ORIGINAL RESEARCH

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The Effect of Radiofrequency Waves on Pregnant Mice in Association with Genes Involved in Neuronal Migration

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ABSTRACT Objective: We aimed to evaluate alterations in expression of the genes, which are known to have a role in neuronal migration by the administration of daily life exposure doses of radiofrequency to pregnant mice. **Material and Methods:** Two groups were established. Each of them contained 6 female, 2 male Balb/c mice. They were weighted 15-20 g. For the occurrence of pregnancy, male and female mice were placed in cages mixed. The study and control groups were exposed to the radiofrequency field with the average specific absorption rate value of 0.725 W/kg, 12 hours a day until birth. Total RNA and cDNA were obtained from postnatal brain tissue of newborn mice. Alterations in the expression of 7 (ARX, FLNA, DCX, LARGE, RELN, TUBA1, YWHA) genes that are known to have a role in neuronal migration were investigated by real-time polymerase chain reaction. **Results:** The expressions of 6 of the 7 genes were found to be significantly increased. These genes were ARX, FLNA, DCX, LARGE, RELN and YWHAE. This study proved that even at low levels, magnetic field may affect the development of foetuses as a consequence of gene expression changes. **Conclusion:** Magnetic field may affect foetusess during pregnancy and precautions must be taken to prevent exposure.

Keywords: Neuronal migration; neuronal migration disorders; magnetic field; radiofrequency

Radiofrequency is an electromagnetic energy form, which is created from electrical alternating currents. In other words, it is a rate of oscillation. The frequency ranges from 3 kHz to 300 GHz. It is used for telecommunications including radio and television, mobile phones, microwaves, heaters and medical reasons in daily life.[1] It is in the spectrum of nonionizing radiation; therefore, adverse health effects are supposed to be much less compared to ionizing radiation such as X-ray, alpha radiation, beta radiation and ultraviolet. On the other hand, with the advent of technology, many industrial products have been introduced to our daily life. Mobile phones are one of the most common instruments in which the rate of usage per person including children has increased greatly. Consequently, serious concerns about the usage and possible hazardous effects of those types of phones have been raised in the community.[2] Those hazardous effects have been reported to be thermal and nonthermal. While thermal effects have been attributed to heat increase in the tissue, nonthermal effects have been reported to be associated with vibration of radiofrequency waves, effect on changing protein configuration, adverse effect on magnetites, forming radical pairs or free radicals.[3] Many investigations have been reported in the literature searching the hazardous effects and mechanisms of the interactions between mobile phones, wireless communication and base stations which are all associated with similar length of radiofrequency waves.[4-6] Very few studies have been published regarding the association of neurodevelopmental anomalies and ra-

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diofrequency exposure.[7] Doublecortin (*DCX*) gene codes DCX protein which is expressed in migrating neuroblasts and this protein organises microtubule functions. Tubulin alpha 1a (TUBA1A) is a member of alpha tubulin protein family and has a role in neuronal migration. Aristaless related homeobox (ARX) protein is responsible for differentiation of GABAergic neurons and triggers radial neuronal migration. Reelin (*RELN*) gene codes a protein which has an active role in cortical neuron migration and cell positioning in the brain. Filamin A (*FLNA*) gene encodes FLNA protein which provides filopodial motilitiy and its expression increases in cortex during neuronal migration. Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon (*YWHAE*) mediates signal transduction and has a role in Miller-Dieker syndrome. Like-acetylglucosaminyltransferase (LARGE) works in glycosilation of the alpha-destro-glycans. All these genes have a role in neuronal migration and mutations of the genes have been shown in well known neurological diseases like lissencephaly and other neuronal migration disorders.[8] The aim of this study is to investigate the expression levels and changes of 7 (*DCX, TUBA1, YWHAE, ARX, RELN, LARGE, FLNA*) genes which have roles in neuronal migration.

MATERIAL AND METHODS

All the procedures of the experiment mentioned below is summarised in Figure 1.

