Published in final edited form as:

J Toxicol Environ Health B Crit Rev. 2016 ; 19(1): 29–45. doi:10.1080/10937404.2015.1134370.

Exposure to power-frequency magnetic fields and the risk of infertility and adverse pregnancy outcomes: update on the human evidence and recommendations for future study designs

Ryan C. Lewis, Ph.D.^{1,2}, Russ Hauser, M.D., Sc.D., M.P.H.^{3,4}, Andrew D. Maynard, Ph.D.¹, Richard L. Neitzel, Ph.D.¹, Lu Wang, Ph.D.⁵, Robert Kavet, Sc.D.⁶, and John D. Meeker, Sc.D.^{1,*}

¹University of Michigan School of Public Health, Department of Environmental Health Sciences, 1415 Washington Heights, Ann Arbor, Michigan 48109, USA

²Exponent, Inc., Center for Occupational & Environmental Health Risk Assessment, 475 14th Street, Suite 475, Oakland, California 94612, USA

³Harvard T.H. Chan School of Public Health, Departments of Environmental Health and Epidemiology, Building I, 14th Floor, 665 Huntington Avenue, Boston, Massachusetts 02115, USA

⁴Massachusetts General Hospital, Vincent Memorial Obstetrics and Gynecology Service, 55 Fruit Street, Boston, Massachusetts 02114, USA

⁵University of Michigan School of Public Health, Department of Biostatistics, 1415 Washington Heights, Ann Arbor, Michigan 48109, USA

⁶Electric Power Research Institute, 3420 Hillview Avenue, Palo Alto, California 94304, USA

Abstract

Infertility and adverse pregnancy outcomes are significant public health concerns with global prevalence. Over the past 35 years, research has addressed whether exposure to power-frequency magnetic fields is one of the etiologic factors attributed to these conditions. However, no apparent authoritative reviews on this topic have been published in the peer-reviewed literature for nearly 15 years. This review provides an overview and critical analysis of human studies that were published in the peer-reviewed literature between 2002 and July 2015. Using PubMed, 13 epidemiology studies published during this timeframe that concern exposure to magnetic fields and adverse prenatal (e.g., miscarriage), neonatal (e.g., preterm birth or birth defects), and male fertility (e.g., poor semen quality) outcomes were identified. Some of these studies reported associations whereas others did not, and study design limitations may explain these inconsistencies. Future investigations need to be designed with these limitations in mind to address existing research gaps.

*Corresponding author: John D. Meeker, Sc.D., University of Michigan School of Public Health, Department of Environmental Health Sciences, 1415 Washington Heights, Ann Arbor, Michigan 48109, USA, meekerj@umich.edu, telephone: 1.734.764.7184, fax: 1.734.936.7283.

CONFLICT OF INTEREST

Ryan Lewis began this research while he was a Ph.D. student at University of Michigan. However, he has since graduated from the University of Michigan and now works for Exponent, Inc., a firm that provides consultation on the potential human health risks posed by exposure to environmental agents, including power-frequency magnetic fields. Robert Kavet is employed by the Electric Power Research Institute, which partially funded this research. All others authors declare no conflict of interest.

In particular, the following issues are discussed: 1) importance of selecting the appropriate study population, 2) need for addressing confounding due to unmeasured physical activity, 3) importance of minimizing information bias from exposure measurement error, 4) consideration of alternative magnetic field exposure metrics, and 5) implications and applications of personal exposure data that is correlated within female-male couples. Further epidemiologic research is needed given the near ubiquitous exposures to power-frequency magnetic fields in the general population.

Keywords

Magnetic fields; infertility; exposure science; epidemiology; study design

INTRODUCTION

Infertility is one of the most common reproductive diseases, affecting approximately 15% of couples in the U.S. alone during their reproductive lifespan (Eisenberg et al., 2015). The already high prevalence of this disease is likely to rise as the postponement of childbearing increases in developed areas of the world (Evers, 2002; Pinelli and Di Cesare, 2005). Adverse pregnancy outcomes, such as preterm birth (defined as birth at less than 37 weeks of gestation), low birth weight (defined as a birth weight less than 2,500 g), and congenital anomalies (e.g., heart and neural tube defects), are also prevalent globally (Ferguson et al, 2013; WHO, 2004, 2012, 2014). These conditions contribute significantly to neonatal morbidity and mortality and are associated with adverse health conditions that extend into adulthood (WHO, 2004, 2012, 2014). The determinants of infertility and adverse pregnancy outcomes are multifactorial, arising as a complex interplay of environmental, genetic, and/or lifestyle factors evident at the population level.

Over the past 35 years, research has addressed whether exposure to power-frequency magnetic fields (50 or 60 Hz, subsequently referred to as “magnetic fields”) is a risk factor for infertility and adverse pregnancy outcomes. The basis for this research priority arose from reports in 1979–1982 of miscarriage and birth defect clusters among video display terminal (VDT) operators in the U.S. and Canada (Bergqvist, 1984), and from laboratory studies that reported developmental abnormalities in chick embryos following exposures to magnetic fields (Berman et al., 1990; Delgado et al., 1982; Ubeda et al., 1994). Exposure to magnetic fields induces eddy currents within tissues that some postulate may be of biological significance. Patterns of these induced currents within the human body depend upon orientation of the external field and the conductivity of tissues (ICNIRP, 2010). While there is some experimental evidence in mammalian and non-mammalian species that exposure to magnetic fields may disrupt early development and fertility (IARC, 2002; WHO, 2007), currently no apparent biophysical mechanism is known that would trigger biological effects from low-level magnetic field exposure and, as a result, lead to adverse reproductive health outcomes.

Following these cluster reports, much effort was invested to support epidemiology studies that examined the potential association between exposure to magnetic fields from VDT and

adverse pregnancy outcomes (Bryant and Love, 1989; Ericson and Kallen, 1986a; 1986b; Goldhaber et al., 1988; Grasso et al., 1997; Lindbohm et al., 1992; McDonald et al., 1986; Nielsen and Brandt, 1990; Roman et al., 1992; Schnorr et al., 1991; Winham et al., 1990), as well as from sources of exposure in and around the home, such as electric blankets, heated water beds, and power lines (Belanger et al., 1998; Juutilainen et al., 1993; Lee et al., 2000; Savitz and Ananth, 1994; Wertheimer and Leeper, 1986; 1989). These epidemiology studies produced conflicting results and many were characterized by study design limitations that possibly biased effect estimates, most notably from: (1) questionable accuracy of outcome measures, particularly those that were focused on miscarriage (also known as “spontaneous abortion” and defined as a pregnancy loss prior to the 20th week of gestation), (2) exposure misclassification due to the use of surrogate measures of personal exposure, such as residential wire code classification, self-reported use of electric devices, and spot measurements in residences and workplaces, and (3) temporal ambiguity between exposure and outcomes. For these aforementioned reasons, consensus of expert opinion following this 20-year effort was that the evidence potentially linking exposure to magnetic fields and adverse reproductive health outcomes was deemed inadequate (Ahlbom et al., 2001; NIEHS, 1998).

The past 15 years has seen new human evidence concerning magnetic fields as a potential risk factor for infertility and adverse pregnancy outcomes and the investigation of related epidemiologic study design issues. Consequently, there was a need to summarize the current state-of-the-art, which is provided as an overview and critical analysis of recent human evidence herein (Table 1). This review focused on epidemiologic studies that were published in the peer-reviewed literature since 2002 as the authoritative reviews on this topic were published in the literature prior to this date, such as Chernoff et al. (1992) and Ahlbom et al. (2001), and, from a historical standpoint, this was when the debate surrounding magnetic fields and reproductive health was revived following the publication of the studies by Lee et al. (2002) and Li et al. (2002). These two studies are noteworthy as they were the first of their kind to characterize personal magnetic field exposures using personal exposure monitors. The results and subsequent conclusions from these investigations generated important commentary in the peer-reviewed literature (Li and Neutra, 2002; Savitz, 2002), and discussion on that commentary deserves attention in this review as it is informative for the design of future studies. As such, guidance for future studies on the following issues is additionally provided: (1) importance of selecting the appropriate study population, (2) need for addressing confounding due to unmeasured physical activity, (3) importance of minimizing information bias from exposure measurement error, (4) consideration of alternative magnetic field exposure metrics, and (5) implications and applications of personal exposure data that is correlated within female-male couples.

