

BIOMEDICAL**Non-Ionizing Radiation Created by Mobile Phone Progresses Endometrial Hyperplasia: An Experimental Rat Study**

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Background. Non-ionizing radiation is related with many pathologies.

Aim. Determine association between non-ionizing radiation and endometrial hyperplasia.

Methods. Fifty oophorectomized Wistar albino rats were administered Estradiol hemihydrate (4 mg/kg) to induce hyperplasia, and were exposed to 1800 MHz radiation created by a mobile phone and a signal generator working as base station. This study was carried out with 5 groups in two phases. The study groups were. Control group without any exposure; group receiving estrogen in first phase of the study; group receiving estrogen in both phases; group receiving estrogen in the first phase and exposed to non-ionizing radiation during second phase and group taking estrogen in both phases and exposed to non-ionizing radiation during the second phase. Following both phases, uterine horns were excised and evaluated based on glandular density (GD), epithelial cell height (ECH), and luminal epithelial cell height (LECH).

Results. Estrogen increased all parameters during both phases (LECH, GD, and ECH values were 12,2 vs. 16,5 ($p = 0.001$), 34 vs. 47 ($p < 0.001$), and 201 vs. 376.6 ($p = 0.001$), respectively during the first phase; LECH, GD and ECH values were 13,2 vs. 20,3 ($p < 0.001$), 35,5 vs. 65,5 ($p < 0.001$), 219,9 vs. 419,6 ($p < 0.001$), respectively, during the second phase). Non-ionizing radiation increased all values without estrogen exposure (LECH, GD and ECH values were 13,2 vs. 17,2 ($p = 0,074$), 35,5 vs. 59 ($p = 0.074$), and 219 vs. 318,3 ($p < 0.001$), respectively) or with estrogen exposure (LECH, GD, and ECH, values were 20,3 vs. 22,8 ($p = 0,168$), 65,5 vs. 77 ($p = 0,058$), and 419,6 vs. 541,6 ($p = 0.004$), respectively).

Conclusion. Non-ionizing radiation progressed endometrial hyperplasia in an experimental rat model with/without estrogen exposure. © 2019 IMSS. Published by Elsevier Inc.

Key Words: Endometrial hyperplasia, Non-ionizing radiation, Uterotrophic rat model.

Introduction

In recent years, endometrial cancers have become the most common gynecological cancers in developed countries (1). Abnormal uterine hemorrhage is the most common symptom of endometrial hyperplasia and ultrasound examination revealing a thickened endometrium is critical for diagnosis

(2). A definitive diagnosis may be acquired by endometrial sampling (3). Endometrial cancers mostly develop on the basis of endometrial hyperplasia, and according to pioneering studies, it takes approximately 13 years (1–27 years) for the cancer to progress (4). Owing to the long precancerous course of the disease, any environmental exposure may lead to lethal progression of the disease. Together with advancing technologies, non-ionizing radiation, generated especially by mobile phones, is also considered a potential hazardous agent for the development of many tumors and diseases.

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Exposure to non-ionizing radiation is increasing at a high rate owing to the increased use of mobile phones recently. The World Health Organization (WHO) declared that non-ionizing radiation is a “potential carcinogen” (5); however, some press releases or papers contradict this WHO declaration (6). Potential health issues associated with non-ionizing radiation arise from their potential to produce intracellular oxygen radicals, which cause structural malformations (7). Many clinical studies have been conducted recently to determine the association between non-ionizing radiation and specific systems, such as the central nervous and urogenital systems. Due to a possible carcinogenic effect of non-ionizing radiation and the etiological background of endometrial cancers, such as changes in mRNA expression (8), it is reasonable to associate endometrial hyperplasia with non-ionizing radiation.

With this background knowledge, we aimed to examine the effect of non-ionizing radiation on endometrial hyperplasia, using an experimental animal model. The long and silent clinical course of endometrial hyperplasia, which manifests as precancerous lesions, raises questions regarding the possible effect of non-ionizing radiation, which can be considered as a “potential carcinogen.” Owing to different carcinogenetic pathways, each system malignancy should be evaluated separately in terms of potential carcinogens. Endometrial malignancies and precancerous lesions are also very common and necessitate special care and investigation. Thus, we designed this study to investigate whether non-ionizing radiation generated by mobile phones, with or without concurrent estrogen exposure, induces the progression of hyperplasia.

