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JES JOURNAL OF ENVIRONMENTAL SCIENCES

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Review

Effects of environmental contaminants on fertility and reproductive health

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ARTICLE INFO

Article history:
Received 14 May 2018
Revised 20 July 2018
Accepted 30 July 2018
Available online 22 August 2018

Keywords:
Infertility
Reproductive health
Environmental contaminants
Exposure
Adverse effects

ABSTRACT

Recent research indicates that the human infertility rate is increasing. Although various reasons have been hypothesized for the growing infertility rate, environmental contaminants are potentially important causal agents associated with this change. Chemical contaminants are widespread throughout our environment and human exposure is virtually unavoidable. The overall contribution of environmental exposure to infertility is unknown, but studies involving occupational exposure, together with results from animal experiments, suggest that environmental contaminants may adversely affect fertility. We reviewed the adverse effects of environmental exposure on fertility and related reproductive outcomes. Environmental contaminants covered in this review include heavy metals, organic solvents, pesticides and endocrine disrupting chemicals. It is hoped that this review will highlight the need for further research in this area.

Contents

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https://doi.org/10.1016/j.jes.2018.07.015
1001-0742/

Introduction

Reproductive disorders are important health problems. Infertility has been recognized as a worldwide public health issue by the World Health Organization (WHO). Infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" (WHO-ICMART glossary). The reported international prevalence of infertility ranges from 4% to 14% in different countries and regions (Velde and Pearson, 2002; Nachtigall, 2006; Jungwirth et al., 2012). Epidemiological data demonstrated that approximately 80 million people worldwide are infertile (Nachtigall, 2006). According to the WHO reports, a silent population of more than 180 million couples faces the consequences of infertility (Rutstein and Shah, 2004). A new WHO study, published at the end of, 2012, has shown that the overall burden of infertility in women from 190 countries has remained similar in estimated levels and trends from 1990 to 2010 (Mascarenhas et al., 2012; WHO, 2018). While there are various known reasons for infertility, it is estimated that 15% ~20% of couples undergoing evaluation for infertility will eventually have no cause identified for their failure to conceive.

Human exposure to environmental pollutants is widespread and occurs through multiple routes. Organic contaminants can be detected at low concentrations in drinking water, raising concerns for human health, particularly in regard to reproduction (Martínez-Sales et al., 2015). An analysis of National Health and Nutrition Examination Survey data from 2003 to 2004 found that virtually every pregnant woman in the United States was exposed to at least 43 different potentially harmful chemicals (Woodruff et al., 2011). Robust scientific evidence has emerged over the past 15 years, demonstrating that preconceptional and prenatal exposure to toxic environmental agents can have profound and lasting effects on reproductive health across the life course (Diamanti-Kandarakis et al., 2009; Boekelheide et al., 2012; ACOG, 2013). In recent years, more and more experimental and epidemiologic evidence has indicated that certain industrial and environmental chemicals could adversely impact fertility and pregnancy (Russ et al., 2015).

Currently, it is well-appreciated that environmental exposures to chemical contaminants are potential risk factors for infertility and adverse pregnancy outcomes. The goal of this review is to present and discuss the association between environmental contaminants and reproductive disorders, with a particular emphasis on infertility.

1. Association between environmental contaminants and reproductive outcomes

In this sub-section, our review of environmental contaminants is focused on heavy metals, organic solvents, pesticides and endocrine disrupting chemicals (EDCs).

1.1. *Heavy metals*

Human exposure to heavy metals may occur occupationally, environmentally, or through dietary intake (Amaya et al., 2013). It was demonstrated that exposure to Pb could induce reproductive toxicity and cause infertility in women (Chang et al., 2006). For example, Tang and Zhu (2003) reported that occupational exposure to Pb caused shorter menstrual cycles. To investigate the association between infertility and heavy metals, Tanrıkut et al. (2014) compared the Pb levels of 33 infertile women and 32 normal fertile women. Endometrial samples were collected at 20–24 days of the menstrual cycle by endometrial biopsies, and Pb levels in the endometrium were then measured. They found that the detection rate of Pb was 15% in endometrial samples of infertile women, but only 3% in endometrial samples of fertile women. Another study investigated 341 male partners of infertile couples with no occupational exposure to Pb (Wu et al., 2012). The results showed that the Pb concentration in seminal plasma was significantly correlated with a lower sperm count. Smoking can increase the level of Pb in seminal plasma. Kiziler et al. (2007) found that infertile smokers had significantly higher levels of Pb and higher oxidative stress.

