Infertility: Peer-Reviewed Analysis

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Environmental Exposures, Infertility, and Related Reproductive Disorders: An Update

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In 2002-2003 the Collaborative on Health and Environment (CHE) organized the development of a series of papers that summarized data linking environmental exposures to various health outcomes. One of the series addressed infertility and related reproductive disorders. New developments during the ensuing years motivated this supplemental update, although the original summary contains relevant material that is not repeated here.

Two important events with which CHE was deeply involved are also worth noting. In 2005, CHE's Fertility/Early Pregnancy Compromise Work Group partnered with Linda C. Giudice, M.D., Ph.D. (currently Professor and Chair, Department of Obstetrics and Gynecology, University of California, San Francisco) and Stanford University School of Medicine's Women's Health @ Stanford Program (for which Dr. Giudice served as Director at the time) to convene a small multidisciplinary group of experts at the Vallombrosa Retreat Center in Menlo Park, California to assess what the science tells us about the contribution of environmental contaminants—specifically synthetic compounds and heavy metals—to human infertility and associated health conditions. Links to the Vallombrosa documents are here: http://www.healthandenvironment.org/infertility/vallombrosa_documents

In 2007, CHE joined UCSF in sponsoring an Environmental Reproductive Health Summit. This conference was designed for clinical researchers and clinicians/health professionals, scientists; allied and public health professionals; policy makers, government; leaders from patient advocacy, women's health, community and worker health, environment, reproductive advocacy, and environmental justice; and environment/health funders. Its purpose was to raise awareness and promote collaboration on science linking environmental contaminants with male and female reproductive health and fertility compromise. Proceedings were published in Fertility and Sterility (Feb, 2008) and are available here http://www.prhe.ucsf.edu/prhe/events/ucsfche_fs.html. The following update includes occasional reference to that meeting.

Introduction

Scope and Definitions

Environmental chemicals or contaminants can adversely affect human reproduction and child development in a various ways resulting in impaired fertility, miscarriage or fetal death, altered fetal growth, birth defects, and other developmental disorders, some of which may not become apparent for years.[1] The scope of this update is limited to impacts on human fertility, although a brief discussion of additional effects after developmental exposures is included at the end.

Infertility is a term used to describe the failure to have a child, despite unprotected intercourse. Demographers define infertility in terms of the absence of children. The American Society of Reproductive Medicine defines infertility as a condition that can be diagnosed when a couple fails to conceive within 12 months of unprotected intercourse. Approximately 10-15% of couples of reproductive age meet this definition of infertility. The National Survey of Family Growth (NSFG) classifies a woman as having infertility if she has not conceived during the past 12 months, is 15–44 years old, married, not surgically sterilized, and sexually active but not practicing contraception in each of 12 preceding months. This, too, is a commonly used definition but is of limited value in determining trends since a number of social, economic, behavioral, and environmental factors influence the results.[2] [3] These include changes in contraceptive practices, quicker access to assisted reproductive techniques, and changes in the prevalence of cohabiting, unmarried couples, among others.

For research purposes, distinctions between fertility and fecundity may be useful. Fecundity refers to the physiologic ability to have children. Impaired fecundity includes married and unmarried women and includes problems conceiving and carrying a baby to term. Time-to-pregnancy data are useful for estimating infertility for a given population over a relatively short period but less useful for determining time trends since they can be biased by high numbers of unplanned pregnancies, high use of contraception, and abortion rates.

Infertility or impaired fecundity does not necessarily imply lack of conception. A couple might conceive, for example, but the fertilized egg might not implant normally in the uterus, or the developing embryo or fetus might not survive after implantation. Typically, this results in a miscarriage. If the loss occurs early, it might go undetected or a woman might think that her period is simply a few days late. For some women, early pregnancy loss (spontaneous abortion or miscarriage) may be a single event or may be recurrent. In the general population, about 50% of fertilized eggs do not progress to a viable pregnancy, and about 30% of pregnancies are lost in the first six weeks.[4] [5]

Infertility may result from male factors (estimates range from 20-50% of cases), female factors (about 30% of cases), and the rest are attributable to couple-dependent factors or are unexplained.[6] [7] For purposes of understanding or treatment, the distinction among the causes can be important.