Materials and Methods

The necessary permissions for the planned experiment were obtained from the ethical board of Ankara Training and Research Hospital on March 10, 2016 and from Etlik Zübeyde Hanim Obstetrics and Maternity Education Planning Board on August 25, 2016. The study was performed at the Ankara Hospital Experimental Animal Laboratory.

Animals

Fifty female Wistar Albino rats (200–250 g) were used in the experimental model. The rats were fed *ad libitum* and kept under a 12 hour day and 12 hour night cycle, according to their normal physiology. The room temperature was $24^{\circ}\text{C} \pm 1^{\circ}\text{C}$, and a relative humidity of $55 \pm 5\%$ was recorded during the study. No restrictions were applied to the rats.

Study Design

To determine the effects of non-ionizing radiation on the uterotrophic rat model, the study was designed as shown in Figure 1. Bilateral oophorectomy was performed in all

rats to remove endogenous hormonal effects and provide physiological synchronization among the rats before the experiment. After surgery and rest for 2 d, the rats were randomized into five groups according to the study design summarized in Figure 1.

The first phase of the study was completed after 14 d, and all rats except those in group A received oral estradiol hemihydrate (Estrofem 2 mg, Novo Nordisk, Istanbul) at a dose of 4 mg/kg. The tablets were dissolved in water and administered orally at the appropriate dose. Group A was the control group for the uterotrophic experimental model. The dose and duration of estradiol administration were determined in accordance with literature findings and recent studies (9,10). After estradiol administration, cornual excision was performed under general anesthesia, as described for the primary surgery.

In the second phase of the study, the rats were administered oral estradiol hemihydrate and exposed to non-ionizing radiation according to the study model. Group A remained as the control group. Group B was the control group for the uterotrophic model in the second phase of the study and received no exposure. The rats in group C received oral estradiol hemihydrate for 24 d more to determine the effect of continuous estrogen exposure. Estradiol hemihydrate was administered at the same dose as in the first phase of the disease. The rats in group D were exposed to non-ionizing radiation for 3 hours a day at a bandwidth of 1800 MHz for 24 d. The rats in group E were exposed to non-ionizing radiation and administered oral estradiol hemihydrate. Groups D and E were used to demonstrate the effects of non-ionizing radiation either with or without continuous estrogen exposure. A duration of 24 d was determined to reflect 5 or 6 menstrual cycles, as the duration of the estrous cycle of rats is 4 or 5 d. The radiation exposure performed between 12–3 pm for avoiding any circadian rhythm-related differences. After the second phase of the experiment, all rats were decapitated in accordance with the ethical committee rules, and left cornual excision was performed.

Surgeries

At the beginning of the study, oophorectomy was performed to remove endogenous hormonal effects. Xylazine (10 mg/kg; Alfazyne, Alfazen, Amsterdam) and ketamine (50 mg/kg; Ketalar Flacone, Eczacibasi, Istanbul) were administered for neuromuscular block before all surgical procedures. A midline incision beginning just above the urethral orifice and extending 3–4 cm above was created after shaving and cleaning the skin. Each ovary was excised by ligating the ovarii proprium and infundibulopelvic ligament. The abdomen was closed by suturing in layers.

A right cornual excision was performed as a secondary surgery for all the rats by ligating the uterine horns at the level of the uterine cervix. After the secondary surgery, the rats were left to rest for 2 d again. At the end of the

Group A (n = 10)	Control Group	Uterine corn excision	Control Group	Uterine corn excision
Group B (n = 10)	4 mg/kg daily oral estrogen for 14 days	Uterine corn excision	No exposure	Uterine corn excision
Group C (n = 10)	4 mg/kg daily oral estrogen for 14 days	Uterine corn excision	4 mg/kg daily oral estrogen for 14 days	Uterine corn excision
Group D (n = 10)	4 mg/kg daily oral estrogen for 14 days	Uterine corn excision	1800 mHz non-ionizing radiation exposure for 24 days / 3 hours a day	Uterine corn excision
Group E (n = 10)	4 mg/kg daily oral estrogen for 14 days	Uterine corn excision	1800 mHz non-ionizing radiation exposure for 24 days / 3 hours a day + 4 mg/kg daily oral estrogen	Uterine corn excision

Figure 1. Algorithm showing the study design.

study, a third surgery was performed after the rats were decapitated in accordance with the guidelines of the ethical committee, and left cornual excision was performed similar to the right cornual excision.