The general population may be exposed to three forms of mercury (Hg): elemental, inorganic, and organic. Even though the placenta may accumulate extremely high levels of Hg, it is not an absolute barrier to prevent the transfer of Hg from maternal blood to fetal blood (Pugach and Clarkson, 2009; Wu et al., 2013). Elemental Hg has been proved to increase the incidence of spontaneous abortion, and to cause irregular menstruation and severe dysmenorrhea. It was also found that organic Hg exposure would increase the risk of spontaneous abortion and fetal birth defects (Ericson and Kallen, 1989; Myers et al., 1995; Liu et al., 2008). In a case–control study in Hong Kong, it was found that blood Hg concentrations in women with unexplained infertility were significantly higher than those in women with normal fertility (Choy et al., 2002). The possible impact of occupational exposure to Hg on the fertility of women working with amalgam has been explored. Female dental assistants working with amalgam (exposure to Hg vapor) showed a decrease in fecundability (probability of conception through each menstrual cycle) compared with other dental assistants.

The main route of human exposure to cadmium (Cd) is through ingestion, and the main concern about Cd toxicity is chronic exposure (Newbigging et al., 2015). It was speculated that Cd might be one of the causes of unexplained infertility. A case–control study showed that the levels of follicle-stimulating hormone (FSH) were significantly positively correlated with Cd concentrations in women's serum (Gallagher et al., 2010). Another study found that Cd reduced the production of human chorionic gonadotropin and inhibited placental transmission of nutrients and oxygen to

the fetus (Levin and Miller, 1981). Both the detection rate and exposure level of Cd in endometrial samples showed obvious differences between infertile and normal women (Tanrıkut et al., 2014). The detection ratio of Cd was 91% in the endometrium of infertile women, while only 34% in normal women, and the median concentration of Cd was 19.58 μg/L (interquartile range 1.46–30.23 μg/L) in infertile women, and 0.00 μg/L (interquartile range 0.00–0.40 μg/L) in normal women.

Studies found that prenatal and early postnatal exposure to hexavalent chromium (Cr(VI)) was closely associated with the occurrence of premature ovarian failure in the next generation. Ren (2011) used occupational epidemiological methods to investigate the effects of Cr(VI) on the reproductive function of male and female workers. The study demonstrated that Cr(VI)-exposed female workers showed a high occurrence rate of abnormal menstruation (mostly cycle abnormalities and dysmenorrhea). It also found that Cr(VI)-exposed male workers showed a significant reduction in sperm counts, viability, and motility. Other indicators for male reproductive function, including sperm lactate dehydrogenase (LDH), LDH isozyme (LDHx) activity, and the LDHx/LDH ratio were also reduced. Another study investigated the semen quality of Indian welders occupationally exposed to nickel and Cr. It was found that rapid linear sperm motility and sperm concentration were significantly decreased in exposed workers (Danadevi et al., 2003). In exposed workers, the percentage of sperm tail defects was positively correlated with blood nickel concentration, while sperm concentration was negatively correlated with blood Cr concentration. It was also found that semen abnormalities were related to the years of exposure to nickel and Cr in welding fumes.

High levels of other metals also can affect reproductive processes. It was found that stillbirths and offspring with clubfoot in Australia were related to manganese exposure (Laskey et al., 1982; Tsuchiya et al., 1987). Meeker et al. (2008) showed that blood molybdenum was associated with reduced sperm concentration and morphology abnormalities in a concentration-dependent pattern.

1.2. Organic solvents

Organic solvents are widely used in auto repair, electronics, dry cleaning, health-care products, paints, glues and other industries, thus associated occupational populations have higher exposure risks. Organic solvents, such as perchloroethylene, toluene and xylene, were often associated with adverse reproductive outcomes (Sharara et al., 1998). Some studies had investigated women exposed to organic solvents, and the results showed that daily or high exposure to organic solvents significantly increased the risk of infertility (Sallmén et al., 1995; Smith et al., 1997). It was also reported that occupational exposure to volatile organic solvents interfered with male reproductive hormones (Eldesouki et al., 2013). Exposure to organic solvents could have toxic effects on male sex steroids by directly affecting testicular function, especially in workers exposed for many years (Eldesouki et al., 2013).

Female hairdressers can be exposed to organic solvents in hair sprays. It was reported that hairdressers and cosmetologists have a higher risk of reproductive disorders, such as infertility, fetal death and preterm delivery (Baste et al., 2008; Kim et al., 2016). Xu et al. suggested that an increased risk of spontaneous abortion was associated with gasoline exposure (Xu et al., 1998). Another study investigated the reproductive toxicity of gasoline components (Ekpenyong et al., 2013). This cross-sectional study investigated 117 female gasoline station attendants and 118 age-matched control women in Nigeria. Compared with controls, inhalation of gasoline disrupted ovarian function, caused menstrual disorders and changed levels of female sex hormones, and thus affected the fertility of female gasoline pump attendants.