EPIDEMIOLOGIC STUDIES

PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) was utilized to identify the epidemiology studies described in this section. Our search was limited to epidemiology studies that were published in the peer-reviewed literature between 2002 and July 2015. These investigations were identified using various combinations of keywords that correspond to the agent itself (e.g., “magnetic fields”), known sources of magnetic fields (e.g., “power line”), and various

infertility and adverse pregnancy outcomes (e.g., “miscarriage”). A total of 13 epidemiology studies were identified in the peer-reviewed literature.

Prenatal Outcomes

In 2002, the questions surrounding exposure to magnetic fields and adverse pregnancy outcomes were revived following the publication of two epidemiology studies conducted in pregnant women enrolled in the California Kaiser Permanente Medical Care Program (Lee et al., 2002; Li et al., 2002). Following the publication of the Kaiser studies, the California Department of Health Services released a report stating that a “substantial proportion of miscarriages” might be caused by exposure to magnetic fields and that, if true, this would be cause for “personal and regulatory concern” (CDHS, 2002).

In the first study, Lee et al. (2002) conducted a nested case-control study of women from a prospective cohort [described previously in Swan et al. (1998)]. Using an EMDEX-C, which was worn at the hip and recorded the field once every 10 sec for a 24-hr period, personal exposure monitoring occurred at 30 weeks of gestation for women whose pregnancy continued (controls) and at the equivalent gestational week for those that miscarried (i.e., the outcome preceded the exposure estimate). Data were analyzed for the cases and controls that maintained the same address through 30 weeks of gestation: 155 cases and 509 controls. To validate the assumption that exposures at 30 weeks of gestation were similar to those that were experienced in the first trimester, personal exposure monitoring was also conducted in a prospective sub-study of 219 women (201 controls and 18 cases) at 12 weeks of gestation. Exposure data at 12 weeks were correlated with those at 30 weeks of gestation when available (166 controls and 10 cases had measurements at both time points) and were also used to determine whether the potential relationship between magnetic field exposure and miscarriage when examined prospectively generated similar results as the nested case-control study, which was based on exposure measurements at 30 weeks. Magnetic field exposure was also estimated for participants retrospectively using wire code and one-min spot measurements at the front door and inside the home. Ninety-one % pregnancy outcomes were determined by using computerized hospital and medical records, whereas the remaining 9% were ascertained via telephone interviews, mailed questionnaires, or matches to vital records (Swan et al., 1998).

The investigators reported adjusted odds ratios (ORs) for the time-weighted average (TWA); rate of change metric (RCM), average absolute difference between successive measurements; and maximum (MAX) measurement throughout the monitoring period. For the 30-week measurements, there were no statistically significant associations between miscarriage and TWA ≥ 2 mG, wire code classification, or spot measurements. There were, however, statistically significant exposure-dependent increases in miscarriage risk by quartiles for the RCM and MAX, which were strongly correlated ($r = 0.96$). For the TWA analysis by quartile, in which the top cut point was 1.28 mG, the trend across quartiles was not significant, although ORs for the 2nd through 4th quartiles were elevated (all with adjusted ORs of 1.7 and associated 95% CIs of 0.9–3.2 or 0.9–3.3).

In the sub-study, the correlation of personal magnetic field exposures at 12 and 30 weeks of gestation was moderately strong for the TWA ($r = 0.64$), but was poor for both the MAX ($r =$

0.09) and RCM ($r = 0.19$). In contrast to the results of the nested-case control study, the adjusted ORs for TWA ≥ 2 mG for the 12-week measurements were elevated for measurements at home (OR: 3.0, 95% CI: 1.1–8.4), but not statistically significant for the full 24-hr period (OR: 1.9, 95% CI: 0.6–6.1). The 12-week adjusted ORs for the RCM and MAX where the 50th percentile was selected as the cut-off point were suggestive (OR: 2.4, 95% CI: 0.9–6.6 and 2.6, 0.9–7.6, respectively).

In a second study, which was in part motivated by the TWA results of the Lee et al. (2002) sub-study and recruited women from the same parent cohort, Li et al. (2002) conducted a prospective cohort investigation in 969 women with a positive pregnancy test at <10 weeks of gestation (median gestational age of 40 days). Participants were considered to be at risk until they miscarried or were censored (maintained pregnancy beyond 20 weeks of gestation or experienced another pregnancy outcome). Sixteen point four % women experienced a miscarriage, whereas 80% remained pregnant beyond 20 weeks of gestation and 3.6% had ectopic pregnancies or induced abortions, which were censored at the time when they occurred. Employing similar exposure assessment techniques as Lee et al. (2002), immediately following their interview, Li et al. (2002) asked women to wear an EMDEX II personal magnetic field exposure monitor [Lee et al. (2002) used the EMDEX-C,] at the hip for 24 hr with the unit programmed to acquire the magnetic field every 10 sec. Consistent with Lee et al. (2002), Li et al. (2002) also did not report elevated relative risks associated with wire code classification and spot measurements. Using a 3 mG cut-off point [rather than the 2 mG cut-off point in the Lee et al. (2002) study that in part motivated this investigation], Li et al. (2002) noted an adjusted rate ratio (RR) for the TWA that was not statistically significantly elevated (RR: 1.2, 95% CI: 0.7–2.2).

To explore a potential threshold effect of magnetic field exposure, Li et al. (2002) also modeled personal magnetic field exposure using MAX ≥ 16 mG. This threshold was chosen for the following reasons: (1) Li et al. (2002) noted that the rate of miscarriage in the cohort began to increase at around a MAX of 12–18 mG when miscarriage rate was explored in relation to deciles of MAX magnetic field exposure, (2) 16 mG was the cutoff for the first quartile (i.e., 75% of the cohort had MAX exposures ≥ 16 mG), and (3) 16 mG was selected *a priori* as the cut off for several other exposure metrics (total sum of exposure ≥ 16 mG, duration of exposure ≥ 16 mG, and number of exposure events ≥ 16 mG) that were also evaluated in relation to miscarriage. Li et al. (2002) reported a positive association between MAX ≥ 16 mG and miscarriage (adjusted RR: 1.8, 95% CI: 1.2–2.7). When stratifying on gestational age, the association was stronger among those with a miscarriage between 0–9 weeks of gestation (adjusted RR: 2.2, 95% CI: 1.2–4.0) than those with one at 10 weeks of gestation or greater (adjusted RR: 1.4, 95% CI: 0.8–2.5). Miscarriage risk was also greater in women with subfertility and previous miscarriages (adjusted RR: 3.1, 95% CI: 1.3, 7.7), which, as postulated may represent “susceptible” sub-populations. For total sum of exposure ≥ 16 mG, similar increases in risk of miscarriage were noted for the entire cohort [adjusted RRs and associated 95% CIs from lowest to highest tertile of exposure; 1.7 (1.1, 2.8), 1.8 (1.1, 2.9), and 2 (1.2, 3.1)], and for women with sub-fertility [2.3 (0.7, 7.2), 3.7 (1.4, 10.2), and 3.3 (1.2, 9.2)]. Li et al (2002) also found that both duration of exposure and number of exposure events ≥ 16 mG were also positively associated with risk of miscarriage.

After 2002, two additional studies explored the potential association between exposure to magnetic fields and miscarriage. Wang et al. (2013) conducted a prospective cohort study of 413 women (101 cases) residing in the Pearl-River Delta of China. Participants were recruited at a gestational age of at least 8 weeks or if they planned to have a child within one year, and pregnancy outcomes were determined by local obstetricians. Spot measurements collected at the front door and in the alley in front of the house “on days when electric power supply loads were relatively high” were used as surrogates of personal exposure. While no apparent relationship was observed for front door spot measurements, the MAX level measured in the alley in front of the house was positively associated with miscarriage (adjusted hazard ratio: 1.72, 95% CI: 1.10–2.69). Shamsi Mahmoudabadi et al. (2013) performed a matched case-control study in Iran of 116 women that either miscarried prior to the 14th week of gestation (n = 56) or were pregnant in at least the 14th week of gestation. Spot measurements were collected inside the home after outcome status was determined to differentiate exposure levels between cases and controls. Shamsi Mahmoudabadi et al. (2013) adjusted their statistical models for factors that were matched on (maternal age, paternal age, and self- or family history of miscarriage) and reported that magnetic field levels inside the home of cases were significantly higher than those of controls.