Non-Ionizing Radiation Model

Non-ionizing radiation was generated from a signal generator (Rohde-Schwarz CMD52, Rohde-Schwarz, Munich, Germany) and an appropriate mobile phone with Wi-Fi 802.11 b/g connectivity with possible bandwidths of 850, 900, 1800, and 1900 MHzs and an EU SAR value of 1,09 W/kg for the head region. Basically, the signal generator served as a base station, sending signals to the mobile phone to simulate a mobile phone call. The bandwidth selected was 1800 MHz, and a maximum output power of 2 W was established. The mobile phone was placed under a 50 × 30 cm polyvinyl cage. The area under the cage (including the mobile phone under the cage) was covered with aluminum foil to consolidate the electromagnetic fields into the cage and prevent non-ionizing radiation to spread away from the cage (Figure 2). The rats were free to move in the cage, which exposed them to non-ionizing radiation at similar doses. Non-ionizing radiation exposure was performed in an isolated room. The remainder of the rats were kept in another room during the exposure of the study group. None of the researchers entered the rooms with any device creating non-ionizing radiation. The chosen mobile phone was selected because of its connectivity with the signal generator and in accordance with the

measurements of the electromagnetic field. The electromagnetic field was measured using the EMR-300 electromagnetic field measurement tool (Narda, Pfullingen, Germany). The measurements were reported in volts/meter.

Histopathological Analysis

The samples acquired after both surgeries were fixed in 10% formol solution for 48 hours, embedded in paraffin, and cut into 5 µm sections. Routine hematoxylin-eosin staining was performed, and the samples were observed under a light microscope (Figure 3). Epithelial cell height,



Figure 2. Devices used to generate an electromagnetic field in the experimental model.