Other industrial organic chemicals can also affect female fertility. 4-Vinylcyclohexene can potentially alter ovarian follicle reserve (Hoyer et al., 2001; Takai et al., 2003; Mayer et al., 2004). Glycol ethers commonly used in the semiconductor industry induced longer menstrual cycles and reduced female fertility (Eskenazi et al., 1995; Correa et al., 1996; Hsieh et al., 2005). There is an association between occupational exposure to 2-bromopropane (2BP) and premature ovarian failure (POF), which occurs collectively in female workers exposed to 2BP (Koh et al., 1998; Boekelheide et al., 2004). Female workers in a Korean electronics components factory were exposed to high-purity 2BP as an organic solvent. Sixteen of the twenty-six women who were exposed for 4–16 months were diagnosed with POF according to FSH levels (Koh et al., 1998; Boekelheide et al., 2004). Recently, it was found that reduced numbers of mature oocytes were related to increased phthalate concentrations in females undergoing in-vitro fertilization (IVF) (Hauser et al., 2016).

It was found that male workers exposed to benzene, toluene, and xylene have decreased sperm vitality, sperm activity and acrosin activity, mainly due to direct effects on sperm and accessory gonad function (Xiao et al., 2001). A case report found that a male laboratory worker was suffering asthenospermia and fertility problems due to high chloroform exposure (Chang et al., 2001).

1.3. Pesticides

Human exposures to pesticides can occur in the workplace, in the household and through the ambient environment (Ye et al., 2017). Fuortes et al. (1997) compared pesticide exposures and adverse reproductive effects in 281 women with a diagnosis of infertility and in 216 women who had successfully delivered a child. It was found that the women with a history of working in the agricultural industry had an elevated risk of infertility. To determine the effects of pesticide exposure on reproductive health, agricultural workers were evaluated in several different countries. In a Canadian study, exposure to the phenoxy herbicide 2,4-dichlorphenoxy acetic acid (2,4-D) was associated with spontaneous abortion (Arbuckle et al., 2001). Sharma et al. (2013) found that the wild type CYP17 A1A1 genotype combined with high blood levels of organochlorine pesticides may be considered as an important cause of 'idiopathic' preterm delivery in women.

Human sperm chromatin is a sensitive target for organophosphate pesticides. High exposure to organophosphate pesticides could reduce sperm quality and total sperm counts (Recio-Vega et al., 2008; Yucra et al., 2008). In an in vitro analysis, organochlorine pesticides, including γ-hexachlorocyclohexane (HCH), β-HCH, γ-HCH, 1,1-dichloro-2,2-bis (*p*-

chlorophenyl) ethylene (DDE), and 1-dichloro-2,2,-bis (*p*-chlorophenyl) ethane (DDD), were found to reduce sperm motility in concentration- and duration-dependent manners (Pant et al., 2013). Occupational exposure to organophosphate pesticides interfered with male reproductive parameters, which included damaged sperm chromatin, reduced semen quality and altered reproductive hormone levels (increased FSH and luteinizing hormone levels) (Mirandacontreras et al., 2013). Similar results were reported in male farmers who had chronic occupational exposure to carbamate pesticides (Mirandacontreras et al., 2013). Sutyarso and Kanedi (2014) investigated the impacts of herbicides on the seminal parameters of workers in Indonesian oil palm plantations. Participants were divided into three groups according to work years: less than 10 years, 10–20 years and more than 20 years. The results showed that as exposure time increased, semen quality parameters (including semen volume, sperm count, sperm motility, morphology and hypoosmotic swelling) were significantly reduced. This decline in semen quality was greater than the maximum decrease in normal elderly men, thus it was speculated that the decrease of semen parameters in plantation workers was likely due to herbicide exposure (Sutyarso and Kanedi (2014)).

1.4. *Endocrine disrupting chemicals*

EDCs are exogenous substances that interfere with the synthesis, secretion, transport, metabolism, and binding or elimination processes of endogenous hormones responsible for reproduction, development and homeostasis (Kopp et al., 2017). EDCs include a range of chemical substances, including pesticides (e.g., 1,1,1-Trichloro-2, 2-bis (*p*-chlorophenyl) ethane (DDT)), dioxins (e.g., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)), plasticizers (e.g., bisphenol A (BPA)), polycyclic aromatic hydrocarbons (PAHs), and Cr(VI). As shown in Fig. 1, some EDCs interfere with ovarian folliculogenesis and corpus luteum formation and produce undesirable reproductive effects such as estrogen deficiency, dysfunctional ovulation, POF and infertility. Other EDCs can affect reproductive function by altering ovarian sex steroid synthesis and metabolism by interfering with the expression and catalytic activity of certain enzymes. Some EDCs were found to cause ovarian toxicity by altering hormone receptor binding, such as those targeting estrogen, androgen and aryl hydrocarbon receptors (Craig et al., 2011).

