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Intrauterine Effects of Electromagnetic Fields—(Low Frequency, Mid-Frequency RF, and Microwave): Review of Epidemiologic Studies

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ABSTRACT Electromagnetic radiations are named according to frequency or to wavelength (which is inversely proportional to frequency) and create electromagnetic fields (EMFs). Frequencies widely vary according to sources: high-voltage power lines, electrically heated beds, MRI, VDTs, microwave ovens, satellite, and radio/TV transmissions or cellular phone transmitters/receivers. Public concern has increased about the potential health effects of EMFs. There are arguments in favour of EMFs being biologically active, but no mechanism has been identified that explains the link between EMFs and bioeffects. Human data reviewed concern the potential reproductive effects (mainly spontaneous abortions, low birthweight and congenital malformations) of exposure to sources of EMFs: maternal residence, electrically heated beds, occupational exposure (mainly video display terminals), and medical exposures. The available epidemiologic studies all have limitations that prevent to draw clear-cut conclusions on the effects of EMFs on human reproduction. EMFs are ubiquitous and unavoidable exposures. The matter of possible effects cannot be considered closed, but until our understanding of the biologic important parameters of EMFs exposures is stronger,design of new studies will be difficult and small epidemiologic studies are unlikely to provide definitive answers and should not be given high priority. No conclusion can be drawn for radiofrequencies and microwaves because of lack of data. There is no convincing evidence today that EMFs of the sort pregnant women or potential fathers meet in occupational or daily life exposures does any harm to the human reproductive process. *Teratology 59:292–298, 1999.* © 1999 Wiley-Liss, Inc.

Electromagnetic radiations are named according to frequency or to wavelength (which is inversely proportional to frequency)and create electromagnetic fields (EMFs). Frequencies widely vary according to sources, as shown in Figure 1. These include high-voltage power lines, electrically heated beds, or magnetic resonance imaging (MRI) (50 or 60 Hz), video display terminals (VDTs) (≤30 kHz), microwave ovens (e.g., 900–2,500 MHz), satellite and radio/TV transmissions (e.g., 6,000 MHz), or cellular phone transmitters/receivers (e.g., 800–900 MHz). Juutilainen ('91), Chernoff et al. ('92), as well as Brent et al. ('93) have assembled detailed reviews of the available animal and human studies regarding the evaluation of reproductive risks related to EMFs/radiofrequency (RF) radiation. The reader is invited to refer to these articles for completeness as the goal of the present paper is to make a review illustrating the variety of the epidemiologic studies and to interpret them, bearing in mind that experimental studies did not result in either consistent evidence that adverse reproductive outcome can be produced or a clear indication of a mechanism by which they might be provoked.

Among the numerous endpoints to consider when looking at human reproduction, the studies reviewed concern the potential effect of EMFs on infertility, sex ratio, miscarriages, premature births, intrauterine growth retardation (IUGR), low birthweight, congenital malformations or genetic diseases, perinatal deaths, and long-term effects like childhood cancer. These endpoints will be considered for various exposure conditions.

MATERNAL RESIDENTIAL MAGNETIC FIELD EXPOSURE

The possibility of an association of early pregnancy loss (EPL) with residential exposure to ELF magnetic fields was investigated by Matilainen et al. ('90) and Juutilainen et al. ('93) in case-control studies. In the latter, 89 cases and 102 controls were obtained from an earlier study aimed at investigating the occurrence of EPL in a group of women attempting to become pregnant. Magnetic field exposure was characterized by measurements in residences. Strong magnetic fields were measured more often in case than in control residences. In an analysis based on fields measured at the front door, a cutoff score of 0.63 μT resulted in an odds ratio (OR) of 5.1 (95% confidence ratio [CI] =