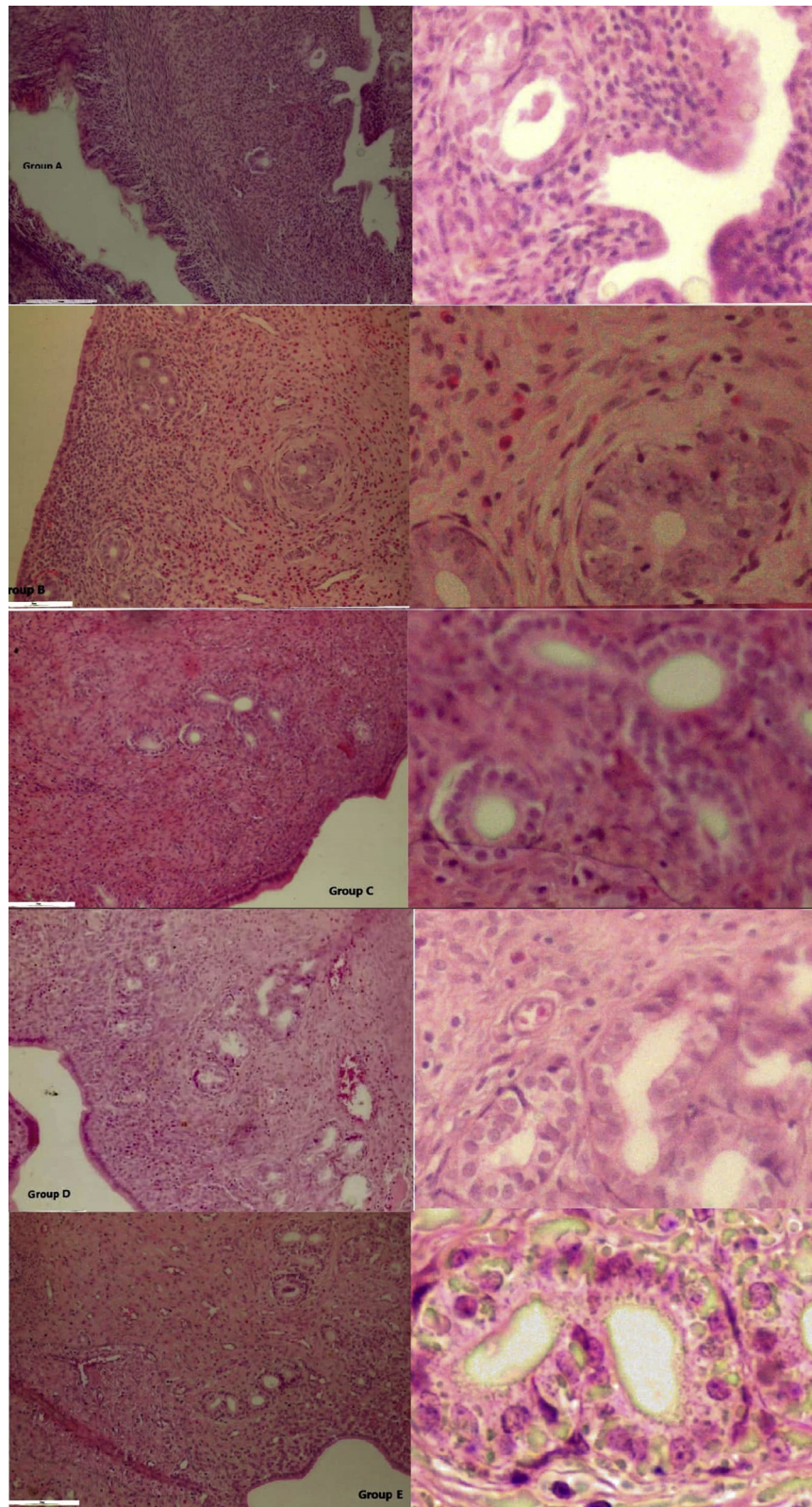


Figure 3. Light microscopic images of whole groups at the end of second phase of the study with 40x magnification (Scale: 200 μ m) and 16x digital magnification focusing on endometrial glands.

luminal epithelial cell height, and glandular density were measured in accordance with the literature, which indicates that these parameters are important markers for measuring the effect of estrogen on the rat endometrium (11,12). Epithelial cell height and luminal epithelial cell height were measured manually by adjusting calipers at the apical and basal membranes of these cells. Epithelial cell height and luminal epithelial cell height were measured at magnifications of 20 and 40 $\times$, respectively. Measurements of epithelial cell height were performed in the sections including at least 100 epithelial cells, not including luminal folds or oblique sections (13). The data were presented in micrometers. Glandular density measurement was performed at 400 $\times$ magnification in non-consecutive sections containing most glands (9).

Figure 4 demonstrates the measurement techniques performed in the study.

Statistical Analysis

Statistical analysis was performed in two stages, according to the model and aim of the study. IBM SPSS Statistics for Windows v23 software (released 2015, IBM Corp., Armonk, NY) was used to conduct all analyses. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they were normally distributed. Descriptive analyses were presented as medians and range for the non-normally distributed variables. Due to lack of normal distribution of the data, Kruskal-Wallis analysis

was used for multiple group comparison and a Mann-Whitney *U* test was performed for two group comparisons with a Bonferroni post-hoc analysis. According to the aim of the analysis and group structures, the Kruskal-Wallis and Mann-Whitney *U* tests were performed, and the median (range) values were evaluated for the analysis.

Results

The electromagnetic field, measured using the EMR-300 electromagnetic field measurement tool, ranged between 12.17 and 17.29 V/m at different points of the cage during the exposure. One rat died 2 d after oophorectomy, and 2 rats died after the second surgery, one each on postoperative 1 and 2 d.

First, statistical analysis was performed to assess the uterotrophic rat model. The analysis was performed between group A and the remainders for the assessment of effect of estrogen in the luminal epithelial cell height, epithelial cell height, and glandular density. Statistical analysis revealed a statistically significant increase in parameters in the estrogen receiving group (LECH, GD, and ECH values were 12,2 vs. 16,5; $p = 0.001$, 34 vs. 47; $p < 0.001$, and 201 vs. 376,6; $p = 0.001$, respectively for group A and the remainder groups).