As a plasticizer in reusable plastic containers, food packaging and beverage bottles (including baby bottles), BPA is one of the most widely used EDCs. It can slowly leach into the contained materials and then impact reproductive health (Craig et al., 2011). In recent years, BPA-induced female reproductive health concerns have attracted much attention. Exposure to BPA may be associated with female infertility, and affect the morphology and function of the uterus, oviduct and ovary, hypothalamic–pituitary–ovarian axis, estrous cycles and embryo implantation (Ziv-Gal and Flaws, 2016). Using IVF as a model to study early reproductive health outcomes in humans, Ehrlich et al. (2012) found a negative dose–response association between urinary BPA concentrations and serum peak estradiol and oocyte yield. In addition, they found significantly decreased metaphase II oocyte count and number of normally fertilizing oocytes, and a suggestive association between BPA urinary concentration and decreased blastocyst formation, thus indicating that BPA may alter reproductive function in susceptible women undergoing IVF.

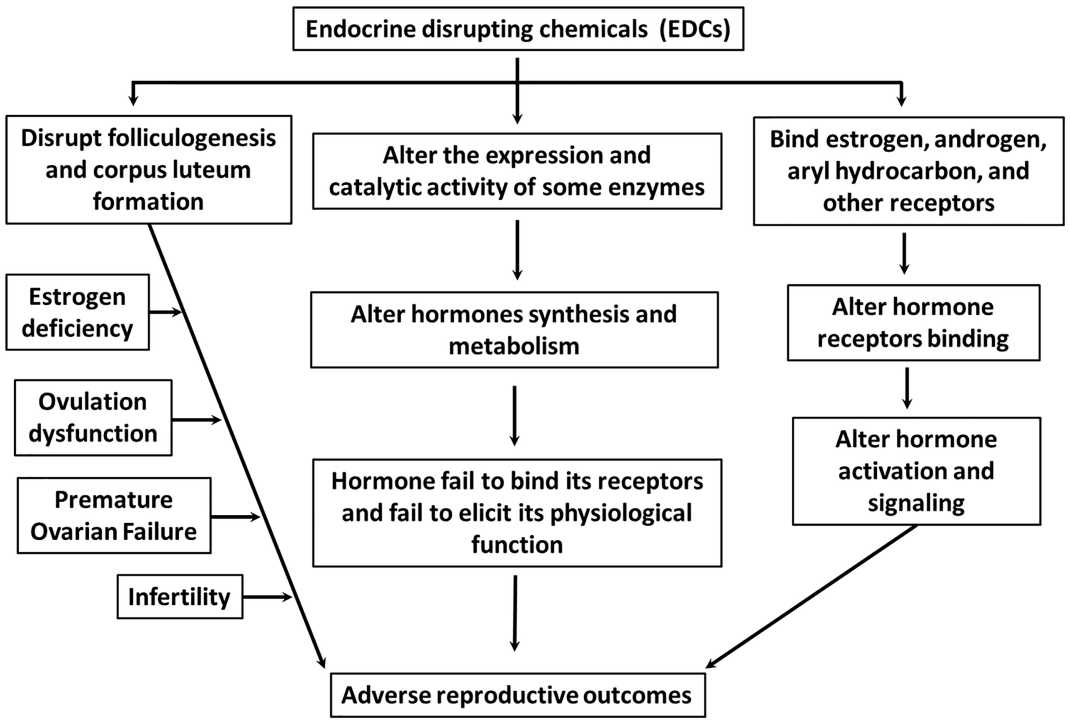

Fig. 1 – Pathways for endocrine disrupting chemicals to produce adverse reproductive outcomes.

A cohort study found that male workers exposed to BPA had an increased risk of ejaculation and erectile difficulty (Li et al., 2010). Compared with unexposed workers, this would cause sexual dysfunction in BPA-exposed workers, decreasing sexual life satisfaction and reducing sexual desire.

Exposure to TCDD, DDT, DDE, polychlorinated biphenyls (PCBs) and other pollutants may cause a series of changes in menstrual and ovarian function (Mendola et al., 2008). Decreased blood levels of progesterone and estrogen were closely related to DDT and DDE exposure (Windham et al., 2005; Perry et al., 2006). Studies found that exposure to organochlorine pollutants (such as PCBs and *p*, *p'*-DDE) caused slight adverse effects on the structural integrity of human sperm chromatin (Rignell-Hydbom et al., 2005). One such class of pollutants was PAHs, which are toxic components of tobacco. The aryl hydrocarbon receptor (AhR) for PAHs is present in oocytes (Jurisicova et al., 2007; Mikkelsen et al., 2007; Tuttle et al., 2009). Maternal cigarette smoking during the second trimester may affect female fetuses and reduce their future fecundity (Fowler et al., 2014). This effect is mediated through the activation of AhR, and the dysregulation of important fetal ovarian genes and endocrine signaling pathways.