ANIMALS

Adult balb/c mice, weighing 15-20 g were used. They were taken from Ege University Animal Research Laboratory. They were kept under normothermic temperature (24°C) and lightning conditions. The animals were divided into 2 groups. Each group consisted of 2 male and 6 female mice, a total of 16 mice were included in the study. They were housed in cages (sizes were 43x30x17 cm) where they could move freely and were given water and food ad libitum. They were maintained on a 12-hour light/12-

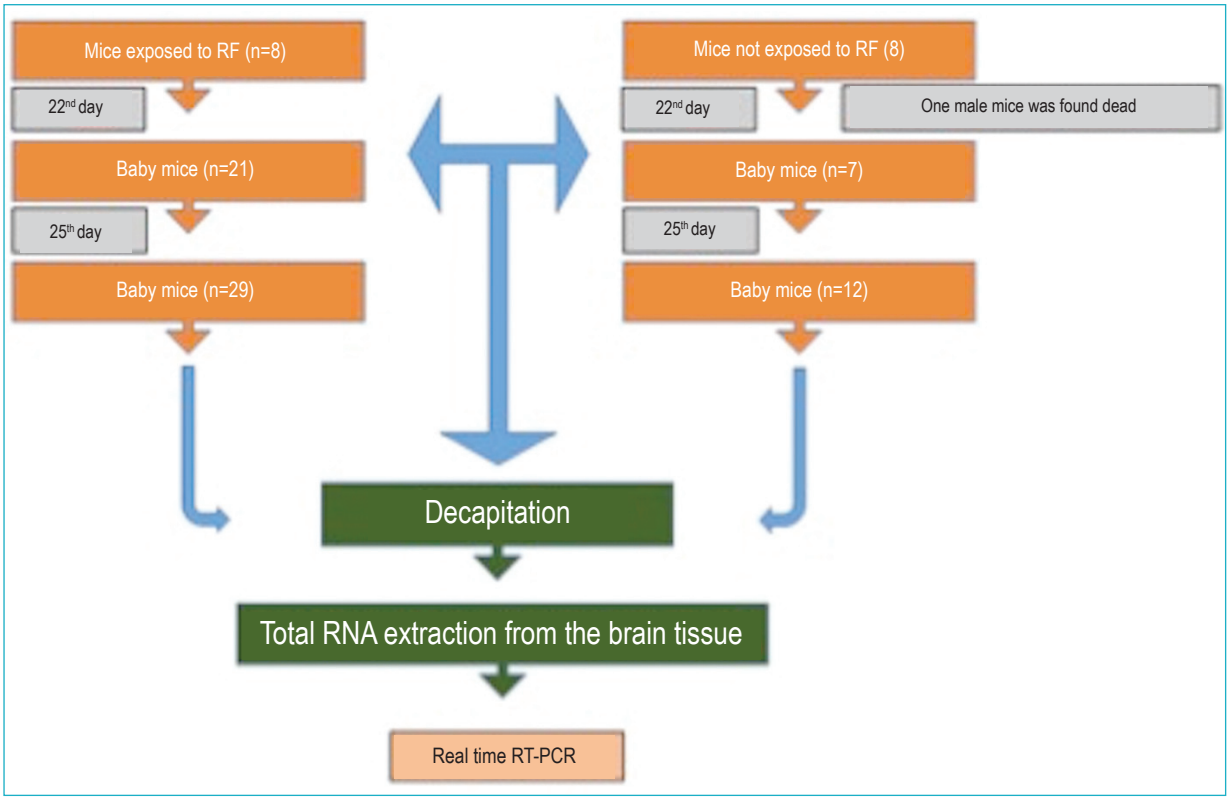

FIGURE 1: Schematic overview of the experimental study design.
RT-PCR: Real-time polymerase chain reaction.

hour dark cycle. At the end of the experiment at day 25, all the offspring were sacrificed and their brains were removed for genetic analysis. The study was approved by the Animal Ethics Committee of Ege University (date: November 25, 2011, no: 2011/163) and conducted in accordance with the Helsinki Declaration.