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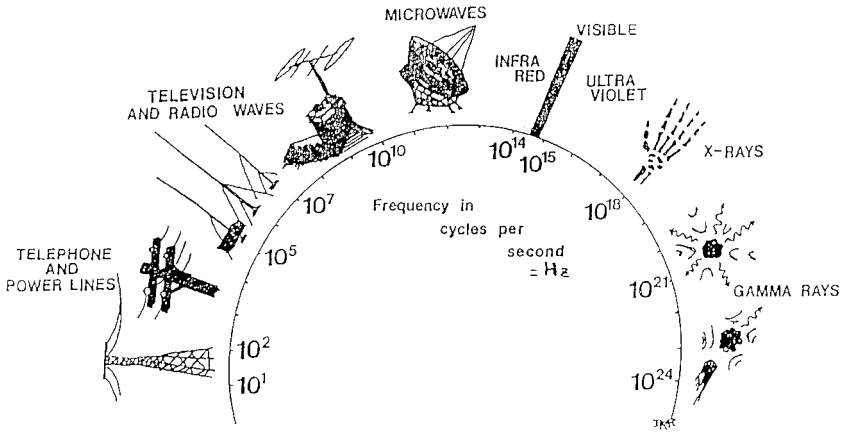

Fig. 1. The electromagnetic spectrum.

1.0–25). The results should be interpreted cautiously because of the small number of highly exposed subjects and other limitations of the data.

Robert ('93) performed a preliminary study in France that did not identify an excess of birth defects among children whose parents live within 500 m of a high-voltage power line (HVPL). It was pointed out that the field strength drops off rapidly with distance from the line and that few people live directly below a power line; therefore, it is unlikely that most of these children were exposed in utero to electromagnetic fields much differently from "nonexposed" children.

Savitz and Ananth ('94) used data collected for a study of childhood cancer to examine the relationship between measured residential EMFs and wire codes to pregnancy outcome. Data consisted of interviewed cases and controls. Pregnancies in homes with measured fields of >0.2 μT or high wire codes were not more likely than others to end in miscarriage, low birthweight, or preterm delivery. According to the authors, as the sample was not specifically collected to test this hypothesis, lack of data on potential confounders and small numbers of cases limit the study's conclusion.

More recently, Robert et al. ('96) conducted a matched case-control study in the same region of France to explore in further detail whether living closer to HVPL increased the risk of congenital anomalies. For every case and control the distance from the HVPL to the maternal residence at the time of birth was measured as a surrogate of EMF exposure. Using 100 m as the cut-point between exposure and nonexposure yielded an OR of 0.95 (95%CI = 0.45–3.22). Among the 11 malformed infants within 100 m, there were two children with Down syndrome, but otherwise there was no pattern in the occurrence of specific anomalies. Patients included in this study were not actually exposed to EMFs if they lived at a distance of >25 m from the center line of overhead powerlines. People living at a shorter distance from a line are so few that no epidemiological study can have enough statistical power to determine whether the prevalence of a specific congenital anomaly is significantly increased as a result of living near a HPLV. One can only conclude that in this sample, there were no differences in residential proximity to HPLV between malformed and control infants.

HEATED WATERBEDS, ELECTRIC BLANKETS AND CEILING HEATING COILS

Wertheimer and Leeper ('86) studied a sample of 1256 births of 4271 women who delivered in two Denver area hospitals in 1982. They obtained information on use of electrically heated beds (electric blankets and heated waterbeds) from a telephone survey and attempted to determine whether such exposures influenced reproductive parameters: gestational length, birthweight, miscarriage rate, and birth defects. They found an increase in spontaneous pregnancy loss during seasons of use and concluded that either thermal or electromagnetic field effects might be involved in human reproductive wastage. The same investigators ('89) showed subsequently a similar seasonal variation in pregnancy loss associated with the use of ceiling heating. Both papers were extensively reviewed by Chernoff et al. ('92) and severe design problems were underlined: more than 70% of eligible births in the study were missing, the rate of congenital malformations in the reference group (1 in 335) was abnormally low, the method for studying miscarriage rate was unappropriate. In both papers the authors tried to adapt their observations to a number of speculations about biologic effects of EMFs on fetal loss, but their findings do not demonstrate that the use of electric blankets or heated waterbeds increases the risk of adverse reproductive outcome.