2. Limitations of existing research

Large numbers of studies have demonstrated the substantial interest in environmental contamination and reproductive health. However, the existing literature represented in this review is limited in several ways.

First, the measurement of reproductive outcomes requires special consideration within the area of occupational infertility studies. The assessment of infertility rate is a widely used measurement of alterations in the reproductive process. It is feasible to apply this measurement to large-scale studies because results can be obtained from questionnaires or review of medical case records, and laboratory investigations are not required. However, assessing the infertility rate does not differentiate between early spontaneous abortion and the inability to conceive (Baranski, 1993). In addition, the parameters of infertility include hormonal imbalance, menstrual disorders, changes in the quality of semen, spontaneous abortions prior to the clinical recognition of pregnancy, stillbirth, perinatal death, low birth weight, structural and functional congenital malformation, and so on. Thus, considering the relevance, sensitivity and feasibility, studies should make sure that the actual measurement of specific reproductive outcomes is a true reflection of fertility. More importantly, confounding factors, including lifestyle, general medical conditions, medication, education, and exposure of the spouse to different agents, were not taken into consideration in some studies.

Second, there are many methodological problems in assessing exposure to various environmental contaminants. Although there are several well-documented cases of infertility occurring in occupational settings, there is less certainty concerning exposure to environmental contaminants in the general population. In fact, whether in the occupationally exposed or general population studies, participants are exposed to combinations of non-target agents. Because the potential effects of contaminant mixtures cannot be separated very well, it is difficult to identify the actions of individual agents. In some studies, no actual measures of exposure were made, and thus it cannot be concluded that environmental contaminants contributed to the observed changes, although they are highly suspected of being important causal agents in the observed differences. Sometimes, the fact that findings of exposure were based on only a few measurements could lead to random misclassification of the presence or absence of exposure. This can explain why not all studies of exposure to the same environmental contaminant revealed a positive association with an adverse effect on fertility. Meanwhile, it is difficult to prove that subfertility or infertility can be attributed to exposure to environmental contaminants at environmentally relevant doses over a long period of time. Compared with epidemiological findings, animal studies would give a clearer demonstration of the adverse reproductive and developmental toxicity of environmental contaminants.

3. Future perspectives

The adverse reproductive health consequences due to environmental exposure at the levels reported in existing studies remain largely unknown and controversial. A further complication is the potential temporal disconnect between exposure and adverse outcomes. Clearly, it is essential to obtain multiple sources of exposure and more reproductive parameters. In comparison to accessing human serum or semen, access to human ovarian tissue and follicular fluid is much more difficult. However, although access to follicular fluid is difficult, this has been made possible through reproductive technologies. Thus researchers, including epidemiologists, environmentalists, and clinicians, should cooperate with each other and pool data across studies. On the other hand, analysis of complex contaminants in environmental samples is an extremely difficult task. The traditional targeted approach gives good sensitivity and reliable identification and quantification of the target compounds. However, it always will miss important compounds that were not selected at the start of the analyses. These unknowns or untargeted substances may even occur at high concentrations or have severe toxic potential. Therefore, it is necessary to improve analytical methods, such as developing a new non-target screening method. Finally, additional mechanistic studies are desperately needed to understand how healthy reproductive function is influenced by environmental contaminants.

4. Conclusions

We have reviewed recent literature linking environmental contaminants and human reproductive health concerns, particularly regarding infertility. Strong evidence proved that exposure to environmental contaminants could interfere with adult female and male reproductive function. These

contaminants include heavy metals, organic solvents, pesticides and endocrine disrupting chemicals. While these results highlight the potential reproductive effects of exposure to environmental contaminants, the patterns of effects for these compounds are complex, and the impact of exposure to environmental contaminants on human fertility remains controversial. We suggest that significant future research is required to examine the underlying molecular and cellular basis for infertility, as well as the environmental factors leading to infertility and related reproductive outcomes.

Acknowledgments

This work was supported by the Strategic Priority Research Program of the Chinese Academy of Sciences (No. XDB14010300), the Beijing Municipal Science and Technology Commission (No. Z151100004015167), the Beijing Municipal Health Technology High-level Talent Project (No. 2014-3-076), and the Open fund of State Key Laboratory of Environmental Chemistry and Ecotoxicology (No. KF-2017-13).

REFERENCES

ACOG Committee Opinion No.575, 2013. Exposure to toxic environmental agents. Fertil. Steril. 100, 931–934.