PROCEDURES

Two groups were consisting of study and control groups where the study group was exposed to radiofrequency waves (n=8), and the control group was not exposed to radiofrequency waves (n=8). The offsprings were decapitated after ether (1.9% concentration) anesthesia administered by exposure in a close container by open-drop method to mice within 12 hours following their birth and their brain tissue were used for RNA extraction. Each of their brain tissue was taken into 1.5 mL eppendorf with 1 mL Tripure solution (Roche, Switzerland). After waiting for 5 minutes in room temperature, 0.2 mL of chloroform was added and the tube was shaken bottom up. Following 2-3 minutes incubation at room temperature, it was centrifuged at 12.000 rpm for fifteen minutes at 4°C. This supernatant was transferred into a clean tube and 0.5 mL isopropanol was added. After incubation period at room temperature, it was again centrifuged at 12.000 rpm at 4°C for 15 minutes. The supernatant was thrown, and the pellet at the bottom of the tube was mixed with 1 mL of 75% ethanol. This mixture was centrifuged at 10.000 rpm for 5 minutes at 4°C. The pellet at the bottom was resuspended with water and used for cDNA synthesis without waiting.

MAGNETIC FIELD APPLICATION

The exposure system was established in an empty testing room without any other device, which might deliver a magnetic field. Electromagnetic radiation originating from electrical supplies was 0.021 W/kg. Microwave equipment was used to perform magnetic field experiments. There were 3 major components of this system as presented in Figure 2 which were a 2.8-cm (Wavelength) Microwave Transmitter (C051-044.672), a 2.8-cm (Wavelength) Microwave Receiver (C052-045.674) and a 12-V DC Power Supply (all UNILAB, Blackburn UK). The hertz magnetic field was used at 10.715 GHz oscillator frequency with 8.0-mW power output. The beam width of the microwave and the exposure per cm^2 over the sample were 6 cm and 0.84 mW/cm^2, respectively. Semcad-X package computer program (Shmidt & Partner Engineering, Switzerland) was used for the specific absorption rate (SAR) value of electromagnetic radiation which corresponds to the value of those in mobile phone systems. The average SAR was 0.725 W/kg. The exposure system was turned on continuously for 12 hours per day and continued until the date of birth. Animals were exposed to magnetic field randomly. The temperature of the experiment room conditions was kept steady at 24°C to provide an appropriate cooling system, and the inside temperature of the cages was monitored (Figure 2).

RNA PROCESSING AND CDNA SYNTHESIS

After the isolation process, total RNA concentration and pureness were measured by spectrophotometry at the wavelengths of 260 and 280 nm. The absorption rate at A260/A280 for ideal pure RNA must be 1.8-2.0. The degradation control of RNA was controlled by agarose gel electrophoresis.

Transcriptor First Strand cDNA Synthesis Kit was used for cDNA synthesis. For each sample, 11 µL of RNA+H_2O was mixed with 2 µL Random hexamer primer. These tubes were placed into thermalcycler and RNA was denaturized at 65°C for 10 minutes. After the denaturation period, the tubes were placed into cooling container and 7µL mastermix so-

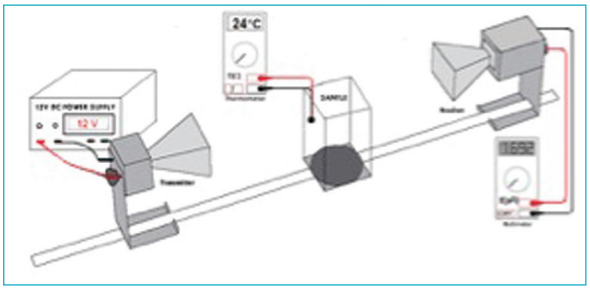

FIGURE 2: Schematic representation of the experimental system. The cage was placed in the middle of the distance between the transmitter and the receiver, which would provide an average SAR of 0.725 W/kg. Mice were exposed to radiofrequency waves continuously for 12 hours per day during the pregnancy period and continued until the date of birth of offspring. The temperature of the experiment room was kept steady at 24°C and the cages were monitored.
SAR: Specific absorption rate.