Su et al. (2014) recently examined the potential relationship between exposure to magnetic fields and abnormal embryonic development in a cross-sectional study, postulating that miscarriage may be preceded by and perhaps causally-related to such developmental effects. In that study, 130 working and nonworking women that were seeking an elective abortion were recruited from a maternal and child health center located in Shanghai, China. These women were between 5–12 weeks’ pregnant and were evaluated for embryonic bud and sac lengths, which were ascertained by radiologists, and apoptosis level in decidua tissue, which was determined by a research technician. Exposures were characterized within 4 weeks following abortions with a personal exposure monitor worn at the hip that collected data once every 4 sec for a single, 24-hr period, and, as a result, there was temporal ambiguity between exposure and outcome. Su et al. (2014) selected the TWA, median, and 75th percentile as potentially biologically-relevant metrics *a priori*. While embryonic sac length and apoptosis levels were not markedly related to personal magnetic field exposure measures, embryonic bud length [cases = 19 (bud length 25th percentile), controls = 46 (bud length >25th percentile)] was inversely associated with a 75th percentile magnetic field exposure 0.82 mG (adjusted OR: 3.95, 95% CI: 1.1, 14.2).

Neonatal Outcomes

A few case-control and cross-sectional epidemiology studies in recent years also examined whether exposure to magnetic fields may adversely influence birth outcome. Consistent among these studies is the potential for temporal ambiguity as it is unclear if the exposure preceded the outcome. Using data from 140,356 births derived from England’s North West Perinatal Survey Unit database, de Vocht et al. (2014) examined the potential relationships between residential proximity to nearest magnetic field source (potential sources included: high voltage cables, overhead power lines, or electricity substations or towers) and the following birth measures: preterm birth, spontaneous preterm birth (which excluded elective deliveries), small-for-gestational-age (defined as birth weight <10th percentile), low birth

weight, and birth weight. While no apparent associations were observed for 4 clinical birth outcomes, de Vocht et al. (2014) found that there was a reduction in average birth weight for participants that lived in homes that were 50 m from a source (adjusted beta: -212 g, 95% CI: -395, -29 g). In a follow-up analysis, de Vocht and Lee (2014) re-analyzed the dataset using statistical measures to address missing data (multiple imputation) and residual confounding (propensity score matching), and again found that babies from mothers residing in homes 50 m from a source had a reduced birth weight (adjusted beta: -116 g, 95% CI: -224, -7 g). Auger et al. (2011) compiled data from the Quebec birth files and conducted a cross-sectional analysis of the relationship between residential distance to nearby power lines and preterm birth, low birth weight, and small-for-gestational-age among a cohort of 707,215 births. No marked relationships were observed between residential proximity to power lines and these clinical birth measures.

Blaasaas et al. (2002) conducted a cross-sectional study of congenital anomalies among a cohort of 836,475 and 1,290,298 children from Norway. The presence of birth defects was identified using the Medical Birth Registry, and both maternal and paternal occupation was ascertained using census data. An expert panel assigned parents to categories of weekly duration of exposure of $>0.1 \mu\text{T}$ (1 mG) (<4 , 4–24, >24 hr/week), a threshold below which background levels in places, such as offices and homes, are expected. In the maternal analysis, for all birth defects combined (including Down's syndrome), there was no significant trend across exposure categories, although the group with 4–24 hr exposure had an adjusted OR of 1.06 (95% CI: 1.01–1.12); the OR for >24 hr was 0.92 (95% CI: 0.77–1.11). Of 11 specifically identified birth defects, maternal exposure was positively associated with spina bifida [adjusted ORs and associated 95% CIs for 4–24 and >24 hr/week relative to <4 hr/week: 1.21 (0.86, 1.69) and 2.33 (1.10, 4.94)], and inversely associated with cleft palate [0.57 (0.35, 0.92) and 0.34 (0.05, 2.34)]. In the paternal analysis, there was a suggestive association between exposure and all birth defects combined [1.03 (0.99, 1.07) and 1.03 (0.97, 1.09)]. Of the same specifically identified birth defects, paternal exposure was positively related to anencephaly [1.52 (1.15, 2.02) and 1.39 (0.91, 2.13)].

Using the same Medical Birth Registry and magnetic field threshold, Blaasaas et al. (2003) determined the association of birth defects with magnetic fields in residential environments. Using an engineering method that included field calculations based on line configuration and historical loading, a cohort of 161,844 births were classified by occupying residences that were either $<0.1 \mu\text{T}$ (unexposed) or $>0.1 \mu\text{T}$ (exposed). For 21 specific defects combined there was no marked association with exposure (adjusted OR: 0.92, 95% CI: 0.82–1.03). There was an elevated risk of esophageal defects (adjusted OR: 2.5, 95% CI: 1.0, 5.9), and a negative association for cardiac (adjusted OR: 0.5, 95% CI: 0.3, 0.9) and respiratory (adjusted OR: 0.4, 95% CI: 0.2, 0.9) defects.

In a follow-up analysis, Blaasaas et al. (2004) re-estimated residential magnetic field exposures associated with 42,223 births within transmission corridors based on maps of scale 1:5000 as they reported that such an approach correlates better with on-site field measurements than GIS. Using a reduced set of birth defects, no marked associations were observed between estimated residential magnetic fields and congenital anomalies, and the positive and inverse associations previously noted were not detected observed in this

analysis. Malagoli et al. (2012) found no significant relationship between residential magnetic fields and birth defects in a case-control study of 456 births (cases = 228) from Italy using a similar exposure assessment approach as Blaasaas et al. (2003).

Male Fertility Outcomes

Only one peer-reviewed study was located during this timeframe that explored the relationship between exposure to magnetic fields and adverse male reproductive health. Li et al. (2010) conducted a case-control study of 148 men (76 cases) that were recruited at sperm bank in Shanghai, China. Case status was determined by comparing sperm motility, morphology, and concentration against thresholds for poor semen quality defined by the World Health Organization. Exposures were characterized using a personal exposure monitor that collected data every 4 sec for a single, 24-hr period after the outcome was assessed. Participants were asked to start the collection of exposure data on a day that likely represented a “typical day” in the past three months. Li et al. (2010) selected the 90th percentile (1.6 mG) as the potentially biologically-relevant exposure metric to determine a threshold effect, and because, based on data collected from a residential temporal variability study, postulated that this metric would also be “relatively stable” over the period of spermatogenesis (2–3 months). Li et al. (2010) reported that men with a 90th percentile personal magnetic field exposure 1.6 mG were at an increased risk of poor semen quality (adjusted OR: 2.0, 95% CI: 1–4.). Duration of exposure 1.6 mG was also associated with risk of poor semen quality in a dose-dependent manner [adjusted ORs and associated 95% CIs for 1–3, 3–6, and 6 hr relative to <1 hr : 1.5 (0.6, 4.1), 1.8 (0.7, 5.2), and 2.7 (0.9, 7.8)].

RECOMMENDATIONS FOR FUTURE STUDIES

Study Population

The population for which a study hypothesis is framed and in which an epidemiologic investigation is conducted need to be selected to maximize validity, minimize biases, and achieve the stated aims of the study with adequate statistical power. However, in reality, certain components of any study may not be feasible due to various issues, such as limitations on what can be reasonably asked of participants and availability of data.

The literature concerning the relationship between magnetic field exposure and miscarriage [e.g., Lee et al. (2002) and Li et al. (2002)] has predominantly dealt with clinical miscarriages, a design that does not necessarily account for the full population of failed conceptions. Wilcox et al. (1988) measured urinary levels of human chorionic gonadotropin (hCG) among 221 healthy women through 707 menstrual cycles. Elevated levels of hCG are an indicator of an early pregnancy. Of 198 positive hCG tests, there were 43 (21.7 %) losses that would not have been recognized clinically, whereas there were 18 (9.1 %) losses that were recognized clinically. Thus, the total losses accounted for 30.8% of all positive hCG tests among this cohort of women.