Amaya, E., Gil, F., Freire, C., Olmedo, P., Fernández-Rodríguez, M., Fernández, M.F., et al., 2013. Placental concentrations of heavy metals in a mother-child cohort. Environ. Res. 120, 63–70.

Arbuckle, T.E., Lin, Z., Mery, L.S., 2001. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. Environ. Health Perspect. 109, 851–857.

Baranski, B., 1993. Effects of the workplace on fertility and related reproductive outcomes. Environ. Health Perspect. 101, 81–90.

Baste, V., Moen, B.E., Riise, T., Hollund, B.E., Øyen, N., 2008. Infertility and spontaneous abortion among female hairdressers: the Hordaland health study. J. Occup. Environ. Med. 50, 1371–1377.

Boekelheide, K., Darney, S.P., Daston, G.P., David, R.M., Luderer, U., Olshan, A.F., et al., 2004. NTP-CERHR expert panel report on the reproductive and developmental toxicity of 2-bromopropane. Reprod. Toxicol. 18, 189–217.

Boekelheide, K., Blumberg, B., Chapin, R.E., Cote, I., Graziano, J.H., Janesick, A., et al., 2012. Predicting later-life outcomes of early-life exposures. Environ. Health Perspect. 120, 1353–1361.

Chang, H.Y., Lin, Y.M., Hsu, P.C., Guo, Y.L., 2001. Reduction of sperm motility in a male laboratory worker exposed to solvents: a case study. Environ. Health Perspect. 109, 753–756.

Chang, S.H., Cheng, B.H., Lee, S.L., Chuang, H.Y., Yang, C.Y., Sung, F.C., et al., 2006. Low blood lead concentration in association with infertility in women. Environ. Res. 101, 380–386.

Choy, C.M., Lam, C.W., Cheung, L.T., Briton-Jones, C.M., Cheung, L. P., Haines, C.J., 2002. Infertility, blood mercury concentrations and dietary seafood consumption: a case-control study. BJOG 109, 1121–1125.

Correa, A., Gray, R.H., Cohen, R., Rothman, N., Shah, F., Seacat, H., et al., 1996. Ethylene glycol ethers and risks of spontaneous abortion and subfertility. Am. J. Epidemiol. 143, 707–717.

Craig, Z.R., Wang, W., Flaws, J.A., 2011. Endocrine-disrupting chemicals in ovarian function: effects on steroidogenesis, metabolism and nuclear receptor signaling. Reproduction 142, 633–646.

Danadevi, K., Rozati, R., Reddy, P.P., Grover, P., 2003. Semen quality of Indian welders occupationally exposed to nickel and chromium. Reprod. Toxicol. 17, 451–456.

Diamanti-Kandarakis, E., Bourguignon, J.P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., et al., 2009. Endocrine-disrupting chemicals: an endocrine society scientific statement. Endocr. Rev. 30, 293–342.

Ehrlich, S., Williams, P.L., Missmer, S.A., Flaws, J.A., Ye, X., Calafat, A.M., et al., 2012. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Hum. Reprod. 27, 3583–3592.

Ekpenyong, C.E., Davies, K., Daniel, N., 2013. Effects of gasoline inhalation on menstrual characteristics and the hormonal profile of female petrol pump workers. J. Environ. Prot. 4, 65–73.

Eldesouki, M.A., Sharaf, N.E., Shakour, A.A.A., Mohamed, M.S., Hussein, A.S., Hasani, I.W., 2013. Study of the effect of occupational exposure to volatile organic compounds (VOC's) on male reproductive hormones. World J. Med. Sci. 8, 6–12.

Ericson, A., Kallen, B., 1989. Pregnancy outcome in women working as dentists, dental assistants or dental technicians. Int. Arch. Occup. Environ. Health 61, 329–333.

Eskenazi, B., Gold, E.B., Samuels, S.J., Wight, S., Lasley, B.L., Hammond, S.K., et al., 1995. Prospective assessment of fecundability of female semiconductor workers. Am. J. Ind. Med. 28, 817–831.

Fowler, P.A., Childs, A.J., Courant, F., Mackenzie, A., Rhind, S.M., Antignac, J.P., et al., 2014. In utero exposure to cigarette smoke dysregulates human fetal ovarian developmental signalling. Hum. Reprod. 29, 1471–1489.

Fuortes, L., Clark, M.K., Kirchner, H.L., Smith, E.M., 1997. Association between female infertility and agricultural work history. Am. J. Ind. Med. 31, 445–451.

Gallagher, C.M., Moonga, B.S., Kovach, J.S., 2010. Cadmium, follicle-stimulating hormone, and effects on bone in women age 42–60 years, NHANES III. Environ. Res. 110, 105–111.