lution (Reaction buffer 4 µL, Protector RNase inhibitor 0.5 µL, Deoxynucleotide Mix 2 µL, Transcriptor Reverse Transcriptase 0.5 µL) was added to each one. The tubes were again placed into thermalcycler and were waited at 25°C for 10 minutes, at 50°C for 60 minutes, at 85°C for 5 minutes, at 4°C for 1 minute, respectively. The cDNA samples that were achieved after this procedure were transferred to ice.

REAL-TIME POLYMERASE CHAIN REACTION

Real-time polymerase chain reaction (PCR) was used to show the expressions of the 7 genes *DCX, TUBA1A, YWHAE, ARX, RELN, LARGE, FLNA* which are known to have roles in neuronal migration, after achieving cDNA. Quantitative real-time PCR analysis was carried out by LightCycler 480 (Roche, Switzerland) device and software.

cDNA was used to determine targeted RNA expression level by having a reaction with specific primers and probes at 96-pack plate (Table 1). The house keeping genes (glyceraldehyde-3-phosphate dehydrogenase and actin-beta) were used for control of the PCR at Real-Time Ready study and relative quantitation of the research gene expression. Real-Time Ready study can measure the expression of housekeeping and research gene at the same time. For this study, 96-pack plate mixture with the final volume of 25 µL which is containing cDNA was prepared with ddH_2 (528 µL) and LightCycler 480 Probe Master (1,056 µL). This mixture was pipetted without vortex and then distributed to every pit as 20 µL. The cDNA concentration was diluted with water at least 480 µL for achieving 5 ng-5 µg/plate rate. Diluted cDNA sample distributed to every pit as 5 µL except for RNA negative control H12 pit. 5 µL of RNA was added to H12 pit as negative control. The plate was covered with sealing foil and centrifuged at 1,500 rpm for 2 minutes to clean up the adhesive droplets on the pits. Denaturation period as one cycle (95°C-10 minutes), amplification period as 45 cycle (95°C-10 seconds, 60°C-30 seconds, 72°C-1 second) and cooling period as one cycle (40°C-30 seconds) were administrated for Real-Time Ready panel.

STATISTICAL ANALYSES

The normalization of gene expressions and their comparative analysis with respect to the control group were performed in the web-based GeneGlobe Data Analysis Center (https://geneglobe.qiagen.com/analyze). This method is used for relative quantitation of

TABLE 1: Primers sequences and information for related genes.

No	Gene	Primer	Tm	Genbank accession number
1	DCX	F: aactggaagaaggggaaagc	59	NC_000086.7
		R: ggttgacattcttggtgtactca	59	
2	TUBA1A	F: aggagctggcaagcatgt	59	NC_000081.6
		R: ggtgcgaacttcatcgatga	60	
3	YWHAE	F: agtaccggcaaatggttgaa	60	NC_000077.6
		R: ccttggactcgccagtgt	59	
4	ARX	F: ttccagaagacgcactaccc	60	NC_000086.7
		R: tctgtcaggtccagcctcat	60	
5	RELN	F: ctttggattcgggatcatgt	59	NC_000071.6
		R: tccagacaaagctgaggttg	59	
6	LARGE	F: ggcattgtggcaggtaaca	60	NC_000074.6
		R: ccacatggatggtctcacac	59	
7	FLNA	F: atccctcgtagcccctacac	60	NC_000086.7
		R: ggctgaaggcctctaccaat	60	
8	ACTB	F:cctgaaccctaaggccaac	59	NC_000071.6
		R: ggggtgttgaaggtctcaaa	59	
9	GAPDH	F: ctcatgaccacagtccatgc	60	NC_000072.6
		R: acgccacagctttccaga	60	