To advance the state-of-the-science, an investigation is required that prospectively follows a cohort of women prior to conception through delivery with exposure monitoring at key points in the study period. Such a study design minimizes temporal ambiguity between

exposure and outcome of interest (i.e., the exposure measure precedes the outcome), which is potentially problematic in case-control and cross-sectional studies and other designs that estimate exposures and outcomes retrospectively. An investigation of women enrolled in infertility clinics offers this opportunity. Due to difficulty conceiving naturally, coupled to technological advances in clinical methods, an increasing number of women are seeking care in clinical centers specializing in assisted reproductive technologies (ART). In addition, the infertility clinic population would allow for the study of men and potential relationship between magnetic fields and semen quality (Missmer et al., 2011). Infertility clinics maintain highly accurate documentation of well-accepted markers of infertility and adverse pregnancy outcomes. Clinical outcomes may include: oocyte fertilization; implantation failure; chemical pregnancy; miscarriage; preterm birth; low birth weight; sperm concentration, motility, morphology, and DNA effects; and other variables that are recorded at birth, such as congenital anomalies. In addition, enrollees in such programs may represent a population of women and men with differentially greater sensitivity to miscarriage due to a variety of endogenous factors and environmental exposures. Due to the ART clinic population's higher frequency of infertility issues relative to the general population, these clinics provide a setting in which to conduct such studies with reliable statistical power. Persons seeking treatment at ART clinics have already served as study populations in epidemiology investigations designed to determine potential adverse effects of exposures to chemicals on female (Ehrlich et al., 2012; Johnson et al., 2012; Mahalingaiah et al., 2012) and male reproductive health (Dodge et al. 2015; Meeker et al. 2010; 2011). Recent evidence also suggests that it is similarly feasible to recruit women and men from infertility clinics to participate in longitudinal investigations of magnetic field exposure and reproductive health (EPRI, 2012; Lewis et al., 2015b). Preconception studies among couples may be possible in the general population [e.g., the LIFE Study (Buck Louis et al., 2011)], but such investigations might be limited by logistical issues (e.g., participant recruitment) and typically can not obtain detailed outcome data that is collected in ART cohorts.

Confounding Due to Physical Activity

A commentary that accompanied the Lee et al. (2002) and Li et al. (2002) studies proposed that the basis for the miscarriage association with MAX personal magnetic field exposure that was reported in those investigations may be rooted in the differences of mobility patterns in women with healthy pregnancies compared to those who miscarried (Savitz, 2002). In the first trimester, women with morning sickness (nausea and vomiting), an indicator of a healthy pregnancy (Fenster et al., 1991; 1997; Savitz, 2002; Stein and Susser, 1991), might be less physically active compared to women destined to miscarry. In late pregnancy [for Lee et al. (2002)'s main study, exposure was measured at 30 weeks], women close to term may have more discomfort and difficulty moving from place to place (Evenson et al., 2002; Hatch et al., 1993; Mottola and Campbell, 2003; Savitz et al., 2006) compared to women that had experienced miscarriage. Savitz (2002) suggested that a decreased mobility of women with healthy pregnancies might lead to a diminished probability of encountering sources of magnetic fields, and, as a result, lower MAX (i.e., instantaneous) magnetic field exposures. On the other hand, increased mobility in women that miscarried might result in greater MAX magnetic field exposures, but not due to a causal relationship between magnetic fields and miscarriage.

Li and Neutra (2002) responded to Savitz (2002) with a supplemental analysis of the Li et al. (2002) data, and reported that nausea at less than 7 or greater than 7 days prior to the interview, but otherwise at unspecified times in pregnancy, was not related to MAX magnetic field exposure. However, analysis of pregnancy-related morning sickness symptoms on the measurement day would be required to accurately test associations between magnetic field exposure and both symptoms and mobility (Savitz et al., 2006). Regarding reduced physical activity accompanying increased gestational age, Li and Neutra (2002) pointed to the prospective sub-study by Lee et al. (2002) reporting that mean values of exposure metrics corresponding to 12 and 30 weeks of gestation were similar (TWA: 1.1 vs. 1.2 mG, MAX: 34 vs. 28 mG), and results of the nested case-control study that used exposures measured at 30 weeks produced effect estimates that were in the same direction as the prospective sub-study that used exposures measured at 12 weeks.

Findings from a small number of exposure studies support a positive association between physical activity and MAX personal magnetic field exposure. Savitz et al. (2006) recruited 100 pregnant women in North Carolina to wear an accelerometer and a personal magnetic field exposure monitor, both recording once per min for 7 consecutive days. Data demonstrated a positive association between accelerometer recordings and MAX magnetic field exposures, but no marked relationship with TWA exposure. An inverse association was also noted for gestational age and MAX magnetic field exposure, which is in agreement with previous studies showing that physical activity falls with increasing gestational age (Evenson et al., 2002; Hatch et al., 1993; Mottola and Campbell, 2003). Similar to Li and Neutra (2002), Savitz et al. (2006) also noted that nausea at unspecified time during pregnancy was not markedly related to physical activity or magnetic field exposure. Using data from Li et al. (2002), Mezei et al. (2006) also found a positive relationship between physical activity and MAX exposure, but physical activity was measured with time-activity diary data instead of accelerometer data. It was observed that the total daily number of activities/environments experienced (e.g., home + work + travel) was positively associated with MAX magnetic field exposure. Recently, Lewis et al. (2015b) conducted an analysis of physical activity and personal magnetic field exposure using repeated data from 40 women recruited at an infertility clinic in Massachusetts. Physical activity was modeled separately using both accelerometer and time-activity diary data (the number of changes in environments experienced over the sampling day). Similarly Lewis et al. (2015b) observed a positive relationship between physical activity and peak (upper percentiles and MAX) magnetic field exposure metrics, but found no association with central tendency metrics (average and median). Data also showed that higher physical activity within the environments examined did not necessarily lead to higher MAX personal magnetic field exposures, suggesting that movement between environments and not within the same environment increases one's probability for encountering a high field source.

Exposure Measurement Error

In recent years, investigators have benefitted from advancements in magnetic field exposure measurement such that personal exposures can be characterized with greater accuracy than exposure surrogates (e.g., wire code classification, self-reported use of electric devices, or spot measurements). While it is true that these surrogate measures place less burden on the

participant and some have shown promise as suitable surrogates in certain contexts, such as expert judgment regarding occupational magnetic field exposures (Flynn et al., 1991) and residential spot and fixed-site measurements (Kavet et al., 1992), the use of personal exposure monitors is usually a superior alternative. The limitations associated with surrogate measures are that humans are not stationary objects and, as a result, these approaches do not incorporate differences in magnetic field exposures that result from moving between different environments. Because personal exposure monitors might capture variability in exposure over space and time, these provide a more valid estimate of personal exposure. Personal exposure monitors need to be worn not only inside the home, but also outside the home (e.g., at work or commuting) as all such activities are important contributors to daily magnetic field exposure (Zaffanella and Kalton, 1998), and failure to include associated exposures from these environments/activities in derived exposure metrics may introduce bias.

Although Lee et al. (2002) and Li et al. (2002, 2010) improved the accuracy of their exposure estimates by incorporating personal exposure monitoring into their studies, data were collected for only a single 24-hr period. Thus, it is reasonable to question the reliability of any derived exposure metrics (regardless of the metric), because the period over which exposure data was collected is very narrow relative to the time window of risk for reproductive health outcomes, such as miscarriage and sperm quality. This may be especially true for the MAX and other peak magnetic field exposure metrics due to their likelihood of high day-to-day variability. Strategies that rely on a single day's worth of data per participant are prone to result in exposure misclassification, which, if non-differential, may likely underestimate an observed association. However, if differential misclassification of exposure occurred, it could bias the effect estimate away from or towards the null depending on the degree of misclassification by outcome or relationship of the error to the outcome. In addition, in some of these epidemiology studies (Lee et al., 2002; Li et al., 2010), exposure data was collected after the outcome was measured, therefore, there may also be an issue regarding temporal ambiguity between exposure and outcome.