Fertility Trends

Trends in infertility are difficult to determine or to interpret for several reasons. Although the birth rate in many countries throughout the world has declined in recent years, this trend is attributable, in large measure, to increased access to contraception, economic improvements, improved social standing of women, and other behavioral and social changes. Effects have been largest in developing countries, but birth rates in developed countries have declined as well. The degree to which impaired fertility may explain this is a matter of considerable debate and probably differs from one country to another, as well as within subgroups within countries.[8] [9] [10]

Perhaps most important, many couples now choose to delay childbearing for a number of years after reaching reproductive maturity. Fertility trends may be influenced by this choice, since fertility naturally declines with age, particularly after age 35. About one-third of women who defer pregnancy until the mid to late 30's, and at least half of women over age 40, will have an infertility problem.[11]

Increased reporting of fertility problems because of newly available treatments may also influence trend data. Assisted reproductive technologies, including pharmaceuticals that stimulate ovulation and in vitro fertilization, result in successful pregnancies and increase the likelihood that a woman or couple will seek medical interventions. Access to medical care will also influence the likelihood that fertility problems will be identified and reported. As a result, trend analyses of infertility are subject to significant limitations and should be interpreted with caution.

Finally, some of the uncertainties about fertility trends and their causes arise from the use of varying definitions of fertility, infertility, and fecundity, making it difficult to normalize data over time or across populations. But significant data gaps also contribute.

A 1998 analysis of nationally-representative data from 1982-1995 taken from the National Survey of Family Growth (NSFG) reported that within all specific age groups, including younger women, impaired fecundity was increasing, suggesting that delayed childbearing could not fully explain the trend.[12] An analysis that includes more recent data from the same survey concludes that overall fertility has not continued to decline, although impaired fecundity continues to increase.[13] The authors noted that the trends, if true, are likely to result from a complex set of variables, some of which will probably remain unknown. Reports from Britain and Sweden also find declining infertility in recent years.[14] [15]

Whether measures of fertility or fecundity are most useful is a matter of considerable debate. One commentary notes that when expressed as percent of couples who are infertile, the result will be influenced by the number and characteristics of people who do not satisfy the criteria (the denominator) as well as by the number who do (the numerator).[16] For example, women who are not sexually active or who have not yet been attempting to conceive for 12 months would fail to meet the infertility criteria and would therefore be included in the comparison group (denominator). These authors argue that impaired fecundity is a better measure.

In sum, impaired fecundity appears to be increasing, but changing social, behavioral, and environmental variables will continue to influence fertility, making it difficult to draw conclusions about trends over time with confidence. One analysis concludes, we may never know.[17]

Male Fertility

Sperm Count Trends

As discussed in the 2003 summary, an analysis of sperm count trends published in 1992 concluded that there was evidence of a decline of the average sperm count in the general population from about 113 million/ml to 66 million/ml over a 50 year period.[18] That report initiated considerable controversy and stimulated additional analyses. One found significant sperm count declines in some, but not all geographical areas.[19] In a recent literature review, the authors concluded that sperm counts appear to have declined in some areas, but differences in study design make it difficult to generalize widely.[20] Recently, Danish investigators responsible for the 1992 analysis found that as many as 30% of young Danish men may have semen quality in a sub-fertile range, and more than 10% may be in the infertile range.[21] Preliminary results of a study of Danish military recruits between 1996 and 2010 show no further decline in sperm counts over that time period.[22] [23]
Environmental agents and semen quality:

This section summarizes data from recent studies addressing the relationship between sperm quality and exposures to phthalates, pesticides, air pollution, heavy metals, solvents, polychlorinated biphenyls, and electromagnetic fields. Study designs vary. Cross sectional studies that measure sperm quality and environmental exposure at a single time must be interpreted with caution, particularly when the environmental agent has a relatively short half-life and nothing is known about exposure levels in the past.
Phthalates and semen quality:

Phthalates comprise a class of chemicals with numerous uses in many kinds of consumer products. High molecular weight phthalates, such as DEHP, are primarily used as plasticizers in flexible polyvinyl chloride products. Lower molecular weight phthalates (e.g. DEP, DBP) are used in personal care products as solvents, and in lacquers, varnishes, and coatings, and in some pharmaceuticals. Because of widespread use, exposure is common, and their metabolites are detectable in the urine of most people in the general population.[24]

Some, but not all phthalates are reproductive and developmental toxicants in laboratory animal studies and limited human studies.[25] In the past few years, studies conducted in the US, Sweden, and India have examined the relationship between phthalate exposures and various measures of semen quality. (Table 1)
Table 1:

