the radiations can cause alterations in the polarization status of the cellular membranes of the Leydig cells which can evolve distinct changes in the composite biochemistry of testosterone synthesis and secretion (Meo and Al-Drees 2010). Further, several studies have reported that mobile phones can downregulate the production of melatonin which plays an important role in testosterone secretion. It is proved to exert an antigonadotropic effect by acting at the hypothalamo-pituitary axis (Yilmaz et al. 2000). Additionally, RT is known to cause damaging effects on the vessels and nerves of the pelvis which result in reduction in sexual function in males (Mahmood et al. 2016).

The cell function of Leydig and Sertoli cells was evaluated in a study conducted by Tsatsoulis et al. on male patients (ranging in age from 21–49 years old) who were subjected to orchidectomy followed by radiotherapy given in total dose of 30 Gy in 20 fractions. The results revealed that these patients had lower levels of testosterone but high LH as compared to the control group. This statistically significantly low testosterone/LH ratio clearly indicated Leydig cell damage (Tsatsoulis et al. 1990). Two relevantly similar studies were conducted on pubertal boys with acute lymphoblastic leukemia who were given direct testicular irradiation. Results showed total ablation and functional reduction of Leydig cells directly after radiotherapy without any observed reversal even after 5 years of the treatment. Androgen supplementation was suggested in most cases for normal sexual maturation (Brauner et al. 1983; Shalet et al. 1985).

LH plays the role of main hormone which controls the function of Leydig cells through its

receptors which are specific to it and are integrated with both phospholipase C and adenylate cyclase pathways (Cooke 1999). Hence radiation exposure would cause steroidogenic lesions seen as a reduction in the LH receptors of the Leydig cells (Payne and O'Shaughnessy 1996).

The downstream effects of LH and HCG on the Leydig cells occur via secondary messenger signaling molecule, cAMP. An estimation of the LH and basal triggered cAMP production in radiation exposed and normal Leydig cells showed that irradiation causes a dose-dependent decrease in the generation of basal and LH stimulated cAMP proving that down effects of HCG and LH on Leydig cells are employed mainly mediated through cAMP associated events (Sivakumar et al. 2006).

Even though the Leydig cells are much more radio-resistant to the germinal epithelial cells of testes and get affected by high doses of radiation, the Leydig cells in children are more sensitive to radiation than adults. Their function is usually preserved up to 20 Gy in pre-pubertal boys and 30 Gy in sexually mature men. Hence Leydig cell dysfunction due to RT can cause hypogonadism as they function to secrete testosterone (Izard 1995).

The most dramatic endocrine effect of irradiation of the testis is the increase in FSH levels. It is not the direct effect but results due to depletion of germ cells. FSH levels have been used as an index of radiation damage (Shapiro et al. 1985).

5.5 Radiation and Genotoxicity

Radiation is well known to induce genotoxicity. EMR induces genotoxic effects by forming SSBs, DSBs, micronuclei, chromosomal damage, alteration in gene expression, cell division, and apoptotic cell death (Meena et al. 2014). Even though it is evident that RT may damage DNA, the extent or significance of such effect on sperm chromatin integrity is unclear. A dose-dependent increase in DNA damage in testis cells has been reported after 14 days of RT (Stahl et al. 2004), and the overall results showed that DNA damage inducted in pre-meiotic germ cells is detectable in primary spermatocytes and is also found in mature spermatozoa. The damage can happen via one of two scenarios.

5.5.1 Direct Action

This refers to the direct impact of radiation on the DNA causing ionization of the atoms within the DNA helix. Such a "direct hit" on DNA is commonly possible due to the small; barely few nanometer diameter of DNA helix. It is advocated that the radiation must produce ionizing effects on DNA within only a few nanometers in order to advocate for the successful occurrence of such an action.

5.5.2 Indirect Action

Refers to the impact of radiation on rather non-critical target atoms, usually water creating reactive oxygen free radicals which damage DNA through successive events. This action does not necessarily require the occurrence of the initial ionization event very close to a DNA molecule, but at some other location from where it can act by initiating a signaling reaction to cause DNA damage at last. Indirect pathway is a more frequent phenomenon than a direct one. Either of the actions causes radiation to attack at specific location of DNA structure and damage it mostly by causing SSBs or nicks which is easily reported by the cell and is usually attended by the DNA damage control machinery of the cells where the opposite strands are used as template. However, if radiation causes DSBs in the DNA structure, the cells suffer difficulty in repairing it and can result in mutation and further lead to cancers or cell death. The ratio of occurrence of double-stranded to single-stranded breaks is about 1:25. Hence, at times, DNA damage due to radiation is repairable (Unknown authors 2012). Nonetheless DNA fragmentation index (DFI) is found to be significantly higher in men who are receiving RT (Lord 1999).