A recent analysis of the personal magnetic field exposures measured over 7 consecutive days in 100 pregnant women from North Carolina demonstrated that measures of central tendency exhibit less intra-individual temporal variability relative to measures of peak (Lewis et al., 2015a). The intra-class correlation coefficient (ICC) for the median and TWA ranged between 0.64–0.66, whereas the ICCs for the peak metrics ranged between 0.37 (MAX)–0.55 (90th percentile). The magnitudes of the ICCs in the North Carolina study were largely in the same range that was observed in an analysis of the fertility clinic population (approximately month-to-month variability), except that the MAX was less stable (ICC: 0.13) (Lewis et al., 2015b). Similar to the North Carolina analysis, it was also observed that for categorical exposure metrics temporal variability appears to be dictated by the selected threshold, with decreasing stability over time with increasing threshold. Taken together, these two longitudinal investigations suggest that peak personal magnetic field exposure metrics tend to be less stable over time compared with central tendency metrics. Other studies also examined temporal variability of continuous and categorical personal magnetic field exposure metrics in women and reported similar findings (Lee et al., 2002; Mezei et al., 2006). Therefore, if there is interest in peak personal magnetic field exposure metrics (e.g.,

upper percentiles or MAX), more than one day of measurement is needed over the relevant exposure window to minimize measurement error, but one day may be sufficient to characterize central tendency personal magnetic field exposure metrics. However, the number of sampling days per participant is study-specific and needs to be balanced by realistic financial and participant burden constraints often associated with large-scale epidemiology investigations.

An additional source of exposure measurement error that needs attention is related to the intrinsic ways in which personal exposure monitors collect and store data. Current technology permits the investigator to collect personal magnetic field exposure data over variable durations, anywhere from a single day up to many days. The limiting factors of sampling duration include the internal memory of the monitor and selected sampling rate. In essence, the more frequent the sample rate, the more data that are collected, such that the internal memory may be consumed quicker than a less frequent sampling rate. Mezei et al. (2006) demonstrated that the MAX magnetic field level that is captured by a personal exposure monitor is inversely related to sampling frequency. Therefore, a less frequent sampling rate may permit the personal exposure monitor to capture data over a longer duration, but at the cost of potentially underestimating the MAX magnetic field. Mezei et al. (2006) also noted that the estimated TWA and 95th and 99th percentiles are not likely affected by sampling rate. These findings suggest that it is best practice to program personal exposure monitors to collect data at the most frequent sampling rate, especially when the MAX is the exposure metric of interest, to minimize bias in estimated exposures.

Alternative Exposure Metrics

One aspect that has been somewhat limited in exploring the relationship between exposure to magnetic fields and infertility is the approach to characterizing personal magnetic field exposures in study populations. Summary measures, such as average or MAX daily personal magnetic field exposures or total daily exposure or time above select exposure thresholds, have been used primarily. Because personal exposure monitors are able to log large numbers of data points over the measurement period, this permits the investigator flexibility to model personal exposure beyond summary measures in a vast number of different ways, which is valuable as the biologically-relevant metric is uncertain and, consequently remains a subject of debate. On the other hand, this flexibility also makes the analysis susceptible to “cut point hunting” to support an *a priori* hypothesis. One may hypothesize that magnetic fields induce toxicity from the effects of cumulative exposure or an acute exposure event above some particular threshold, and with this in mind and given the flexibility of data, exploration of novel exposure metrics might be useful. However, currently there is no basis for a biophysical mechanism to explain the relationship between magnetic fields and adverse reproductive health that was reported in previous epidemiology studies (Swanson and Kheifets, 2006; Valberg et al., 1997) and, consequently, this makes it difficult to select the most appropriate exposure metric to be employed in such studies. Additional experimental research is needed to help refine our understanding of the potential biological mechanism(s) that might explain the relationships that have been noted in previous epidemiologic studies, which may subsequently inform the design of future human studies in this area.

In addition, in many of these epidemiology studies, quantiles of exposure were used to examine relationships with outcome of interest, which may be problematic for accurately determining the strength and shape of non-linear (even non-monotonic) dose-response relationships. As an alternative, splines can be easily added to statistical models to detect associations that normally would not be revealed using a quantile analysis. Splines have been widely used in environmental epidemiology studies (Ashley-Martin et al., 2014; Khalil et al., 2014; Kim et al., 2014; Liu et al., 2014; Wang and Choi, 2014), including those that have focused on magnetic fields (Greenland et al., 2000; Kheifets et al., 2010). While it may be true that splines are sensitive to placement of knots, others investigators argued that quantiles are equally sensitive to the selection of cut-off points (Bennette and Vickers, 2012). While not a primary approach employed in epidemiology studies reviewed in this manuscript, the aforementioned issues associated with quantile analyses are even more problematic when exposure is modeled as a continuous variable because the relationship between the exposure and outcome is presumed to be linear when, in fact, that may not be the case.

Correlation of Exposure Data within Couples

The spectrum of reproductive health outcomes of concern in epidemiology studies concerning magnetic field exposures range from influence on gametes (sperm/ovum) to effects that occur after fertilization through birth. To examine associations between magnetic field exposures and adverse effects on gametes (e.g., sperm DNA damage), a study would need to collect a biological sample (e.g., semen sample) and personal magnetic field exposure data from the corresponding gender (e.g., a study on sperm DNA damage collects personal magnetic field exposure data from the corresponding men). This approach was adopted by Li et al. (2010) in their investigation of personal exposure to magnetic fields and sperm quality among men in China. A similar study design has not been adopted for any female-focused cohorts, but it is conceivable that a relationship between exposure to magnetic fields and various pre-fertilization female measures may be conducted in future studies. Examples include research from an infertility clinic that measured number of oocytes retrieved (Mok-Lin et al., 2010) and antral follicle count (Souter et al., 2013), both of which were examined in epidemiology studies in relation to exposure to bisphenol A, an environmental agent with ubiquitous exposure in the population (CDC, 2014) akin to magnetic fields.

However, after fertilization, teasing apart whether or not the observed associations are due to the magnetic field exposures experienced by the mother, father, or embryo/fetus would be a challenge because any damage to sperm and ovum is no longer measureable, but may influence later pregnancy outcomes. Based on previous epidemiology studies, the norm for examining the potential association between exposure to magnetic fields and adverse pregnancy outcomes is to estimate exposures to the mother as it is presumed that maternal exposures are the most biologically-relevant. However, fertilization and embryo and fetal development are also directly dependent on the father's health. For example, a male factor might explain the etiology of up to 50% of couples with infertility (Eisenberg et al., 2015). In this situation, the interpretation of the results is dependent on whether or not magnetic field exposures are correlated within female-male couples. If exposures are not correlated

within couples, associations might reflect adverse effects related to exposures experienced by the mother that was sampled. No definitive conclusions can be made regarding the father's exposures as his were not measured. In this situation, there is an opportunity to study maternal versus paternal contributions to the observed associations with the outcome of interest if the exposures for both parents are measured. On the other hand, if exposures are correlated within couples, the exposure for the mother that was sampled may serve as an exposure surrogate for the father that was not sampled and vice versa, and associations may reflect effects related to the exposures that were experienced by the mother, father, or both. One advantage, however, of such a scenario is that maternal exposure data might potentially be used as an exposure surrogate in the absence of paternal exposure data to determine associations with male reproductive health outcomes prior to fertilization (e.g., sperm quality parameters). This could be especially valuable if there is differential recruitment between women and men based on their willingness to wear a personal magnetic field exposure monitor independent of their willingness to provide a biological measurement, or if there is availability of exposure data from one of the partners and also an opportunity to obtain outcome data (e.g., semen quality measures) from archived data or biological samples. Correlation of magnetic field exposures within female-male couples has yet to be reported on in the peer-reviewed literature despite the fact that this information would add value to designing and interpreting the results of comprehensive reproductive health studies. Nevertheless, the correlation of magnetic field exposures within female-male couples needs to be recognized as a potential limitation in the interpretation of results from future studies.

CONCLUSIONS

In conclusion, infertility and adverse pregnancy outcomes are public health priorities and many questions remain whether or not exposure to magnetic fields, a ubiquitous environmental agent, may be linked to their etiology. Taken together, additional research that addresses the many shortcomings (e.g., accurate collection of outcome data, and addressing exposure measurement error and residual confounding) of previous investigations is still needed. With improved study designs that minimize important sources of bias, understanding of the potential relationship between exposure to magnetic fields and infertility and adverse pregnancy outcomes will be greatly improved and, in turn, will inform risk assessment and risk management of magnetic field exposures as they relate to adverse reproductive health.