Study population	Sperm/other parameter	Phthalate exposure metric	Results	Ref
168 men; 20-54 yrs. old;	Sperm concentration	Urinary metabolites	Adjusted direct dose-response	Duty, 2003a[26]

subfertility clinic (US)	(conc); sperm motility	(MBP, MBzP, MEHP)	(D-R) relationship between MBP and sperm motility and conc.; Adjusted D-R reln MBzP and sperm conc.	
168 men; 20-54 yrs old; subfertility clinic (US)	Comet tail assay (measures DNA integrity)	Urinary metabolites	Higher MEP assoc. with more DNA damage (comet assay); No assoc. with MBP, MBzP, MMP, MEHP	Duty, 2003b[27]
463 men; subfertility clinic (incl 168 from 2003 study; US)	Sperm conc; motility	Urinary metabolites (MBP, MBzP, 3 DEHP metabolites, MEP, MMP)	D-R reln; Higher MBP assoc. with lower sperm conc; Suggestive reln highest MBzP and sperm conc; no reln MEP, MMP, 3 DEHP metabolites	Hauser, 2006[28]
300 men; 21-40 yrs old; 100 fertile; 200 infertile* (India)	Sperm conc, motility, morphology	Phthalate conc. in semen (DBP, DEHP, DEP, DMP, DOP)	Higher DEHP, DBP, DEP assoc with lower sperm conc; Higher DEHP, DBP assoc with lower sperm motility	Pant, 2008[29]
234 men; 18-21 yrs old; (Sweden)	Sperm conc, motility; serum hormones (estrogen, T, FSH, LH) SHBG	Urinary phthalate metabolites (MEP, MEHP. MBzP, MBP, phthalic acid	No assoc. MBP, MBzP, MEHP with any parameter; Highest MEP level assoc. with more immotile sperm, lower LH; phthalic acid assoc with more motile sperm	Jonsson, 2005[30]

*failure to achieve pregnancy after 12 months unprotected intercourse; no diagnosed fertility disorder

DBP: dibutyl phthalate; metabolite is MBP, monobutyl phthalate

DEP: diethyl phthalate; metabolite is MEP, monoethyl phthalate

DEHP: diethyl hexyl phthalate; metabolites include MEHP, MEOHP, MEHHP

BBzP: butyl benzyl phthalate; metabolite is MBzP, monobenzyl phthalate

DMP: dimethyl phthalate

DOP: dioctyl phthalate

Participants in the US studies are drawn from a subfertility clinic. The Swedish study participants are young healthy men whose fertility status is not known. The study in India includes a mix of fertile and infertile men. In the US and India analyses, higher exposures to some phthalates are associated with impaired semen quality. This was not seen in the Swedish study. This inconsistency may have several explanations. The relationship between phthalate exposures and semen quality, if it exists, could be age-dependent. It is also possible that men with sub-fertility are more susceptible to phthalates than men who are not being evaluated in a fertility clinic.

The study in India (Pant) should be interpreted with caution since the authors measured the parent phthalate compounds rather than metabolites. Inasmuch as phthalates are so widely used and dispersed throughout the environment, laboratory and specimen contamination is difficult to avoid.

Since laboratory animal studies consistently show DEHP to be similar to DBP in terms of reproductive toxicity, it is somewhat surprising that the studies in the US found no relationship between DEHP metabolite levels and semen quality. Hauser suggests that MEHP may be the toxic metabolite and further transformation of MEHP into its oxidative metabolites may lower the burden of MEHP, thereby protecting sperm from further damage.[31] If this is true, future studies should take into account inter-individual variability in DEHP metabolism that may influence susceptibility and study results.

It should also be noted that there may be important species differences in susceptibility to phthalates. A recent study in which 11 pregnant marmosets were given 500 mg DBP/kg/day (orally) from weeks 7-15 of gestation showed minimal impacts on testicular development, germ cell numbers, or fertility in male offspring.[32] Identical doses in 5 newborns for 14 days also showed no effects. These same doses are associated with marked effects in rodents. In general, primate studies are considered useful for predicting toxicological effects of a chemical in humans, but there is some disagreement about whether marmosets are a good primate model for studying reproductive toxicology since their hormonal regulatory system, including testosterone

levels, differs significantly from humans.[33] Thus, the relevance of the negative findings to humans is unclear.