In an epidemiologic study in New York State, Dlugosz et al. ('92) did not find that electric bed heating increased the risk of congenital defects or fetal loss. Li et al. ('95) interviewed 118 women having a child born with a congenital urinary tract anomaly. Interviews were also made with 369 mothers of control infants. They found an association between electric blanket use during the first trimester of pregnancy and congenital urinary tract abnormalities (OR = 4.4; 95% CI = 1.2–85.5) in women with a history of subfertility. The participation rate in this study was relatively low

(62.6% for cases and 67.6% for controls), and the results relied only on three exposed cases, and a selection bias cannot be excluded. No association was found in the study with electrically heated waterbeds or work with VDTs. The authors interpret their findings as the fact that only a very sensitive segment of the population (subfertile women) would likely be affected by electric blankets which generate magnetic fields five times higher than electrically heated waterbeds or VDTs, are used longer and have a closer proximity to the target (in utero embryo). Many maternal characteristics were analyzed as subsamples. For these reasons the conclusions of the study are questionable, and confirming data are needed.

Bracken et al. ('95) conducted a prospective study to evaluate the relation of birthweight and fetal growth retardation with use of electrically heated beds (electric blankets or heated water beds) during pregnancy. None of the exposure measures showed a dose-response relation to risk.

One study by Savitz et al. ('90) examined cancer in children who resided in Denver specifically as a possible effect of prolonged in utero EMF exposure to the child, using interview data from a case-control study. The investigators reported an increased risk of both leukemia (OR = 1,7; 95%CI = 0.8–3.6) and brain cancer (OR = 2.5; 95%CI = 1.1–5.5) among children whose mothers used electric blankets during pregnancy. The results of this study are limited by the rate of nonresponse and the small sample size resulting from the rarity of appliance use. They were not subsequently confirmed and warrant further evaluation.

WORKING WITH VIDEO DISPLAY TERMINALS

The issue of VDTs as possible reproductive hazards has been much discussed in recent years. The first statements made to that effect were met with absolute denial from officials and scientists: there was no measurable ionizing radiation around the VDTs that can reasonably affect the embryo or the fetus. VDTs are similar to the video screens of television sets. Many VDTs involve the modulation of a scanning electron beam targeted on the surface of a fluorescent tube. The magnetic flux density at the very low frequency corresponding to the screen scanning beam (15–30 kHz) would be 0.01–0.2 μT with occasional values of $\leq$0.6 μT and 0.07–0.7 μT, with occasional values of $>$1 μT at the extremely low frequencies corresponding to the electric main supply of alternating current (50–80 Hz) (Advisory Group on Non-Ionizing Radiations, '94). These ELF fields are no greater than those produced by other domestic appliances. Although early television sets were found to be a significant source of ionizing radiation, the use of leaded glass to fabricate picture tubes, begun during the early 1960s, eliminated this source of radiation. As explained by Blackwell and Chang ('88), some newer television and computer systems are using smaller and lighter liquid crystal displays, which are much simpler than VDTs, and emit little radiation of any sort. These authors as well as Marha and Charron ('85) mention that other forms of electromagnetic radiation emitted by VDTs have been measured for a variety of the commercial units on the market: by measuring radiation at the back and sides of the units attention has also been given to the possible exposure to people positioned near the VDT. These two papers, as well as a number of other studies confirm the finding that nonionizing radiation and magnetic fields associated with these units are not produced in biologically important quantities (Liden et al., '86; Juutilainen and Saali, '86; Marriott and Stuchly, '86; Murray, '86).

The major concern started in Canada in 1980, where a cluster of four infants with severe malformations was described; the mothers worked at the same place, a newspaper department in Toronto. The cluster was linked to the fact that the women had worked with VDTs during pregnancy. The publication of this cluster in the Toronto Globe and Mail soon brought forward reports on other clusters of reproductive failure in North America, reviewed by Bergqvist ('84). A cluster of miscarriages was subsequently investigated at the General Telephone Company of Michigan (Lichty, '85), where 6 of 29 pregnancies in VDT-exposed women aborted spontaneously compared to 8 miscarriages in 97 pregnancies not exposed to VDTs. Although this difference was statistically significant, the author left open the possibility that work-related factors other than VDT exposure might be involved because the jobs performed by VDT-exposed and nonexposed women at this company differed considerably.