Hauser, R., Gaskins, A.J., Souter, I., Smith, K.W., Dodge, L.E., Ehrlich, S., et al., 2016. Urinary phthalate metabolite concentrations and reproductive outcomes among women undergoing in vitro fertilization: results from the EARTH Study. Environ. Health Perspect. 124, 831–839.

Hoyer, P.B., Devine, P.J., Hu, X., Thompson, K.E., Sipes, I.G., 2001. Ovarian toxicity of 4-vinylcyclohexene diepoxide: a mechanistic model. Toxicol. Pathol. 29, 91–99.

Hsieh, G.Y., Wang, J.D., Cheng, T.J., Chen, P.C., 2005. Prolonged menstrual cycles in female workers exposed to ethylene glycol ethers in the semiconductor manufacturing industry. Occup. Environ. Med. 62, 510–516.

Jungwirth, A., Giwercman, A., Tournaye, H., Diemer, T., Kopa, Z., Dohle, G., et al., 2012. European Association of Urology guidelines on male infertility: the 2012 update. Eur. Urol. 62, 324–332.

Jurisicova, A., Taniuchi, A., Li, H., Shang, Y., Antenos, M., Detmar, J., et al., 2007. Maternal exposure to polycyclic aromatic hydrocarbons diminishes murine ovarian reserve via induction of Harakiri. J. Clin. Invest. 117, 3971–3978.

Kim, D., Kang, M.Y., Choi, S., Park, J., Lee, H.J., Kim, E.A., 2016. Reproductive disorders among cosmetologists and hairdressers: a meta-analysis. Int. Arch. Occup. Environ. Health 89, 739–753.

Kiziler, A.R., Aydemir, B., Onaran, I., Alici, B., Ozkara, H., Gulyasar, T., et al., 2007. High levels of cadmium and lead in seminal fluid and blood of smoking men are associated with high oxidative stress and damage in infertile subjects. Biol. Trace Elem. Res. 120, 82–91.

Koh, J.M., Kim, C.H., Hong, S.K., Lee, K.U., Kim, Y.T., Kim, O.J., et al., 1998. Primary ovarian failure caused by a solvent containing 2-bromopropane. Eur. J. Endocrinol. 138, 554–556.

Kopp, R., Martínez, I.O., Leqradi, J., Leqler, J., 2017. Exposure to endocrine disrupting chemicals perturbs lipid metabolism and circadian rhythms. J. Environ. Sci. 62, 133–137.