Pesticides and Semen Quality

Historically, exposure to some pesticides has led to poor semen quality and infertility in farm workers, resulting in restricted uses or bans. For example, the nematocide, dibromochloropropane (DBCP), and the fumigant, ethylene dibromide (EDB), were banned from agricultural use because of spermatotoxicity, although EDB is still used for other purposes. In recent years, several studies have examined the relationship between exposures to current-use pesticides and semen quality. (see table 2). Two studies (Padungtod, Kamijima) compared sperm parameters in men occupationally exposed to pesticides to a control group. Two studies (Swan, Perry) compared pesticide biomarkers in a single urine specimen in men with above and below average sperm quality. Meeker, et al. and Ji, et al. collected single urine and semen samples from men in an infertility clinic and examined the relationship between urinary pesticide metabolite levels and sperm quality.

Table 2:

Study population	**Sperm/other parameter**	**Exposure metric**	**Results**	**Reference**
Male workers; 32 exposed to organophosphate pesticides; 43 not exposed (China)	Sperm conc,; motility; morphology	Urinary p-nitrophenol (metabolite of certain organophosphate pesticides)	Exposure assoc. with reduction in sperm conc. and motility, but not morphology	Padungtod, 2000[34]
86 males from couples attending prenatal clinic; 34 cases (sperm conc < median), 52 controls (sperm conc > median)	Sperm conc, motility, morphology	Urinary pesticides or metabolites (alachlor, IMPY, atrazine, metolachlor, 2,4D, 1-naphthol, TCPY, 4-nitrophenol)	Men with below average sperm quality had significantly higher levels of alachlor, IMPY, atrazine	Swan, 2003[35]
272 men from infertility clinic	Sperm conc, motility, morphology, DNA damage*	Urinary pesticide metabolites (1-naphthol, TCPY)	Higher 1-napthol assoc. with lower sperm conc, motility; suggestive negative assoc. TCPY and sperm motility; both assoc. with DNA damage*	Meeker, 2004 [36] [37]
207 men from infertility clinic	Sperm conc, motility,	Urinary metabolites of	Highest 3PBA assoc with lower	Meeker, 2008[38]

	morphology; DNA damage*	pyrethroids (3PBA, CDCCA, TDCCA)	sperm conc, DNA damage; highest TCDDA assoc with lower sperm conc, motility, morphology; higher CDCCA assoc. with DNA damage	
240 men from infertility clinic, China	Sperm conc, motility, morphology, DNA damage	Urinary metabolite of pyrethroids (3PBA)	Higher 3PBA levels assoc with lower sperm conc and more DNA damage	Ji, 2010[39]
94 men with sperm conc, motility below median (cases); 95 controls (sperm conc > median)	Sperm conc, motility	6 metabolites of organophosphate pesticides	Cases more likely to have higher levels of DMP than controls; no assoc with other metabolites	Perry, 2010[40]
18 insecticide sprayers (mostly organophosphates, pyrethroids), 18 controls	Sperm conc, motility, hormone levels	Employment as sprayer; cholinesterase levels	Sperm motility impaired in sprayers in summer (highest pesticide use); sperm conc no different;	Kamijima, 2004[41]

IMPY—2-isopropoxy-4-methyl-pyrimidinol; metabolite of diazinon.

TCPY—3,5,6-trichloropyridinol; metabolite of chlorpyrifos

3PBA—3-phenoxybenzoic acid

DMP—dimethylphosphate

CDCCA, TDCCA—cis- and trans--3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid

1-naphthol—metabolite of carbaryl and naphthalene

*as measured by comet tail assay

These studies show that exposures to pesticides in current use may alter semen quality. Two exposure scenarios are of concern: (1) Agricultural workers, their families, and agricultural communities are routinely exposed to higher levels of certain pesticides than the general population; and (2) The general population incurs wide-spread exposure to lower-level, mixed exposures to these pesticides.

A recent systematic review of published literature addressing this topic over the past 15 years identified 20 studies of sufficient quality, 13 of which reported an association between pesticide exposure and semen parameters.[42] Of 6 studies evaluating DNA damage, 3 reported an association with exposure. Of 6 studies assessing sperm aneuploidy or diploidy (abnormal numbers of chromosomes), 4 reported an association with exposure. The author concluded that the epidemiologic evidence accumulated thus far, although suggestive, remains equivocal as to the spermatotoxic and aneugenic potential of pesticides given the small number of published studies. Inasmuch as pesticide exposure is so widespread, this question warrants more investigation, although other health effects for which data are more consistent will in some cases justify use restrictions or other interventions to reduce exposures.