Clusters of adverse reproductive outcomes should be expected to occur at different work places, including numerous places where VDT work is common. Bergqvist ('84) published mathematical models of clusters trying to estimate whether the reported number of clusters was larger than reasonable from mere random distributions and this latter model was judged to be true. Abenhaim and Lert ('91) performed an analysis of case clusters in an office setting that included VDT exposures and reached the same conclusions.

In addition to the preceding report on clusters of miscarriages, four case-control studies have been unable to find an association between congenital anomalies and exposure of the mother to VDTs (Kurppa et al., '85; McDonald et al., '86; Ericson and Källén, '86a; Tikkanen et al., '90). A significant excess of hydrocephalus was reported as result of a case-control study performed by Brandt and Nielsen (1990), but no similar excess was reported by any of the other investigators. Another case-control study was done by Ericson and Källén ('86b) including as cases miscarriages, perinatal deaths, severe malformations, and low birthweight infants. A total of 522 such cases and 1,032 matched controls were studied. When the possible effect of VDT work on poor reproductive outcome was analysed, a significantly increased risk was registered for birth defects, but these effects were reduced and lost statistical significance when a stratification for smoking and

stress was made. There was no detectable effect on miscarriage rate. The epidemiological value of this study is high and this perfectly illustrates how hazardous it might be to draw quick conclusions from a few positive findings. For instance, Goldhaber et al. ('88), in a large case-control study, suggested a small but significantly elevated risk of miscarriage for women who reported using VDTs for more than 20 hr/week during the first trimester of pregnancy. As is true for any retrospective method of investigation, recall bias may have impaired data collection in this study. Women were questioned about their VDT use more than 2 years after the pregnancies in question. It is also possible that estimates regarding exposure to VDTs were not accurately recalled by the subjects and, as stated by Robinson ('89), pregnancy outcome may have distorted the recollection of VDT exposures. The increased miscarriage rate may have also been due to unmeasured factors confounded with high VDT use such as poor ergonomic conditions or job related stress. This thesis is supported by the finding in the case-control study that miscarriages were increased in certain job categories without regard to VDT exposure. McDiarmid et al. ('94) made a comparison between apparent associations with VDT exposure that were established with either retrospective and prospective data collection. The prospectively collected data did not support the data collected retrospectively, which implicated recall bias as a confounding factor in the retrospective data.

Schnorr et al. ('91) performed a study at the National Institute for Occupational Safety and Health (NIOSH), where they monitored the incidence of spontaneous abortion in 882 pregnancies that included occupational use of VDTs during gestation. The data in this very thorough investigation did not indicate any association between the use of VDTs and exposure to the accompanying electromagnetic fields and an increased risk of spontaneous abortion. Similar negative findings were also reported by Lindbohm et al. ('92), and by Roman et al. ('92) who made a case-control study that was designed to minimize a possible role of nonoccupational factors in the incidence of spontaneous abortions. Although the study by Lindbohm et al. ('92) did not find an overall increased risk of spontaneous abortion associated with use of VDTs, they did find an increased risk for women who worked with terminals that emitted a high level of extremely low frequency magnetic field. The small number of subjects (less than 20 per group) makes the significance of this observation questionable.

The Council on Scientific Affairs ('87) officially stated that available data were not sufficient to rule out all possibility that a factor associated with VDT use may be hazardous to pregnancy, and subsequently a meta-analysis by Parazzini et al. ('93), as well as a review by Delpizzo ('94) concluded that the available data indicate that the magnitude of the risk from the VDT itself, if risk exists at all, is quite small. In a more recent case-referent study, Smith et al. ('97) conclude that women exposed to various environmental agents, including "nonionizing radiations from VDTs," in their occupation have higher risks of infertility than do those not exposed. According to these authors, VDT exposure would be more likely to be found among women diagnosed with endometriosis. Different criticisms can lower the significance of these results: the selection of referent women for the study was not restricted to working women, which might have resulted in a "healthy worker effect," and other factors were not controlled for among the working conditions. Because of these reasons, conclusions reached in the previously quoted reviews are not to be modified.