References

- Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A. Review of the epidemiologic literature on EMF and health. *Environ Health Persp.* 2001; 109(Suppl 6):911–933.
- Ashley-Martin J, Dodds L, Arbuckle TE, Ettinger AS, Shapiro GD, Fisher M, Morisset AS, Taback S, Bouchard MF, Monnier P, Dallaire R, Fraser WD. A birth cohort study to investigate the association between prenatal phthalate and bisphenol A exposures and fetal markers of metabolic dysfunction. *Environ Health.* 2014; 13:84. [PubMed: 25336252]
- Auger N, Joseph D, Goneau M, Daniel M. The relationship between residential proximity to extremely low frequency power transmission lines and adverse birth outcomes. *J Epidemiol Community Health.* 2011; 65:83–85. [PubMed: 20628083]

- Belanger K, Leaderer B, Hellenbrand K, Holford TR, McSharry JE, Power ME, Bracken MB. Spontaneous abortion and exposure to electric blankets and heated water beds. *Epidemiology*. 1998; 9:36–42. [PubMed: 9430266]
- Bennette C, Vickers A. Against quantiles: Categorization of continuous variables in epidemiologic research, and its discontents. *BMC Med Res Methodol*. 2012; 12:21. [PubMed: 22375553]
- Bergqvist UO. Video display terminals and health. A technical and medical appraisal of the state of the art. *Scand J Work Environ Health*. 1984; 10(Suppl 2):1–87. [PubMed: 6533781]
- Berman E, Chacon L, House D, Koch BA, Koch WE, Leal J, Lovtrup S, Mantiply E, Martin AH, Martucci GI, Mild KH, Monahan JC, Sandström M, Shamsaifar K, Tell R, Trillo A, Ubeda A, Wagner P. Development of chicken embryos in a pulsed magnetic field. *Bioelectromagnetics*. 1990; 11:169–187. [PubMed: 2242052]
- Blaasaas KG, Tynes T, Irgens A, Lie RT. Risk of birth defects by parental occupational exposure to 50 Hz electromagnetic fields: A population based study. *Occup Environ Med*. 2002; 59:92–97. [PubMed: 11850551]
- Blaasaas KG, Tynes T, Lie RT. Residence near power lines and the risk of birth defects. *Epidemiology*. 2003; 14:95–98. [PubMed: 12500055]
- Blaasaas KG, Tynes T, Lie RT. Risk of selected birth defects by maternal residence close to power lines during pregnancy. *Occup Environ Med*. 2004; 61:174–176. [PubMed: 14739386]
- Bryant HE, Love EJ. Video display terminal use and spontaneous abortion risk. *Int J Epidemiol*. 1989; 18:132–138. [PubMed: 2722356]
- Buck Louis GM, Schisterman EF, Sweeney AM, Wilcosky TC, Gore-Langton RE, Lynch CD, Boyd Barr D, Schrader SM, Kim S, Chen Z, Sundaram R. Designing prospective cohort studies for assessing reproductive and developmental toxicity during sensitive windows of human reproduction and development – the LIFE Study. *Paediatr Perinat Epidemiol*. 2011; 25:413–424. [PubMed: 21819423]
- CDC (Centers for Disease Control and Prevention). Fourth national report on human exposure to environmental chemicals, updated tables. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Laboratory Sciences; 2014.
- CDHS (California Department of Health Services). An evaluation of the possible risks from electric and magnetic fields (EMFs) from power lines, internal wiring, electrical occupations and appliances. Oakland, CA: California Department of Health Services; 2002.
- Chernoff N, Rogers JM, Kavet R. A review of the literature on potential reproductive and developmental toxicity of electric and magnetic fields. *Toxicology*. 1992; 74:91–126. [PubMed: 1519247]
- Delgado JM, Leal J, Monteagudo JL, Gracia MG. Embryological changes induced by weak, extremely low frequency electromagnetic fields. *J Anat*. 1982; 134:533–551. [PubMed: 7107514]
- de Vocht F, Hannam K, Baker P, Agius R. Maternal residential proximity to sources of extremely low frequency electromagnetic fields and adverse birth outcomes in a UK cohort. *Bioelectromagnetics*. 2014; 35:201–209. [PubMed: 24482293]
- de Vocht F, Lee B. Residential proximity to electromagnetic field sources and birth weight: Minimizing residual confounding using multiple imputation and propensity score matching. *Environ Int*. 2014; 69:51–57. [PubMed: 24815339]
- Dodge LE, Williams PL, Williams MA, Missmer SA, Toth TL, Calafat AM, Hauser R. Paternal urinary concentrations of parabens and other phenols in relation to reproductive outcomes among couples from a fertility clinic. *Environ Health Persp*. 2015; 123:665–671.
- Eisenberg ML, Chen Z, Ye A, Buck Louis GM. Relationship between physical occupational exposures and health on semen quality: data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. *Fertil Steril*. 2015; 103:1271–1277. [PubMed: 25765658]
- EPRI (Electric Power Research Institute). A pilot study of pregnancy outcome, physical activity and magnetic field exposure: a technical update prepared for EPRI Environment Division. Palo Alto, CA: Electric Power Research Institute; 2012. Product ID: 1025386
- Ericson A, Kallen B. An epidemiological study of work with video screens and pregnancy outcome: II a case-control study. *Am J Ind Med*. 1986a; 9:459–475. [PubMed: 3717170]

- Ericson A, Kallen B. An epidemiological study of work with video screens and pregnancy outcome: I. a registry study. *Am J Ind Med.* 1986b; 9:447–457. [PubMed: 3717169]
- Ehrlich S, Williams PL, Missmer SA, Flaws JA, Ye X, Calafat AM, Petrozza JC, Wright D, Hauser R. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. *Human Reprod.* 2012; 27:3583–3592.
- Evenson KR, Siega-Riz AM, Savitz DA, Leiferman JA, Thorp JM Jr. Vigorous leisure activity and pregnancy outcome. *Epidemiology.* 2002; 13:653–659. [PubMed: 12410006]
- Evers JLH. Female subfertility. *Lancet.* 2002; 360:151–159. [PubMed: 12126838]
- Fenster L, Eskenazi B, Windham GC, Swan SH. Caffeine consumption during pregnancy and spontaneous abortion. *Epidemiology.* 1991; 2:168–164. [PubMed: 2054397]
- Fenster L, Hubbard AE, Swan SH, Windham GC, Waller K, Hiatt RA, Benowitz N. Caffeinated beverages, decaffeinated coffee, and spontaneous abortion. *Epidemiology.* 1997; 8:515–523. [PubMed: 9270953]
- Ferguson KK, O'Neill MS, Meeker JD. Environmental contaminant exposures and preterm birth: a comprehensive review. *J Toxicol Environ Health B.* 2013; 16:69–113.
- Flynn MR, West S, Kaune WT, Savitz DA, Chen CC, Loomis DP. Validation of expert judgment in assessing occupational exposure to magnetic fields in the utility industry. *Appl Occup Environ Hyg.* 1991; 6:141–145.
- Goldhaber MK, Polen MR, Hiatt RA. The risk of miscarriage and birth defects among women who use visual display terminals during pregnancy. *Am J Ind Med.* 1988; 13:695–706. [PubMed: 3389364]
- Grasso P, Parazzini F, Chatenoud L, Di Cintio E, Benzi G. Exposure to video display terminals and risk of spontaneous abortion. *Am J Ind Med.* 1997; 32:403–407. [PubMed: 9258394]
- Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh MA. A pooled analysis of magnetic fields, wire codes, and childhood leukemia. Childhood Leukemia-EMF Study Group. *Epidemiology.* 2000; 11:624–634. [PubMed: 11055621]
- Hatch MS, Shu XO, McLean DE, Levin B, Begg M, Reuss L, Susser M. Maternal exercise during pregnancy, physical fitness, and fetal growth. *Am J Epidemiol.* 1993; 137:1105–1114. [PubMed: 8317440]
- IARC (International Agency for Research on Cancer). IARC monographs on the evaluation of carcinogenic risks to humans. Volume 80, non-ionizing radiation, part 1: static and extremely low-frequency (ELF) electric and magnetic fields. Lyons, France: International Agency for Research on Cancer, World Health Organization; 2002.
- ICNIRP (International Commission on Non-Ionizing Radiation Protection). Guidelines for limiting exposure to time-varying electric and magnetic fields (1 Hz to 100 kHz). *Health Phys.* 2010; 99:818–836. [PubMed: 21068601]
- Johnson PI, Altshul L, Cramer DW, Missmer SA, Hauser R, Meeker JD. Serum and follicular fluid concentrations of polybrominated diphenyl ethers and in-vitro fertilization outcome. *Environ Int.* 2012; 45:9–14. [PubMed: 22572111]
- Juutilainen J, Matilainen P, Saarikoski S, Laara E, Suonio S. Early pregnancy loss and exposure to 50-Hz magnetic fields. *Bioelectromagnetics.* 1993; 14:229–236. [PubMed: 8323573]
- Kavet R, Silva JM, Thornton D. Magnetic field exposure assessment for adult residents of Maine who live near and far away from overhead transmission lines. *Bioelectromagnetics.* 1992; 13:35–55. [PubMed: 1550600]
- Khalil N, Ebert JR, Wang L, Belcher S, Lee M, Czerwinski SA, Kannan K. Bisphenol A and cardiometabolic risk factors in obese children. *Sci Total Environ.* 2014; 470–471:726–732.
- Kheifets L, Ahlbom A, Crespi CM, Draper G, Hagihara J, Lowenthal RM, Mezei G, Oksuzyan S, Schüz J, Swanson J, Tittarelli A, Vinceti M, Wunsch Filho V. Pooled analysis of recent studies on magnetic fields and childhood leukaemia. *Br J Cancer.* 2010; 103:1128–1135. [PubMed: 20877339]
- Kim MH, Zhao D, Cho J, Guallar E. Cadmium exposure and age-related macular degeneration. *J Expo Sci Environ Epidemiol.* 2014 Nov 12. Epub ahead of print.
- Lee GM, Neutra RR, Hristova L, Yost M, Hiatt RA. The use of electric bed heaters and the risk of clinically recognized spontaneous abortions. *Epidemiology.* 2000; 11:406–415. [PubMed: 10874547]