Secondly, the five groups were compared to each other, according to the second phase results (Table 1). Statistical significance was acquired in all parameters ($p < 0,001$). Further analyses were carried out to compare the groups

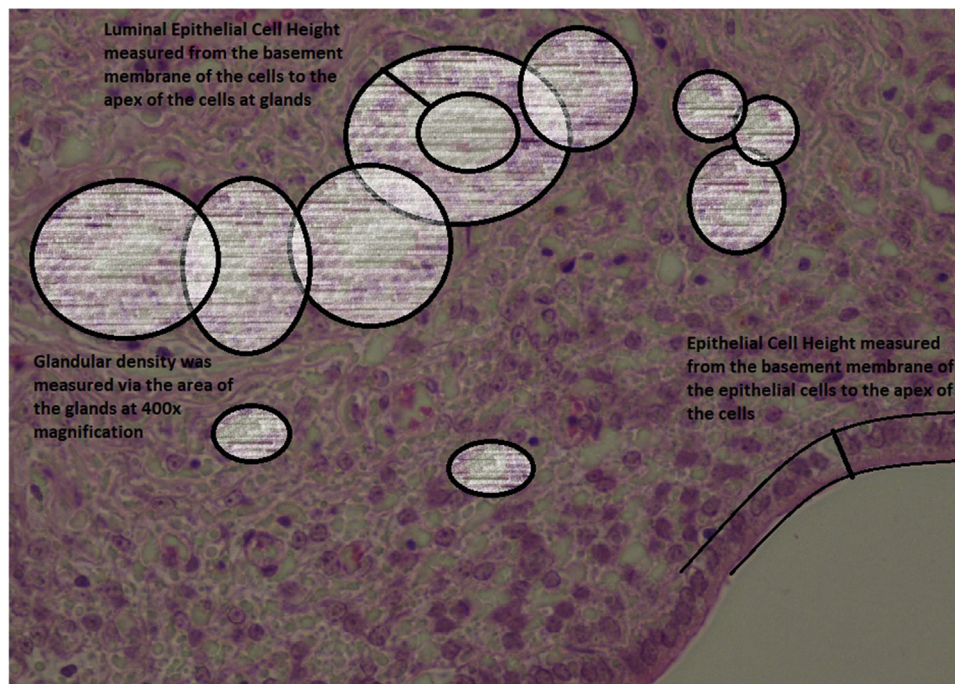


Figure 4. Illustration of the measurement techniques.

Table 1. Comparison of five groups at the second phase of study

	Luminal epithelial cell length	Glandular density	Epithelial length
Group A	12,2 (11,2–14,3)	34 (31–42)	201 (171,6–218,3)
Group B	13,2 (11,2–15)	35,5 (29–55)	219,9 (203,3–262,5)
Group C	20,3 (16–24,5)	65,5 (56–87)	419,6 (358,3–458)
Group D	17,2 (13–22,7)	59 (39–72)	318,3 (261,6–440)
Group E	22,8 (19,5–30,5)	77 (72–92)	541,6 (438,3–690)
p^a	<0,001	<0,001	<0,001

^aKruskal-Wallis test was performed for multiple group comparison.

with respect to non-ionizing radiation exposure and a Bonferroni post-hoc analysis was performed for paired comparisons.

In the second phase of the experiment, the significance of the ongoing estrogen exposure was assessed. For this purpose, group B (without estrogen exposure) and group C (maintained with estrogen exposure) were compared. Similarly, the ongoing estrogen exposure significantly increased all of the parameters in this phase ($p < 0.05$; Table 2).

The first analysis conducted to assess the effect of non-ionizing radiation was performed between group B, which was not exposed to estrogen in the second phase of the study, and group D, which had been subjected only to non-ionizing radiation exposure. This assessment revealed that, despite the absence of estrogen exposure, non-ionizing radiation increased the height of the epithelial cells, which was statistically significant. Increases in the

luminal epithelial cell height and glandular density in terms of median values were observed despite a lack of statistical significance ($p < 0.001$, 0.074, and 0.074, for epithelial cell height, luminal epithelial cell height and glandular density, respectively; Table 2).