Solvent Exposure and Male Factor Fertility

Five recent (within the past five years) studies of male occupational exposures to solvents and semen quality or fertility status were identified through a PubMed search.

A case-control study of men in an infertility clinic in Spain found that cases were more likely than controls to experience current or past occupational exposures to solvents, glues, and heavy metals. [43]

A study of 402 men consulting because of couple infertility (314 with sperm abnormalities and 88 with normal semen) found significant associations between semen abnormalities and occupational factors such as exposure to heavy metals, solvents, fumes, and polycyclic aromatic hydrocarbons, as estimated by questionnaire.[44]

In a case-control study of 2118 men seen in fertility clinics across the UK, 871 with low motile sperm counts were significantly more likely to have a history of occupational exposure to solvents, particularly glycol ethers.[45]

A multi-center retrospective case-control study in the US of 650 infertile men and 698 controls did not identify links between fertility status and male occupational exposure to metals, fumes, or solvents.[46] These results must be interpreted with caution since the study limited exposure estimates to the month prior to evaluation.

A study of 109 men in France evaluated semen quality and occupational histories.[47] Glycol ether metabolites were measured in urine. Previous exposure to glycol ethers (as estimated from questionnaires) was associated with increased risk of low sperm concentration and impaired sperm motility and morphology. However, no association was seen with exposure to current use glycol ethers, as estimated by urinary metabolites. Some short-chain glycol ethers are well-known spermatoxins, with long-lasting effects. In some cases, they are likely to have been replaced with safer alternatives.

These recent data are consistent with previous information showing that occupational exposure to solvents, perhaps in combination with other workplace exposures, can increase the risk of impaired semen quality and subfertility.

Air Pollution and Sperm Quality

Air pollution is a complex mixture of gases, aerosols, and particulates. Particulate air pollution can be comprised of products of incomplete combustion of fossil fuels, metals, and various organic and inorganic chemicals. The composition of this mixture can vary with geography, season, and temperature. Animal studies show that air pollution can adversely affect sperm quality.[48] [49]

A study in the Czech Republic found air pollution, primarily from coal combustion, at or above US air quality standards to be associated with increased sperm DNA fragmentation. This was not observed in the same men during periods of lower pollutant concentrations.[50]

A study of 228 men in the US did not find a relationship between sperm quality and air pollution when pollutant levels were below US air quality standards.[51] However, in 169 men from Salt Lake City, higher levels of air pollution during the winter months were associated with decreased sperm motility, recorded 2-3 months later.[52] This suggests that higher levels of air pollution can interfere with normal spermatogenesis, although the authors concluded that the effect on motility was minimal and unlikely to affect reproductive success.

In summary, these studies suggest a link between higher levels of air pollution and impaired semen quality. Whether or not a threshold exists is unclear, but these exposures may be clinically relevant in areas failing to meet air quality standards or in occupations in which workers are exposed to higher levels.

Metals and Sperm Quality

In a recent review summarizing the results of studies examining impacts of low-level metal exposures on male reproductive parameters, the authors concluded that occupational studies consistently find elevated blood lead levels associated with lower sperm count, poor motility, and abnormal morphology.[53]

Moderate to high levels of cadmium exposure can also adversely impact sperm parameters, although the data are not as consistent in humans as in laboratory animals. Variation in study designs may explain conflicting results. For example, some human studies fail to control for smoking or other confounders and do not have large study populations. Blood cadmium levels do not correlate well with semen cadmium levels. And, the impacts of cadmium on sperm quality may be more marked in infertile couples than in those with normal fertility. [54]

Human studies of the impacts of mercury suggest that moderate to high levels can adversely impact sperm quality. However, since exposures often come primarily from mercury-contaminated fish consumption and since these fish can also contain other toxic contaminants, the results may be attributable to a more complex exposure scenario. . [55]

A cross-sectional study of 200 clients from a fertility clinic found a correlation between elevated serum manganese (Mn) levels and increased risk of low sperm motility and concentration.[56] When the data were analyzed by quartile of Mn levels, the increased risk of low sperm motility and concentration was seen in both the lowest and highest quartiles. This is biologically plausible since Mn is essential for a number of biochemical processes important to normal reproduction and abnormally low as well as high levels could have adverse impacts on sperm parameters.
PCBs and sperm quality:

Polychlorinated biphenyls (PCBs) are a class of synthetic, persistent, and lipophilic compounds that were widely used in industrial and consumer products for decades before being banned in the US in 1977. Because of their extensive use and persistence, they continue to be environmental contaminants to which people and wildlife are exposed primarily through food contamination. Fortunately, in recent years, levels in the general population have been declining, but exposures remain widespread. (CDC)