- Lee GM, Neutra RR, Hristova L, Yost M, Hiatt RA. A nested case-control study of residential and personal magnetic field measures and miscarriages. *Epidemiology*. 2002; 13:21–31. [PubMed: 11805582]
- Lewis RC, Evenson KR, Savitz DA, Meeker JD. Temporal variability of daily personal magnetic field exposure metrics in pregnant women. *J Expo Sci Environ Epidemiol*. 2015a; 25:58–64. [PubMed: 24691007]
- Lewis RC, Hauser R, Wang L, Kavet R, Meeker JD. Personal power-frequency magnetic field exposure in women recruited at an infertility clinic: association with physical activity and temporal variability. *Radiat Prot Dosimetry*. 2015b pii: ncv365. [Epub ahead of print].
- Li DK, Odouli R, Wi S, Janevic T, Golditch I, Bracken TD, Senior R, Rankin R, Iriye R. A population-based prospective cohort study of personal exposure to magnetic fields during pregnancy and the risk of miscarriage. *Epidemiology*. 2002; 13:9–20. [PubMed: 11805581]
- Li DK, Neutra RR. Magnetic fields and miscarriage. *Epidemiology*. 2002; 13:237–238. [PubMed: 11880770]
- Li DK, Yan B, Li Z, Gao E, Miao M, Gong D, Weng X, Ferber JR, Yuan W. Exposure to magnetic fields and the risk of poor sperm quality. *Reprod Toxicol*. 2010; 29:86–92. [PubMed: 19910156]
- Lindbohm ML, Hietanen M, Kyyronen P, Sallmen M, von Nandelstadh P, Taskinen H, Pekkarinen M, Ylikoski M, Hemminki K. Magnetic fields of video display terminals and spontaneous abortion. *Am J Epidemiol*. 1992; 136:1041–1051. [PubMed: 1462964]
- Liu J, Liu X, Wang W, McCauley L, Pinto-Martin J, Wang Y, Li L, Yan C, Rogan WJ. Blood lead concentrations and children's behavioral and emotional problems: A cohort study. *J Am Med Assoc Pediatr*. 2014; 168:737–745.
- Mahalingaiah S, Missmer SA, Maity A, Williams PL, Meeker JD, Berry K, Ehrlich S, Perry MJ, Cramer DW, Hauser R. Association of hexachlorobenzene (HCB), dichlorodiphenyltrichloroethane (DDT), and dichlorodiphenyldichloroethylene (DDE) with in vitro fertilization (IVF) outcomes. *Environ Health Persp*. 2012; 120:316–320.
- Malagoli C, Crespi CM, Rodolfi R, Signorelli C, Poli M, Zanichelli P, Fabbi S, Teggi S, Garavelli L, Astolfi G, Calzolari E, Lucenti C, Vinceti M. Maternal exposure to magnetic fields from high-voltage power lines and the risk of birth defects. *Bioelectromagnetics*. 2012; 33:405–409. [PubMed: 22826845]
- McDonald AD, Cherry NM, Delorme C, McDonald JC. Visual display units and pregnancy: evidence from the Montreal survey. *J Occup Med*. 1986; 28:1226–1231. [PubMed: 3806262]
- Meeker JD, Ehrlich S, Toth TL, Wright DL, Calafat AM, Trisini AT, Ye X, Hauser R. Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic. *Reprod Toxicol*. 2010; 30:532–539. [PubMed: 20656017]
- Meeker JD, Yang T, Ye X, Calafat AM, Hauser R. Urinary concentrations of parabens and serum hormone levels, semen quality parameters, and sperm DNA damage. *Environ Health Persp*. 2011; 119:252–257.
- Mezei G, Bracken TD, Senior R, Kavet R. Analyses of magnetic-field peak-exposure summary measures. *J Expo Sci Environ Epidemiol*. 2006; 16:477–485. [PubMed: 16249799]
- Missmer SA, Pearson KR, Ryan LM, Meeker JD, Cramer DW, Hauser R. Analysis of multiple-cycle data from couples undergoing in vitro fertilization: methodologic issues and statistical approaches. *Epidemiology*. 2011; 22:497–504. [PubMed: 21558857]
- Mok-Lin E, Ehrlich S, Williams PL, Petrozza J, Wright DL, Calafat AM, Ye X, Hauser R. Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. *Int J Androl*. 2010; 33:385–393. [PubMed: 20002217]
- Mottola M, Campbell M. Activity patterns during pregnancy. *Can J Appl Physiol*. 2003; 28:642–653. [PubMed: 12904639]
- National Institute of Environmental Health Sciences (NIEHS). Assessment of health effects from exposure to power-line frequency electric and magnetic fields. Research Triangle Park, NC: National Institute of Environmental Health Sciences, U.S. National Institutes of Health, U.S. Department of Health and Human Services, Public Health Service; 1998.
- Nielsen CV, Brandt LPA. Spontaneous abortion among women using video display terminals. *Scand J Work Environ Health*. 1990; 16:323–328. [PubMed: 2255872]