Genomic instability is emergence of genetic alterations during cell division. Radiation leads

to high frequency of mutations in the genome of a cellular lineage. Microtubule based structures may suffer alterations in their ultrastructure causing deviation in normal morphology of sperm tail. This causes defects in sperm motility and increase in sperm fatality (Sha et al. 2014). Kesari and Behari examined spermatozoa of RF-EMF radiation-exposed rat under transmission electron microscopy (TEM) and reported major changes in the axonemal microtubules, mid piece region, and outer dense fibers and membranes of mitochondria. They also found that the sperm nucleus showed distortion of the membrane head on the sagittal section. They concluded that the exposure of sperm to RF-EMF of cell phone in excess can cause disarray of sperm mitochondria and result in production of highly reactive free radicals. This hampers motility of sperm and also causes deformation of the acrosome which might lead to a lack of ability to penetrate oocytes resulting in infertility (Kesari and Behari 2012). Though studies have revealed that EMF exposure may lead to molecular irregularities, some have also shown that it may not cause direct DNA damage. The increase in autophagy can help in balancing homeostasis and apoptosis (Shen et al. 2016). A range of studies conducted on effects of exposure to extremely low-frequency EMF demonstrated alterations in important basic cell functions like protein and cell cycle regulation.

Luukkonen et al. found that exposing the human SH–SYSY neuroblastoma cell lines to extremely low-frequency EMF causes decreased p21 protein level after menadione treatment. p21 is a tumor suppressor gene. It induces tumor growth suppression through wild-type p53 activity. Its cleavage and inactivation in normal as well as cancerous human cells occurs by the action of caspase-3 (Fig. 5.3). p21 expression is a poor prognostic marker linked to poor survival rate and resistance to chemotherapy. Also, post menadione treatment and EMF exposure conditions are accompanied by an increase in number of cells in the G1 phase and reduction in number of cells in the S phase. EMR displaces electrons in DNA, which is accompanied by electron transfer (Luukkonen et al. 2017). These displaced electrons break hydrogen bonds causing separation of DNA strands followed by transcription.

Very risky situation can also be encountered in case of assisted reproductive techniques (ART) using irradiated sperm. The specific selection processes of a sperm which occur during natural conception are circumvented in ART. This may result in fertilization of oocyte with a sperm containing damaged DNA. Such occurrences may however result in successive transfer of genetic aberrations into the dividing embryo and also lead to future complications and reproductive failure (Fatehi et al. 2006). Hence fertility is negatively affected by injury to nuclear DNA of sperm. Compliantly Kamiguchi and Tateno have also shown that despite the fact that human spermatozoa are extremely radiosensitive, they retained the fertilization capacity even after a high dose (4.23 Gy of γ rays) of irradiation. They also inferred that the sperm having damages may escape selection process during fertilization and cause the damage of DNA to pass into the next generation (Kamiguchi and Tateno 2002).

5.6 Effects on Semen Parameters

Highlighting effects on semen parameters, a study done by Vakalopoulos et al. showed a statistically significant reduction in semen volume, sperm concentration per ml and total sperm count, as well as forward motility with a statistically significant increase in occurrence of abnormal forms of sperm in the semen continually up to 12 months following the therapy (Vakalopoulos et al. 2015). Another study revealed no differences at the beginning and 24-month post therapy for any semen parameters except in volume, which could indicate a return of sperm quality to pre-radiotherapy conditions (Stahl et al. 2004).