With the growing use of computer technology around the world, we should expect the continuing appearance of isolated and anecdotal case reports that identify an abnormal birth and maternal VDT exposure (Kultursay et al. '94). This prompted a reaction by Rodriguez-Pinilla and Martinez-Frias ('95), who rejected the hypothesis by a case-control analysis of a sample of malformations drawn from the Spanish registry and stressed the necessity to be cautious when interpreting case reports.

OTHER OCCUPATIONAL EXPOSURES

Nordström et al. ('83) found an increase in the incidence of congenital malformations in a survey of 372 married couples in which the male worked at one of two Swedish power companies between 1953 and 1979. The finding could not be explained by confounding or reporting biases, but it is not clear by what mechanism such adverse outcomes might have been transmitted via the father, and no consistent pattern of malformations was evident. Coleman and Beral (88) suspect a chance association. Lundsberg et al. ('95) conducted a nested case-control to compare men with abnormal semen parameters and controls. They showed no association between occupationally related categories of magnetic field exposure and male subfertility, as evaluated by morphology, motility, and concentration. These findings do not support theories of deleterious effects to male reproductive health from magnetic field exposure.

One finding that has been reported twice is an excess of low birthweight and prematurity in women employed in the electrical industry. In Canada, McDonald et al. ('88) set up a study to investigate associations between reproductive outcome and occupation. Low birthweight and/or prematurity was found among women employed in 5 of the 59 occupations studies, with a relative risk of 1.57 ($P < 0.01$) for employment in the manufacture of electrical and metal goods. In Scotland, Sanjose et al. ('91) studied more than 250,000 livebirths in the period 1981–1989 and found an increased risk of low birthweight and/or prematurity in 4 of 15 occupational groups, one of which being work with electrical goods (relative risk for low birthweight 1.4, $P = 0.05$). These two studies are too vague with respect to exposure assessment to justify attributing low birthweight or premature births to one cause or another. In a smaller study in California, Lipscomb et al. ('91) found an

excess of low-birthweight babies in women who worked as electronic assemblers, but this excess was attributed by the authors themselves to concomitant exposure to solvents.

Infante-Rivard ('95) carried out a case-control study in Spain and suggested that in utero exposure to EMFs generated by sewing machines (60 Hz) used by pregnant women might be a risk factor for childhood leukemia. This would indicate that EMFs would have a transplacental carcinogenetic action, which needs to be further explored.

In a questionnaire study of physiotherapists exposed to varying amounts of microwave and ultrasound (10^{12}–10^{14} Hz), Källén et al. ('82) found no relationship between adverse pregnancy outcome and nonionizing radiation exposure, with the exception of a possible relationship between stillbirth and birth defects and exposure to shortwave radiation. This association was questioned by the authors as possibly due to chance or to bias in response of the study women.

In a questionnaire sent to men occupationally exposed to shortwave, microwave, infrared, and acoustic radiation radiation, Logue et al. ('85) found an increase in total congenital anomalies in the offspring of such men compared with the offspring of matched controls. There was no increase in any particular subgroup of anomalies and the total anomaly rate was only 3.7%. In addition, the response rate was low (58%) and it is possible that respondents had more abnormalities to report than nonrespondents. No estimation of exposure was made in this study and it is not possible to conclude based on these data that this type of radiations are a paternally mediated risk factor for the offspring.

Two different studies, made in Denmark by Larsen et al. ('91) and in Switzerland by Guberan et al. ('94), studied sex ratio in offspring of women working as physiotherapists. The Danish investigators found a deficit of male births, while the Swiss ones, using the same protocol, failed to confirm the finding. The low sex ratio might be explained by an increased sensitivity of Y germ cells to nonionizing radiations, but as this is not even confirmed for ionizing radiations, the results are likely to be random.

Childhood brain cancer among offspring of EMF-exposed fathers has been examined in several different case-control studies. The reported risk ratios are generally in the order of 2, but in certain subpopulations they are higher and sometimes reach statistical significance (Spitz and Johnson, '85; Wilkins and Koutras, '88). Other studies have shown high, but not statistically significant, results (Johnson and Spitz, '89; Nasca et al., '88), while Bunin et al. ('90) found negative results. As in most occupational studies, exposure assessment is based on job title, and therefore results must be interpreted with caution.