Finally, to evaluate the effect of non-ionizing radiation, estrogen-receiving groups C and E were compared. The rats in group C received estrogen only in both phases, while the rats in group E were also exposed to non-ionizing radiation during estrogen administration in the second phase of the study. The analyses showed a statistically significant increase in the epithelial height in the non-ionizing radiation-exposed rats, similar to that in the other group evaluations (Table 2) ($p = 0.004$). Higher median values were observed in terms of glandular density and luminal epithelial cell heights, and the p values obtained nearly reached a significance in terms of glandular density ($p = 0.058$ and 0.168 for glandular density and luminal epithelial cell height, respectively). Additionally we have compared group D and E which resulted in statistically significantly higher values in all parameters in group E ($p = 0.004$; <0.001; <0.001; respectively) (Table 2).

Discussion

We found a positive association between non-ionizing radiation generated by a mobile phone and endometrial hyperplasia progression in this experimental study on rats. This association in uterotrophic rats was found to be consistent regardless of concomitant estrogen exposure.

Table 2. Pair-wise comparison of the groups

	Median (range) Group B ($n = 10$)	Median (range) Group C ($n = 10$)	p^a
Luminal Epithelial Cell Length	13,2 (11,2–15)	20,3 (16–24,5)	<0,001
Glandular Density	35,5 (29–55)	65,5 (56–87)	<0,001
Epithelial Length	219,9 (203,3–262,5)	419,6 (358,3–458)	<0,001
	Group B ($n = 10$)	Group D ($n = 10$)	
Luminal Epithelial Cell Length	13,2 (11,2–15)	17,2 (13–22,7)	0,074
Glandular Density	35,5 (29–55)	59 (39–72)	0,074
Epithelial Length	219,9 (203,3–262,5)	318,3 (261,6–440)	<0,001
	Group C ($n = 10$)	Group E ($n = 8$)	
Luminal Epithelial Cell Length	20,3 (16–24,5)	22,8 (19,5–30,5)	0,168
Glandular Density	65,5 (56–87)	77 (72–92)	0,058
Epithelial Length	419,6 (358,3–458)	541,6 (438,3–690)	0,004
	Group D ($n = 10$)	Group E ($n = 8$)	
Luminal Epithelial Cell Length	17,2 (13–22,7)	22,8 (19,5–30,5)	0,004
Glandular Density	59 (39–72)	77 (72–92)	<0,001
Epithelial Length	318,3 (261,6–440)	541,6 (438,3–690)	<0,001

^aPair-wise comparisons were performed via Mann-Whitney U test with a Bonferroni post-hoc analysis.

The electromagnetic field created by the experimental model ranged between 12.17 and 17.29 V/m, which was similar to that in previous experimental models, despite the extreme values achieved, such as 90 V/m (14). The values achieved in our study are important for referring to the electromagnetic fields generated by the daily use of mobile phones, which are restricted to a maximum level of 41.2 V/m by the International Commission on Non-Ionizing Radiation Protection and a maximum level of 15.1 V/m by the Information Technology and Communication Institution in Turkey. Many countries such as Belgium, Italy, and Russia also set restrictions at levels of 10 V/m. The electromagnetic field generated using our experimental model mimicked the values restricted by many countries. It was important for these values to be similar to the daily restrictions for interpretation and application of results directly to daily life. By creating an electromagnetic field similar to that experience in daily life when using a mobile phone, we aimed to present daily exposure levels. This makes our study the first to use a mobile phone directly to create an electromagnetic field to investigate the association between non-ionizing radiation and endometrial hyperplasia.

The first phase of the study was aimed at assessing the uterotrophic rat model. The analysis revealed that our experimental model successfully induced endometrial hyperplasia by oral estrogen exposure, consistent with the literature (9,10). The first analysis conducted in the second phase of the study also revealed a persistent effect of oral estrogen. The two analyses revealed that the significant difference observed in our model was sufficient to initiate further analyses related to non-ionizing radiation. The designed study was aimed to simulate endometrial hyperplasia in an uterotrophic model. This model is widely used in literature for questioning the possible relationship between any environmental exposure with endometrial hyperplasia. Exogenous estrogen exposure is shown to be resulting in increase in glandular density, luminal epithelial length and luminal epithelial cell length. Increase in these parameters also take part in pathophysiology of endometrial hyperplasia. Despite lack of demonstration of atypia in this study model, this model is one of the most commonly used experimental model for establishing uterotrophic uterine model and studying on topics related to endometrial hyperplasia (12–16).