- Pinelli A, Di Cesare M. Human fertility: sociodemographic aspects. *Contraception*. 2005; 72:303–307. [PubMed: 16181976]
- Roman E, Beral V, Pelerin M, Hermon C. Spontaneous abortion and work with video display units. *Br J Ind Med*. 1992; 49:507–512. [PubMed: 1637711]
- Savitz DA. Magnetic fields and miscarriage. *Epidemiology*. 2002; 13:1–4. [PubMed: 11805578]
- Savitz DA, Ananth CV. Residential magnetic fields, wire codes, and pregnancy outcome. *Bioelectromagnetics*. 1994; 15:271–273. [PubMed: 8074741]
- Savitz DA, Herring AH, Mezei G, Evenson KR, Terry JW Jr, Kavet R. Physical activity and magnetic field exposure in pregnancy. *Epidemiology*. 2006; 17:222–225. [PubMed: 16477264]
- Schnorr TM, Grajewski BA, Hornung RW, Thun MJ, Egeland GM, Murray WE, Conover DL, snf Halperin WE. Video display terminals and the risk of spontaneous abortion. *N Eng J Med*. 1991; 324:727–733.
- Shamsi Mahmoudabadi F, Ziaei S, Firoozabadi M, Kazemnejad A. Exposure to extremely low frequency electromagnetic fields during pregnancy and the risk of spontaneous abortion: A case-control study. *J Res Health Sci*. 2013; 13:131–134. [PubMed: 24077469]
- Souter I, Smith KW, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, Hauser R. The association of bisphenol-A urinary concentrations with antral follicle counts and other measures of ovarian reserve in women undergoing infertility treatments. *Reprod Toxicol*. 2013; 42:224–231. [PubMed: 24100206]
- Stein Z, Susser M. Miscarriage, caffeine, and the epiphenomena of pregnancy: the causal model. *Epidemiology*. 1991; 2:163–167. [PubMed: 2054396]
- Su XJ, Yuan W, Tan H, Liu XY, Li D, Li DK, Huang GY, Zhang LW, Miao MH. Correlation between exposure to magnetic fields and embryonic development in the first trimester. *PLoS One*. 2014; 9:e101050. [PubMed: 24977708]
- Swan SH, Waller K, Hopkins B, Windham G, Fenster L, Schaefer C, Neutra RR. A prospective study of spontaneous abortion: Relation to amount and source of drinking water consumed in early pregnancy. *Epidemiology*. 1998; 9:126–133. [PubMed: 9504279]
- Swanson J, Kheifets L. Biophysical mechanisms: A component in the weight of evidence for health effects of power-frequency electric and magnetic fields. *Radiat Res*. 2006; 165:470–478. [PubMed: 16579660]
- Ubeda A, Trillo MA, Chacon L, Blanco MJ, Leal J. Chick embryo development can be irreversibly altered by early exposure to weak extremely-low-frequency magnetic fields. *Bioelectromagnetics*. 1994; 15:385–398. [PubMed: 7802707]
- Valberg PA, Kavet R, Rafferty CN. Can low-level 50/60 Hz electric and magnetic fields cause biological effects? *Radiat Res*. 1997; 148:2–21. [PubMed: 9216613]
- Wang L, Choi H. Using semiparametric-mixed model and functional linear model to detect vulnerable prenatal window to carcinogenic polycyclic aromatic hydrocarbons on fetal growth. *Biometrical J*. 2014; 56:243–255.
- Wang Q, Cao Z, Qu Y, Peng X, Guo S, Chen L. Residential exposure to 50 Hz magnetic fields and the association with miscarriage risk: A 2-year prospective cohort study. *PLoS One*. 2013; 8:e82113. [PubMed: 24312633]
- Wertheimer N, Leeper E. Possible effects of electric blankets and heated waterbeds on fetal development. *Bioelectromagnetics*. 1986; 7:13–22. [PubMed: 3729998]
- Wertheimer N, Leeper E. Fetal loss associated with two seasonal sources of electromagnetic field exposure. *Am J Epidemiol*. 1989; 129:220–224. [PubMed: 2910064]
- WHO (World Health Organization). Low birthweight: country, regional, and global estimates. Geneva, Switzerland: World Health Organization; 2004.
- WHO (World Health Organization). Environmental health criteria 238: extremely low frequency fields. Geneva, Switzerland: World Health Organization; 2007.
- WHO (World Health Organization). Born too soon: the global action report on preterm birth. Geneva, Switzerland: World Health Organization; 2012.
- WHO (World Health Organization). Fact sheet: congenital anomalies. Geneva, Switzerland: World Health Organization; 2014.

- Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *N Engl J Med*. 1988; 319:189–194. [PubMed: 3393170]
- Windham GC, Fenster L, Swan SH, Neutra RR. Use of video display terminals during pregnancy and risk of spontaneous abortion, low birthweight, or intrauterine growth retardation. *Am J Ind Med*. 1990; 18:675–688. [PubMed: 2264566]
- Zaffanella, LE.; Kalton, GW. Survey of personal magnetic field exposure, phase II: 1000-person survey. Lee, MA: Enertech Consultants; 1998.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Epidemiologic studies (2002–2015) of exposure to power-frequency magnetic fields and risk of infertility and adverse pregnancy outcomes

Table 1

Year	Authors	Country	Study design	Sample size	Exposure characterization	Outcome (relationship)	Potential biologically-relevant exposure metric
Prenatal Outcomes							
2002	Lee et al.	USA	Case-control	664 (cases = 155)	PEM over a single 24-hr period	Miscarriage (+)	Maximum
					PEM over a single 24-hr period	Miscarriage (+)	Rate-of-change
					SM inside home	Miscarriage (none)	
					Wire-code classification	Miscarriage (none)	
			Prospective cohort	219 (cases = 18)	PEM over a single 24-hr period	Miscarriage (+)	Maximum
					PEM over a single 24-hr period	Miscarriage (+)	Rate-of-change
2002	Li et al.	USA	Prospective cohort	969 (cases = 159)	PEM over a single 24-hr period	Miscarriage (+)	Maximum 16.0 mG ^{a,b}
					PEM over a single 24-hr period	Miscarriage (+)	Total sum 16.0 mG ^a
					SM inside home	Miscarriage (none)	
					Wire-code classification	Miscarriage (none)	
2013	Shamsi Mahmoudabadi et al.	Iran	Case-control	116 (cases = 58)	SM inside home	Miscarriage (+)	
2013	Wang et al.	China	Prospective cohort	413 (cases = 101)	SM in alley in front of home	Miscarriage (+)	Maximum
					SM at front door of home	Miscarriage (none)	
2014	Su et al.	China	Cross-sectional	65 (cases = 19)	PEM over a single 24-hr period	Apoptosis level (none)	
				130 (cases = 36)	PEM over a single 24-hr period	Embryonic bud length (–)	75 th percentile 0.82 mG
				130 (cases = 20)	PEM over a single 24-hr period	Embryonic sac length (none)	
Neonatal Outcomes							
2002	Blaasaas et al.	Norway	Cross-sectional	836,475 (cases = 415)	JEM for weekly maternal exposure	Cleft palate (–)	Duration 1.0 mG
				836,475 (cases = 447)	JEM for weekly maternal exposure	Spina bifida (+)	Duration 1.0 mG
				1,290,298 (cases = 427)	JEM for weekly paternal exposure	Anencephaly (+)	Duration 1.0 mG
2003	Blaasaas et al.	Norway	Cross-sectional	161,844 (cases = 16)	Power line distance from home	Cardiac defects (–)	Home level 1.0 mG
				161,844 (cases = 6)	Power line distance from home	Esophogeal defects (+)	Home level 1.0 mG
				161,844 (cases = 5)	Power line distance from home	Respiratory defects (–)	Home level 1.0 mG
2004	Blaasaas et al.	Norway	Case-control	128,680 (cases = 522)	Power line distance from home	Various birth defects (none)	
2010	Auger et al.	Canada	Cross-sectional	699,939 (cases = 42,009)	Power line distance from home	Low birth weight (none)	

Year	Authors	Country	Study design	Sample size	Exposure characterization	Outcome (relationship)	Potential biologically-relevant exposure metric
				705,020 (cases = 32,302)	Power line distance from home	Preterm birth (none)	
				697,763 (cases = 67,760)	Power line distance from home	Small-for-gestational-age (none)	
2012	Malagoli et al.	Italy	Case-control	456 (cases = 228)	Power line distance from home	Any birth defect (none)	
2014	de Vocht et al.	England	Cross-sectional	562	Distance of closest source from home ^c	Birth weight (–)	Source 50 m from home
				139,967 (cases = 9,294)	Distance of closest source from home ^c	Low birth weight (none)	
				135,809 (cases = 8,638)	Distance of closest source from home ^c	Preterm birth (none)	
				138,980 (cases = 12,208)	Distance of closest source from home ^c	Small-for-gestational-age (none)	
				135,809 (cases = 7,865)	Distance of closest source from home ^c	Spontaneous preterm birth (none)	
2014	de Vocht and Lee	England	Cross-sectional	898	Distance of closest source from home ^c	Birth weight (–)	Source 50 m from home
Male Fertility Outcomes							
2010	Li et al.	China	Case-control	148 (76 cases)	PEM over a single 24-hr period	Poor sperm quality (+)	90 th percentile 1.6 mG
					PEM over a single 24-hr period	Poor sperm quality (+)	Duration 1.6 mG

Abbreviations: JEM, job-exposure matrix; PEM, personal exposure monitor; SM, spot measurement.

^aRisk estimates were stronger among women whose miscarriage occurred early in gestation (0–9 weeks).

^bRisk estimates were stronger among women with a history of subfertility and previous miscarriage.

^cSources included high voltage cables, overhead power lines, or electricity substations or towers.