Recent reviews of up to eleven epidemiologic studies addressing PCB exposures and sperm quality conclude that the evidence consistently shows a relationship between higher PCB levels and impaired sperm motility, with no evidence of a threshold below which exposure causes no effects.[57] [58]

Electromagnetic Fields (EMF) from Cell Phone Use and Sperm Quality

A dramatic increase in the use of mobile phones in recent years has raised growing concerns about possible hazardous health effects of radio-frequency electromagnetic fields emitted from them.[59] Recent laboratory animal and epidemiologic studies suggest a potential adverse impact of cell phone use on male fertility.

Cell-phone use of 371 men from an infertility clinic in Hungary was evaluated.[60] Candidates with other identified cause of infertility, drug use, or excessive smoking or alcohol use were excluded. EMF exposure was estimated by duration of possession of cell phone (in months), duration of standby position closer than 50 cm to the patient (in hours) and duration of daily transmission (in minutes). Increasing duration of possession and daily transmission time correlated with fewer rapidly progressive motile sperm and more slowly progressive motile sperm. There was no correlation between the duration of the standby position and any measures of sperm quality.

A study of 304 men from an infertility clinic in Poland divided participants into three 3 groups: Group A: 99 patients who did not use mobile phones, Group B: 157 males who had used GSM (mobile communication) equipment sporadically for the period of 1-2 years, and Group C: 48 people who have been regularly using mobile phone for more than 2 years. [61] The authors reported an increase in the percentage of sperm cells with abnormal morphology and decrease in sperm motility associated with increasing GSM phone use.

A case-control study of 148 sperm donors in China (cases defined as men with at least one abnormal semen parameter by World Health Organization criteria; men with known cause or occupational exposures to known spermatoxins excluded) found that an increasing duration of

magnetic field exposure >1.6 milligauss was associated with a dose-response increased risk of having poor sperm quality (as measured by sperm motility and morphology) compared to exposure durations of >1.6 mG less than 1 hour/day. [62] (OR 1.5, 1.8, and 2.7 for duration of 1–3, 3–6, and ≥6 h/day, respectively) In this study, each participant wore an exposure meter for 24 hours on a day considered typical for the past three months.

A study of 361 men undergoing infertility evaluation in the US were divided into four groups according to their active cell phone use: group A: no use; group B: <2 h/day; group C: 2–4 h/day; and group D: >4 h/day. Participants were further divided into those with sperm counts above and below 20 million/mL. After adjustment for participant age, mean sperm motility, viability, and normal morphology significantly decreased within the two sperm count groups in all four cell phone user groups as the duration of daily exposure to cell phones increased.[63]

An in vitro study of ejaculated semen from 23 healthy sperm donors and 9 infertile patients divided the specimen from each participant and exposed half to cell phone radiation for one hour (cell phone in talk mode) while the other half served as control. Exposure decreased sperm motility and viability in donors but not in patients.[64] Concentration of reactive oxygen species was also significantly increased with exposure, and this was most notable among patients. There was no significant difference in DNA integrity in the exposed vs. unexposed specimens. Another in vitro study of 27 men whose semen was exposed to cell phone radiation reported similar impairment of sperm motility.[65] Another in vitro study found that EMF exposure decreased sperm motility and viability, increased generation of reactive oxygen species, and also caused DNA damage with increasing SAR (Specific Absorption Rate—a measure of the amount of radio frequency (RF) energy absorbed by the body when using a cell phone).[66]

These studies document primarily adverse impacts of cell phone radiation on sperm motility and to some extent sperm morphology under current conditions of use. However, there are important limitations to keep in mind. The studies are of various design and potential confounders and effect modifiers are dealt with in a variety of ways. Moreover, cell phone technology continues to evolve and the radio-frequency energy emitted often differs significantly among devices, thus potentially affecting biologic effects.

Nevertheless, the dramatic increase in cell phone use worldwide raises well-founded concerns about adverse impacts, including effects on human fertility.

Female fertility

Environmental agents can interfere with female reproductive function by multiple mechanisms, including altered hormonal balance, direct damage of oocytes, interference with fertilization and implantation, and abnormal reproductive tract development or function.