Magnetic Resonance Imaging

MRI is a tissue imaging technique that uses a magnetic field that is not different of other electric appliances and radiofrequency radiation. The exposure level of operators of MRI devices ranges within 5–100 mT. Evans et al. ('94) designed a questionnaire study of MRI workers. The study did not uncover indications that employment exposure to these magnetic fields had adverse effects on fertility or infant birth weight. The relative risk of miscarriage in comparison with women pregnant at other jobs or at home was 1.27 (95% CI = 0.92–1.77; $P = 0.07$). The completeness and validity of the self-reported data in such studies are open to question.

Radiofrequency

The effects of RF seen in animal studies are likely to be related to maternal hyperthermia, and not to some direct effect of RF on the embryo or fetus. RF do not induce significant hyperthermia in humans, so that any adverse reproductive outcome due to RF is unexpected. Nevertheless, there are few epidemiologic studies of reproductive outcomes in populations exposed to RF (10^5–10^{11} Hz). Most surveys have been conducted in men. A case-control study of Down's syndrome conducted by Sigler et al. ('65) in Baltimore suggested that fathers of Down children gave more frequent histories of occupational exposure to radar during military service than did fathers of unaffected children, the difference being of borderline statistical significance. A subsequent expansion of the study by Cohen et al. ('77) did not confirm the primary results. There is no available epidemiologic study on the effects of exposures to cellular telephones or amateur radio-operating on reproduction.

MEDICAL EXPOSURES

Magnetic Resonance Imaging

The patient's exposure during MRI is up to about 2 T. MRI examinations are avoided in patients with metallic implants, such as some intrauterine contraceptive devices. During the last decade, obstetrical use of MRI imaging has increased and indications are becoming larger and larger (Lowe et al., '85) as this technique proves to be efficient in the evaluation of position of the placenta (Powell et al., '86), as well as in the observation of fetal anatomy, e.g., ventriculomegaly (Hanigan et al., '86), growth retardation (Stark et al., '85), or conjoined twins (Turner et al., '86). First-trimester exposures were, however, performed on women coming for termination of pregnancy. Second- and third-trimester MRI examinations have been reported by Baker et al. ('94) not to increase the incidence of adverse pregnancy outcome or of abnormal hearing tests in children, although the number of cases with long-term follow-up is small.

Diathermy

The use of shortwave and microwave diathermy, to relieve the pain of uterine contractions during labor was reported from Belgium by Daels ('73, '76). More

than 10,000 women received about 2,450 MHz and no side effects were observed in the newborns. There are few other reports on diathermy during human pregnancy. In a paper published by Rubin and Erdman ('59), five pregnancies in four women were exposed to diathermy at 2,450 MHz, using a 100-W machine. Four pregnancies ended with the birth of normal children and one ended in miscarriage. The investigators concluded that diathermy was safe during pregnancy, but the technique is no longer used.

CONCLUSION

The public concern about EMFs is motivated mainly by the fact that they are ubiquitous and nobody can totally avoid this type of exposure. The available epidemiologic studies all have limitations that prevent to draw clear-cut conclusions on the effects of EMFs on human reproduction. This is because the four usual steps necessary for a good risk assessment are incomplete: hazard identification, exposure characterization, dose-effect relationships and risk characterization. There is a lack of biologic plausibility, a lack of consistency in studies, RRs and ORs are sometimes higher than one but low, factors influencing the metric of utility wirecodes (age of the house, urban location, traffic density) are usually not controlled for, and very often, biases in controls selection and potential confounders can be suspected. Moreover, in case of actual adverse effect of EMFs on reproduction, time trends would have been observed in the results of studies because of drastic increase in electricity use. Finally, no study has assessed both in-home and away-from-home EMF exposures.

The matter of possible effects cannot be considered closed, but until our understanding of the biologic important parameters of EMFs exposures is stronger, design of new studies will be difficult and small epidemiologic studies are unlikely to provide definitive answers and should not be given high priority. No conclusion can be drawn for radiofrequencies and microwaves because of lack of data, but there is no convincing evidence today that EMFs of the sort pregnant women or potential fathers meet in occupational or daily life exposures do any harm to the human reproductive process.

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