expression of reference genes and *DCX, TUBA1A, YWHAE, ARX, RELN, LARGE, FLNA* genes. The RT2 Profiler PCR Arrays & Assays Data Analysis Software (Qiagen, Germany) analyzes computed tomography (CT) values to calculate changes in gene expression. Δ/Δ Ct method was used to make a relative quantitation. By this method, gene expression Ct values were normalized with *ACTB* house-keeping gene and the groups were compared with each other. The result gave the Δ/Δ Ct value. Fold changes were calculated beyond 2 -Δ/Δ Ct value. Student's t-test was used for the evaluation.

RESULTS

A total of 15 mice have been included in the study. Study group consisted of 6 female and 2 male mice and control group, 7 (6 female and 1 male) mice. Seven offsprings from the control group and 21 offsprings from the magnetic field exposure group were achieved on the 22nd day of the experiment. Eight offsprings from the study group and 5 offspring from the control group were achieved on the 25th day of the experiment (a total of 29 offspring from the study group and 12 offspring from the control group). Body weights of the offspring were ranged between 1.5-2 g. Mice were killed by cervical dislocation. After decapitation of offspring, brains were removed. A total of 588.8 ng/mL of total RNA was achieved from their brain tissue.

After static analyses, the expressions of 6 out of 7 genes were found to be significantly increased. These genes were *ARX, DCX, FLNA, LARGE, RELN* and *YWHAE* (Table 2, Figure 3). Compared to the control group, we observed the highest fold changes in *ARX, LARGE* and *RELN* expressions which were over 4 times. Fold change was between 2-4 times for DCX, YWHAE and FLNA expressions. When groups were compared as male and female mice, no statistical difference was found between both groups. The experiment is summarized in Figure 3.

DISCUSSION

Although current novel developments in technology facilitate human life, it may adversely affect human biology in different aspects. In particular, their effect on malignancy, cell proliferation, hormonal impact and DNA breakages, apoptosis, and infertility were widely studied. As these devices were mostly used near head and neck region, their effect on central nervous system has also been studied.[9-12] In a review by Morgan et al., mobile phone radiation has been proposed as a potential carcinogen for the brain tumours. Therefore, mobile phone usage should be evaluated for their adverse health effects in a large range of aspects.[13] In this study, the effects of exposure to doses of radiofrequency in daily life due to mobile phones or other devices emitting electromagnetic field, has been investigated by analysing the genes that have important roles in neuronal migration.[14] We obtained 29 offsprings from the study group and 12 offsprings from the control group which could be due to the lost of one male mice in the control cage at the beginning of the experiment. Among the genes studied in this

TABLE 2: Fold change (log2) expressions of the genes that were statistically significant.

Gene	Fold change	p value
ARX	4.14	0.000003
DCX	3.32	0.000016
FLNA	2.44	0.000049
LARGE	4.02	0.000001
RELN	4.03	0.000053
TUBA	1.47	0.000050
YWHAE	2.88	0.000047

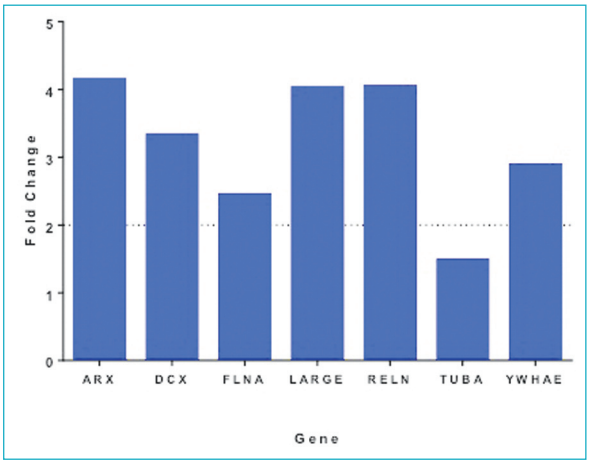

FIGURE 3: The relative fold change of the related gene expressions comparing with and without radiofrequency exposure by using real-time-qPCR. qPCR: Quantitative polymerase chain reaction.