Heavy metals and female fertility:

In 2008, a review of literature published during the 1999-2007 timeframe dealing with environmental contaminants and fertility in the adult female was prepared for the UCSF-CHE Summit on Challenges to Reproductive Health and Fertility.[67] [68] The authors concluded that the strongest evidence linking environmental exposures to effects on reproductive function in women is for heavy metals, particularly lead. Beginning at low levels, increasing blood lead

levels are consistently associated with later onset of menarche.[69] [70] [71] Higher levels of blood lead are also associated with an increased risk of infertility.[72]
Pesticides and female fertility:

Some, but not all, studies find increased time-to-pregnancy and/or reduced fertility or fecundability in women occupationally exposed to pesticides.[73] Menstrual cycle abnormalities and an increased risk of spontaneous abortion from preconception but not post-conception exposure are also documented. Accurate exposure assessment remains a significant limitation since, in most studies, exposure is estimated from responses to questionnaires and interviews.

Since the 2008 review, a study in Denmark using the Danish Occupational Hospital Register found no increased hospital contact for infertility among women working in the horticultural industry.[74] A study in Italy found no differences in fertility rates (a measure of the number of children born standardized by the number of women of reproductive age living in an area) in three geographic areas differing by the amount of pesticide use.[75] Neither of these studies was designed to evaluate spontaneous abortions or delayed time to pregnancy. Nor, did they include any biomarkers of actual exposure.
Solvents and female fertility:

Studies published since the 2003 summary paper continue to support a link between occupational solvent exposures in women and increased risk of infertility, subfertility, or increased time to pregnancy. Sallmen et al. (2006) conclude that occupational solvent exposures can affect fertility of either gender but the evidence is stronger in women than in men.[76] This conclusion is supported by a recent analysis using data from the Danish Occupational Hospital Register that found increasing use of infertility treatments by women but not men working in the plastics industry.[77] A study of time to pregnancy in 250 Portuguese women exposed to solvents in shoe manufacturing reported reduced fertility compared to controls. The authors concluded that this could be due to any of the solvents used, including n-hexane, toluene, methyl ethyl ketone, ethyl acetate, and dichloromethane.[78]

PCBs and Female Fertility

A recent study examined the relationship between serum PCB levels and early pregnancy loss in a cohort of over 800 women undergoing in vitro fertilization. Women with the highest levels of PCBs were approximately 2-fold more likely to experience implantation failure and reduced odds of a live birth than women with the lowest levels.[79] These findings are consistent with previous reports of reduced fecundity in women exposed to higher levels of PCBs (reviewed in Meeker, et al.)

Early Life Exposures and Reproductive Function in Adulthood

Virtually all of the above data have examined the fertility-related impacts of environmental exposures incurred during adulthood. Extensive laboratory animal research and epidemiologic investigations, however, continue to explore the consequences of fetal and neonatal exposures to various environmental agents and subsequent effects on reproductive tract development and function in males and females.

Fetal Exposure to Environmental Contaminants and Testicular Dysgenesis Syndrome

In males, Testicular Dysgenesis Syndrome (TDS) continues to be a working hypothesis that links fetal exposure to environmental contaminants to a collection of adverse male reproductive health outcomes.[80] [81] TDS is proposed to consist of varying combinations of cryptorchidism, hypospadias, testicular cancer, and low sperm counts resulting from disrupted fetal development of the male reproductive tract. Endocrine disrupting chemicals, which may be estrogenic or anti-androgenic, are likely to play a role in TDS. However, there is no general consensus that these conditions represent a syndrome that can be traced to a unifying origin(s) in a significant number of individuals.[82]

Although there is general agreement that the incidence of testicular cancer continues to increase in many countries, trends in cryptorchidism, hypospadias, and sperm counts are still debated, with analysts reaching different conclusions—even while looking at similar data. Regardless, there is little doubt that cryptorchidism and testicular cancer are much more common in some countries than in others. For example, the incidence of congenital cryptorchism and testicular cancer in Denmark is much higher than in Finland. The reasons for this have never been clear. However, a recent study reporting on levels of 121 environmental chemicals in 68 breast milk samples from the two countries may provide some explanation.[83]

Participants included 36 Danish and 32 Finnish women who gave birth to healthy boys. Results showed distinct country-specific chemical signatures of endocrine disrupting compounds in breast milk with Danes having generally higher exposure than Finns to persistent bioaccumulative chemicals. Some dioxins, PCBs, and the pesticides hexachlorobenzene and dieldrin were significantly higher in Denmark than in Finland. In animal studies, these chemicals can disrupt fetal reproductive tract development, lending support to the view that environmental exposures may help to explain geographical differences in reproductive tract disorders. These findings are consistent with an anti-androgenic effect of PBDEs identified in animal testing.[84]

Another study of polybrominated diphenyl ether (PBDE) concentrations in 86 samples of breast milk and placentas from women in Denmark and Finland found higher levels of these chemicals in the breast milk of women who gave birth to boys with cryptorchidism.[85] Levels were not higher in their placentas, however, raising questions about variability in placental sequestration and permeability to fat soluble chemicals.