Radiation effects on sperm counts may be subdivided into three phases. Phase 1 is the 8-week period post radiation when sperm production is still maintained at normal levels, especially after low doses of irradiation. Phase 2 is represented by the gradual reduction of sperm production reaching its lowest 3–8 months after irradiation as a possibility associated with

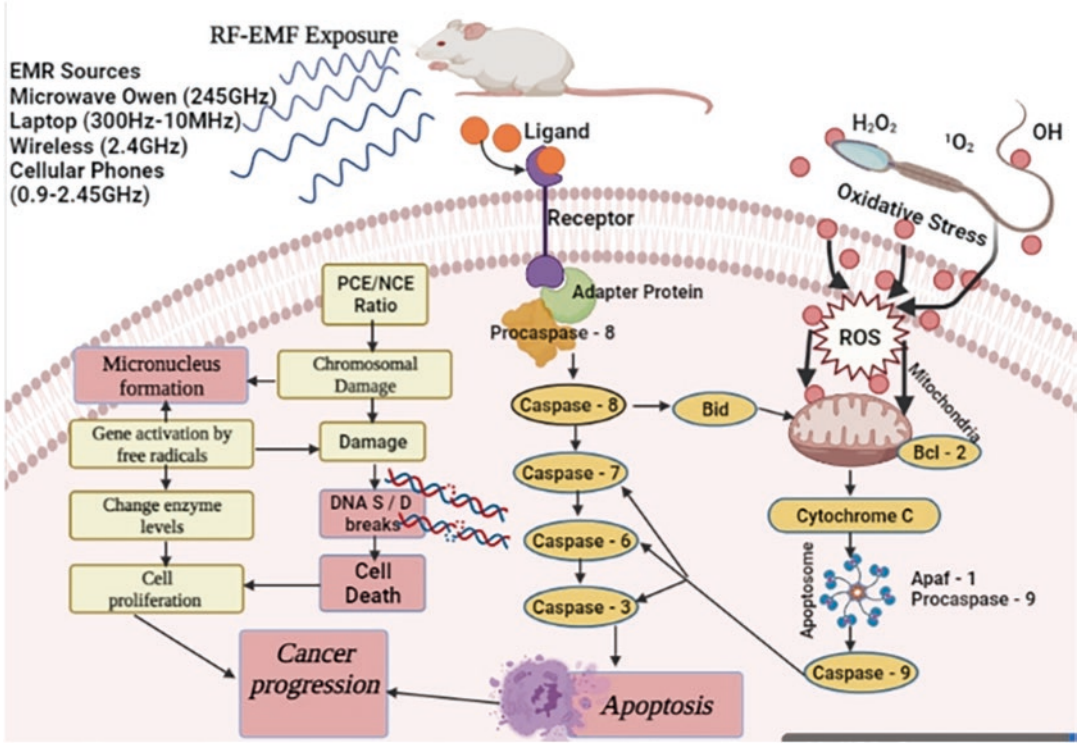

Fig. 5.3 Diagrammatic representation of the effects of exposure from EMF from various sources (mobile phone, microwave ovens, wireless devices, computers) causing genotoxicity. (Reproduced from Kesari et al. 2018)

azoospermia. Phase 3 is signified by the initiation of recovery from oligospermia or azoospermia. The final phase is marked by recovery of sperm production to control levels.

5.7 Conclusion

Several studies advocate that the direct or diffused exposure of human testes to ionizing and non-ionizing radiations emitted from sources like cell phones, microwave oven, laptops, X rays, γ-rays, etc. exerts damaging effects on the male reproductive system resulting in serious defects in sperm morphology, sperm count, and functions (mobility and fertilization). These effects are predominantly caused due to damage in sperm DNA which attenuates micronucleus formations and genomic instability. Disturbed functions of protein kinases, hormones, and antioxidant enzymes are also evident and participate in causing such abnormalities. On the one hand where direct ionization of DNA may result in mutations in chromosome, injury to DNA ultimately leading to cell cycle arrest, apoptosis, and cancer, the indirect effects are demarcated by excess accumulation of mitochondrial and cytoplasmic ROS by over-powering the cellular antioxidant machineries. It is the ROS that are considered the prime initiators for activating the intracellular signaling pathways ultimately resulting in severe DNA damages and apoptotic changes in the testicular cells.

Most notably, there exists a range of response to radiation exposure, and it is invariably dependent on the type of source and effective irradiation dosages. This is further dependent upon the duration of exposure and most importantly on the genetic and epigenetic makeup of the exposed individual. Also these observations give us a reasonable shift from assumptions like only a direct cellular interaction or a long-standing exposure

to radiation can lead to significant damage to the fact that indirect damage and a conglomerated effect of short-term exposures can also lead to significant impacts resulting in male infertility.

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