After the experimental model was assessed, the effect of non-ionizing radiation remained unclear in the groups with and without estrogen exposure. Both arms of the study revealed a positive association with endometrial hyperplasia and non-ionizing radiation generated by a mobile phone. Despite the correlated results in this study, statistical significance was not attained for some parameters, likely because of the lack of experimental rats.

To our knowledge, this study is the first to mimic mobile phone signals exactly using a mobile phone and a signal

generator as the base station. All previous studies oriented the waves created by a vector signal generator in the experiments using a horn antenna (15–17). In our study, we used a signal generator as the base station, and non-ionizing radiation was generated directly from a mobile phone and directed toward the rats. Connectivity between the signal generator and mobile phone was established at a bandwidth of 1800 MHz and an output power of 2 W, which models a mobile phone connecting to a base station with maximum output power. Although previous studies used similar models and frequencies, the duration of the application varied widely. We aimed to mimic radiation exposure in daily life and exposed the rats to radiation for 3 hours daily for 24 d to simulate 6 estrous cycles.

Owing to the absence of studies related to non-ionizing radiation and endometrial malignancies, our results cannot be compared with other literature findings (18). However, studies that showed a relationship between other systemic malignancies and non-ionizing radiation and the declaration of non-ionizing radiation as a “potential carcinogen” by the WHO support our results. Non-ionizing radiation has been studied extensively and linked to numerous systemic malignancies, especially those in the central nervous system (5,19). Glioma and acoustic neuroma have been strongly associated with mobile phone use over 10 years in a case-control study (20). The studies that evaluated the relationship between the genital system and non-ionizing radiation mostly focused on fertility and intrauterine processes (21–23). Only one study reported an association of non-ionizing radiation with oxidative stress in endometrial cells and showed significant apoptosis and inflammation in the endometrial layers (24).

The main limitation of this study is the relatively small number of experimental rats owing to ethical issues. This resulted in an insignificant statistical analysis for some parameters despite a positive correlation being observed. The second major limitation is that the results of the animal experiments cannot be directly applied to human models and cannot be interpreted directly. Many factors can change the results, such as variation in the exposure duration, method and place of use of the device, and depth of penetration of the radiofrequency waves. Nevertheless, the unique design of the study and the use of exact GSM waves at a standard frequency are strengths of our study. The malignant potential of non-ionizing radiation is found to be conflicting in the literature. Owing to the existence of conflicting results regarding each organ system, evaluations must be conducted carefully. To our knowledge, this study is the first to use a mobile phone directly to generate a steady electromagnetic field, and the results indicate a possible association between non-ionizing radiation generated by a mobile phone and endometrial hyperplasia. However, these data are only experimental results and must be confirmed by further prospective studies. Owing to ethical concerns, performing prospective human studies in this

subject is challenging; this makes animal studies important. The acquired data might serve as a basis for further studies, but cannot be implicated to daily medical practice yet. The previous studies relating non-ionizing radiation and different tumors also support our results, making such a topic important.

In conclusion, this is the first study in the literature to evaluate the association between endometrial hyperplasia prognosis and non-ionizing radiation generated by mobile phones. Non-ionizing radiation, both in cases with and without estrogen exposure, has been shown to worsen the endometrial pathology significantly in rats. The acquired results cannot be applied directly to humans but may motivate researchers to investigate the relationship between non-ionizing radiation and endometrial hyperplasia. Moreover, these results may also motivate clinicians to warn their patients against excessive non-ionizing radiation exposure to avoid progression of endometrial hyperplasia.

Conflict of Interest

The authors declare no conflict of interest.