experiment, which play important roles in the neuronal migration, the expressions of *ARX, DCX, FLNA, LARGE, RELN* and *YWHAE* were found to be significantly increased. When those genes were evaluated separately, the overexpression of all those genes was found to be close related with cell cycle and neuronal anomalies. To the best of our knowledge, it is the first study revealing the effects of RF waves on the genes related to neuronal migration.

The development of the central nervous system is a highly complex process. Neuronal migration is the most crucial step in this development. Timing and orientation of this process is very well programmed. Genetic defects or external factors may lead to neuronal migration problems by disrupting this program. For instance, exposure to cell phone radiation has been shown to upregulate apoptosis genes in primary cultures of neurons and was concluded that radiofrequency may upregulate elements of apoptotic pathways.[14,15] Loeliger et al. studied vulnerability of human embriyonic brian development to ionizing radiation. They used stem cell cultures and studied neuronal development under high dose and low dose radiation. They found significant expression changes in genes which have a great impact on neuronal development like ARX.[16] In another study performed on human HL-60 cells, RF of 2.45 GHz has been shown to upregulate 221 genes after 2-hour-exposure. Interestingly, the number of genes that were upregulated increased to 759 after 6-hour-exposure. These genes have been reported to be mostly apoptotic genes.[17] In a detailed review, radiofrequency radiation and gene/protein expression were discussed. It was stated that many studies were performed on the potential ability of RF radiation to modify gene transcription and protein levels in a variety of models. Heat-shock proteins, proto-oncogenes and genes associated with signal transduction pathways were investigated. Some of the parameters were found to have no effect but many of them were revealed to induce alterations in gene expressions including neuronal formation.[18] *ARX* gene, a member of homeobox gene family, is a transcription factor, which controls the formation of many organs such as testes, pancreas, skeletal muscle and brain in the embryonic period.[19] Friocourt et al. demonstrated that *ARX* gene is responsible for the cell cycle regulation of cortical progenitor cells, radial migration of pyramidal neurons and tangential migration of ventral telencephalon. Its overexpression has been reported to be related with the length of the cell cycle and radial migration of pyramidal neurons.[20] *DCX* protein binds to microtubules in the cytosol and allows their stabilization. Microtubules form a framework for cells and allows the progression of these cells in a certain direction.[21] Matsumoto et al. showed that the mutations in the *DCX* gene lead to neuronal migration anomalies such as lissencephaly and subcortical band heterotopia.[22] No effect of DCX was found on morphological maturation or migration of mouse brain.[23] *LARGE* is involved in the addition of xylose and glucuronic acid molecules to α-dystroglycan protein. α-dystroglycan protein is responsible for the formation of cell cytoskeleton and the extracellular matrix. In skeletal muscle, it provides the stabilization and protection of muscle fibers. Most importantly, it is involved in the neuronal migration during early development.[24] Qu and Smith showed that the radial migration pathway that is present in cortex and cerebellum is affected by *LARGE* gene defects.[25] In another study, Qu et al. demonstrated that tangential migration defect occurring in the precerebellar nucleus formation was observed having mutations in the *LARGE* gene of rats.[26] Its overexpression induced hyperglycosylation of a-dystroglycan which could be related with neuronal migration anomaly.[27] *RELN* is secreted from Cajal-Retzius cells and it has a critical role in early cortical development. Lissencephaly with cerebellar hypoplasia is associated with *RELN* gene mutations that are inherited as autosomal recessive.[28] It is presented as developmental delay, hypotonia, severe ataxia, seizures, diffuse pachygyria, hippocampal dysplasia and hypoplastic cerebellum and brain stem. Chang et al. showed that the serum expression of RELN protein was absent in a similar group of patients.[29] *YWHAE* gene is located on 17p13.3 and encodes 14-3-3 epsilon (ε) protein. This protein has a role in insulin sensitivity and cell cycle. It also has a role in brain development and neuronal migration.[30] A very well-known and described disease, Miller-Dieker syndrome is caused by a deletion in the short arm of chromosome 17 which covers the *YWHAE* gene. The reduction of 14-