Swan, et al. examined the anogenital distance (AGD) and other genital measures in relation to prenatal phthalate exposure in 134 U.S. boys 2-36 months of age.[86] Anogenital distance is normally longer in boys than in girls, and in animal testing, prenatal exposures to estrogenic or anti-androgenic chemicals can significantly shorten the AGD in males. This study also reported a correlation of shorter AGD with smaller penile volume and incomplete testicular descent. Nine phthalate metabolites were measured in a single prenatal maternal urine sample. Higher urinary concentrations of the metabolites of di-ethyl phthalate, dibutyl phthalate, butylbenzyl phthalate, and diisobutyl phthalate were associated with shorter AGD. These findings are also consistent with an anti-androgenic effect and support the hypothesis that prenatal exposures can interfere with normal reproductive tract development in humans. Recently, Mendiola, et al. reported a significant correlation between shorter anogenital distance and reduced sperm count in young

adult men.[87] These findings are consistent with laboratory animal data showing that shorter anogenital distance in males predicts lower sperm count in adulthood.

Fetal Exposure to Environmental Contaminants and Female Fertility

Data addressing the impacts of fetal exposure to environmental contaminants in females are less extensive and were briefly summarized in a paper prepared for the UCSF-CHE summit in 2008[88] and in a publicly available report "Shaping Our Legacy: Reproductive Health and the Environment" summarizing the proceedings of the Summit.[89] The role of endocrine disrupting compounds in female reproductive disorders was also reviewed in Crain et al.[90] In humans, maternal exposure to diethylstilbestrol (DES) in the 1950s and 1960s during pregnancy caused abnormal development of the reproductive tract and increased the risk infertility, reproductive tract malignancies, and breast cancer in their daughters. More recently, animal studies show that developmental exposures to DES can increase the risk of leiomyomas (uterine fibroids) and adenocarcinoma of the uterus. These early exposures leave an estrogenic "imprint" and alter the expression of a variety of genes throughout life.

In animal studies, bisphenol A, an estrogenic chemical found in a number of consumer products to which virtually all people in the general population are exposed, and genestein, a phytoestrogen in soy products, can also program gene expression in the uterus. Neonatal exposure also disrupts ovarian development, causing abnormal numbers and structure of ovarian follicles.[91] Bisphenol A can also interfere with oocyte development, resulting in abnormal numbers of chromosomes (aneuploidy), although this finding has not been repeated in all laboratories and may be dependent on diet as well as BPA exposure.[92] The clinical relevance of these findings to human fertility is unknown.

Summary

Exposures to a variety of environmental agents increase the risk of impaired fertility and fecundity in some people. Workers who regularly incur higher occupational exposures to some substances are at particular risk, but exposures in the general population are often sufficient to increase risks as well.

Recent studies confirm that exposures to heavy metals, solvents, PCBs, and some pesticides increase the risk of infertility. The effects of phthalates, halogenated flame retardants, air pollution, and electromagnetic fields are receiving increasing attention. New data add support to the growing concern that developmental exposures to environmental agents can influence reproductive success decades later.

The personal and economic consequences of subfertility, infertility, or impaired fecundity are considerable and vary from one country to another.[93] [94] [95] Whereas purposely delayed child bearing may explain much of the growing demand for fertility assessment, treatment, and assisted reproduction (in vitro fertilization, etc), it is not fully explanatory. Despite some evidence that increasing infertility trends in many countries have stabilized, general consensus is lacking. In the US, impaired fecundity appears to be increasing.

Interventions that will help eliminate or reduce exposures to these hazards are often readily available. They include the introduction of safer chemical substitutes or non-chemical

technologies, improved workplace practices, product labeling enabling more informed purchasing decisions, enforcement of existing regulations, and long-overdue reform of Federal and state chemical regulations. These are important pieces of a broader public health agenda intended to help prevent a variety of diseases and disorders with profound personal, family, and community consequences. http://www.health

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