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References

- Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
- Getpook C, Wattanakumtornkul S. Endometrial thickness screening in premenopausal women with abnormal uterine bleeding. *J Obstet Gynaecol Res* 2006;32:588–592.
- Başaranoğlu S, Ağaçayak E, Hatırnaz Ş, et al. The diagnostic accuracy of endometrial sampling in endometrial hyperplasia. *Gynecol Obstet Reprod Med* 2017;23:37–40.
- Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of “untreated” hyperplasia in 170 patients. *Cancer* 1985;56:403–412.
- IARC. Classifies radiofrequency electromagnetic fields as possibly carcinogenic to humans. 2011. http://www.iarc.fr/en/media-centre/pr/2011/pdfs/pr208_E.pdf. Accessed November 30, 2017.
- Little MP, Rajaraman P, Curtis RE, et al. Mobile phone use and glioma risk: comparison of epidemiological study results with incidence trends in the United States. *BMJ* 2012;344:e1147.
- Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ Res* 2000;86:494–501.
- Hiroki E, Akahira J, Suzuki F, et al. Changes in microRNA expression levels correlate with clinicopathological features and prognoses in endometrial serous adenocarcinomas. *Cancer Sci* 2010;101:241–249.
- Tas M, Kutuk MS, Serin IS, et al. Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats. *Gynecol Endocrinol* 2013;29:311–314.
- Erdemoglu E, Guney M, Giray SG, et al. Effects of metformin on mammalian target of rapamycin in a mouse model of endometrial hyperplasia. *Eur J Obstet Gynecol Reprod Biol* 2009;145:195–199.
- Loeb L, Suntzeff V, Burns EL. Growth processes induced by estrogenic hormones in the uterus of the mouse. *Am J Cancer* 1938;34:413–427.
- Fong CJ, Burgoon LD, Williams KJ, et al. Comparative temporal and dose-dependent morphological and transcriptional uterine effects elicited by tamoxifen and ethynylestradiol in immature, ovariectomized mice. *BMC Genomics* 2007;8:151.
- Papaconstantinou AD, Umbreit TH, Fisher BR, et al. Bisphenol A-induced increase in uterine weight and alterations in uterine morphology in ovariectomized B6C3F1 mice: role of the estrogen receptor. *Toxicol Sci* 2000;56:332–339.
- Paparini A, Rossi P, Gianfranceschi G, et al. No evidence of major transcriptional changes in the brain of mice exposed to 1800 MHz GSM signal. *Bioelectromagnetics* 2008;29:312–323.
- Nisbet HO, Akar A, Nisbet C, et al. Effects of electromagnetic field (1.8/0.9 GHz) exposure on growth plate in growing rats. *Res Vet Sci* 2016;104:24–29.
- Ozlem Nisbet H, Nisbet C, Akar A, et al. Effects of exposure to electromagnetic field (1.8/0.9 GHz) on testicular function and structure in growing rats. *Res Vet Sci* 2012;93:1001–1005.
- Bodera P, Stankiewicz W, Antkowiak B, et al. Influence of electromagnetic field (1800 MHz) on lipid peroxidation in brain, blood, liver and kidney in rats. *Int J Occup Med Environ Health* 2015;28:751–759.
- Jauchem JR. Effects of low-level radio-frequency (3kHz to 300GHz) energy on human cardiovascular, reproductive, immune, and other systems: a review of the recent literature. *Int J Hyg Environ Health* 2008;211:1–29.
- WHO. Electromagnetic fields and public health: electromagnetic hypersensitivity. WHO Factsheet 296.; 2005. <https://www.who.int/peh-emf/publications/facts/fs304/en/>.
- Hardell L, Carlberg M, Soderqvist F, et al. Long-term use of cellular phones and brain tumours: increased risk associated with use for > or= 10 years. *Occup Environ Med* 2007;64:626–632.
- Adams JA, Galloway TS, Mondal D, et al. Effect of mobile telephones on sperm quality: a systematic review and meta-analysis. *Environ Int* 2014;70:106–112.
- Lerchl A. Animal studies on growth and development. *Prog Biophys Mol Biol* 2011;107:404–407.
- Bahreyni Toossi MH, Sadeghnia HR, Mohammad Mahdizadeh Feyzabadi M, et al. Exposure to mobile phone (900–1800 MHz) during pregnancy: tissue oxidative stress after childbirth. *J Matern Fetal Neonatal Med* 2018;31:1298–1303.
- Guney M, Ozguner F, Oral B, et al. 900 MHz radiofrequency-induced histopathologic changes and oxidative stress in rat endometrium: protection by vitamins E and C. *Toxicol Ind Health* 2007;23:411–420.