3-3 ε proteins causes lissencephaly.[8] Mignon-Ravix et al. demonstrated that periventricular heterotopia and corpus callosum hypoplasia occurs due to deletions in *YWHAE* gene.[31] In addition, Zhao et al. indicated that the gene expression of rat neuron could be altered by exposure to RF under certain experimental conditions.[15]

In our study, the expression of all those genes has been shown to be significantly increased in the embryos exposed to RF. We can assume that RF fields might affect heat-sensitive gene or protein expression to an extent larger than would be predicted from temperature change only. But in all likelihood, this would concern intensities higher than those relevant to usual human exposure. If RF radiation at intensities relevant to human exposure produces any biological effect, this result must notably imply changes in cell behaviour and changes in gene and protein expression.[32] These might be also due to thermal effect. Effects of the exposure of 2.14GHz W-CDMA RF EMF to rats on body temperature increase and heat shock alter the proteins expression.

The effects of EMF exposure on mitogen-stimulated lymphocyte growth have been studied in numerous studies. In a review by Lacy-Hulbert et al., it was stated that EMF (50 Hz at least 6 hours) exposure increased thymidine incorporation by 20% in lymphocytes, which are stimulated with phytohemagglutinin. This effect was observed by 60% in lymphocytes obtained from older donors. Most striking results were achieved in B cells of patients having chronic lymphocytic leukemia, which there was 100% increase in thymidine incorporation. Other studies revealed different findings and rates but overall, these results suggest that there are comitogenic effects of EMF on stimulated cell cultures and it may be regarded as tumour promoters.[33] Previous experiments also emphasize the effect of magnetic field on Ca and K ion channels. This may have an effect on altering the gene expressions by activating Na/K ATPase in order to restore ion homeostasis. This hypothesis of course needs further investigation.[34,35]

CONCLUSION

This prospective randomized controlled study is the first study assessing the effects of magnetic field exposure on the foetuses and neuronal migration. It was revealed that, even in low doses of magnetic field, the expression of genes that are responsible for neuronal migration were found to be increased in foetuses. Gene expression changes may disrupt normal development of tissue. Further large-scale studies are needed to determine the exact RF dose and length of exposure that will cause neuronal migration anomalies. Furthermore, this study confirms that, magnetic field may cause negative effects on the foetuses, therefore revealed the need for protective measures to be taken to reduce exposure during pregnancy.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özgür Çoğulu, Alkım Gülşah Şahingöz Yıldırım, Sermet Sağol;* ***Design:*** *Emin Karaca, Oğuz Gözen, Burak Durmaz, Teoman Yıldız, Ersin Köylü;* ***Control/Supervision:*** *Sermet Sağol, Özgür Çoğulu;* ***Data Collection and/or Processing:*** *Alkım Gülşah Şahingöz Yıldırım, Mete Ergenoğlu, Nuri Yıldırım, Özgür Yeniel;* ***Analysis and/or Interpretation:*** *Alkım Gülşah Şahingöz Yıldırım, Emin Karaca, Cumhur Gündüz;* ***Literature Review:*** *Alkım Gülşah Şahingöz Yıldırım;* ***Writing the Article:*** *Alkım Gülşah Şahingöz Yıldırım;* ***Critical Review:*** *Özgür Çoğulu, Sermet Sağol;* ***References and Fundings:*** *Alkım Gülşah Şahingöz Yıldırım, Ege University Scientific Project;* ***Materials:*** *Teoman Yıldız, Oğuz Gözen, Alkım Gülşah Şahingöz Yıldırım.*

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