Laskey, J.W., Rehnberg, G.L., Hein, J.F., Carter, S.D., 1982. Effects of chronic manganese (Mn_3O_4) exposure on selected reproductive parameters in rats. J. Toxicol. Environ. Health 9, 677–687.
Levin, A.A., Miller, R.K., 1981. Fetal toxicity of cadmium in the rat: decreased utero-placental blood flow. Toxicol. Appl. Pharmacol. 58, 297–306.
Li, D., Zhou, Z., Qing, D., He, Y., Wu, T., Miao, M., et al., 2010. Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. Hum. Reprod. 25, 519–527.
Liu, J., Goyer, R.A., Waalkes, M.P., 2008. Toxic effects of metals. Casarett and Doull's Toxicology - The Basic Science of Poisons. McGraw-Hill, pp. 931–979.
Martínez-Sales, M., García-Ximénez, F., Espinós, F.J., 2015. Zebrafish as a possible bioindicator of organic pollutants with effects on reproduction in drinking waters. J. Environ. Sci. 33, 254–260.
Mascarenhas, M.N., Flaxman, S.R., Boerma, T., Vanderpoel, S., Stevens, G.A., 2012. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 9, e1001356.
Mayer, L.P., Devine, P.J., Dyer, C.A., Hoyer, P.B., 2004. The follicle-deplete mouse ovary produces androgen. Biol. Reprod. 71, 130–138.
Meeker, J.D., Rossano, M.G., Protas, B., Diamond, M.P., Puscheck, E., Daly, D., et al., 2008. Cadmium, lead, and other metals in relation to semen quality: human evidence for molybdenum as a male reproductive toxicant. Environ. Health Perspect. 116, 1473–1479.
Mendola, P., Messer, L.C., Rappazzo, K., 2008. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. Fertil. Steril. 89, 81–94.
Mikkelsen, T.F., Graff-Iversen, S., Sundby, J., Bjertness, E., 2007. Early menopause, association with tobacco smoking, coffee consumption and other lifestyle factors: a cross-sectional study. BMC Public Health 7, 149.
Mirandacontreras, L., Gómezpérez, R., Rojas, G., Cruz, I., Berrueta, L., Salmen, S., et al., 2013. Occupational exposure to organophosphate and carbamate pesticides affects sperm chromatin integrity and reproductive hormone levels among Venezuelan farm workers. J. Occup. Health 55, 195–203.
Myers, G.J., Marsh, D.O., Davidson, P.W., Cox, C., Shamlaye, C.F., Tanner, M., et al., 1995. Main neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet: outcome at six months. Neurotoxicology 16, 653–664.
Nachtigall, R.D., 2006. International disparities in access to infertility services. Fertil. Steril. 85, 871–875.
Newbigging, A.M., Yan, X., Le, X.C., 2015. Cadmium in soybeans and the relevance to human exposure. J. Environ. Sci. (China) 37, 157–162.
Pant, N., Pant, A.B., Chaturvedi, P.K., Shukla, M., Mathur, N., Gupta, Y.K., et al., 2013. Semen quality of environmentally exposed human population: the toxicological consequence. Environ. Sci. Pollut. Res. Int. 20, 8274–8281.
Perry, M.J., Ouyang, F., Korrick, S.A., Venners, S.A., Chen, C., Xu, X., et al., 2006. A prospective study of serum DDT and progesterone and estrogen levels across the menstrual cycle in nulliparous women of reproductive age. Am. J. Epidemiol. 164, 1056–1064.
Pugach, S., Clarkson, T., 2009. Prenatal mercury exposure and postnatal outcome: clinical case report and analysis. Clin. Toxicol. 47, 366–370.
Recio-Vega, R., Ocampo-Gómez, G., Borja-Aburto, V.H., Moran-Martínez, J., Cebrian-Garcia, M.E., 2008. Organophosphorus pesticide exposure decreases sperm quality: association between sperm parameters and urinary pesticide levels. J. Appl. Toxicol. 28, 674–680.
Ren, L.M., 2011. Effect of hexavalent chromium on reproductive system in exposing workers. Modern Med. Health 27, 1129–1130.
Rignell-Hydbom, A., Rylander, L., Giwercman, A., Jönsson, B.A., Lindh, C., Eleuteri, P., et al., 2005. Exposure to PCBs and p,p'-DDE and human sperm chromatin integrity. Environ. Health Perspect. 113, 175–179.
Russ, H., Gaskins, A.J., Irene, S., Smith, K.W., Dodge, L.E., Shelley, E., et al., 2015. Urinary phthalate metabolite concentrations and reproductive outcomes among women undergoingin vitrofertilization: results from the EARTH Study. Environ. Health Perspect. 124, 831–839.
Rutstein, S.O., Shah, I.H., 2004. Infecundity infertility and childlessness in developing countries. DHS Comparative Reports 9. World Health Organization.
Sallmén, M., Lindbohm, M.L., Kyyrönen, P., Nykyri, E., Anttila, A., Taskinen, H., et al., 1995. Reduced fertility among women exposed to organic solvents. Am. J. Ind. Med. 27, 699–713.
Sharara, F.I., Seifer, D.B., Flaws, J.A., 1998. Environmental toxicants and female reproduction. Fertil. Steril. 70, 613–622.
Sharma, T., Banerjee, B.D., Mustafa, M., Guleria, K., Ahmed, R.S., Tripathi, A.K., 2013. Gene environment interaction in preterm delivery with special reference to organochlorine pesticide: a case control study. Int. J. Biochem. Mol. Biol. 4, 209–214.
Smith, E.M., Hammonds-Ehlers, M., Clark, M.K., Kirchner, H.L., Fuortes, L., 1997. Occupational exposures and risk of female infertility. J. Occup. Environ. Med. 39, 138–147.
Sutyarso, S., Kanedi, M., 2014. Impacts of herbicide exposure on seminal parameters among oil palm plantation workers in Lampung province, Indonesia. Am. J. Biomed. Res. 2, 83–87.
Takai, Y., Canning, J., Perez, G.I., Pru, J.K., Schlezinger, J.J., Sherr, D. H., 2003. Bax, caspase-2, and caspase-3 are required for ovarian follicle loss caused by 4-vinylcyclohexene diepoxide exposure of female mice in vivo. Endocrinology 144, 69.
Tang, N., Zhu, Z.Q., 2003. Adverse reproductive effects in female workers of lead battery plants. Int. J. Occup. Med. Environ. Health 16, 359–361.
Tanrıkut, E., Karaer, A., Celik, O., Celik, E., Otlu, B., Yilmaz, E., et al., 2014. Role of endometrial concentrations of heavy metals (cadmium, lead, mercury and arsenic) in the aetiology of unexplained infertility. Eur. J. Obstet. Gynecol. Reprod. Biol. 179, 187–190.
Tsuchiya, H., Shima, S., Kurita, H., Ito, T., Kato, Y., Kato, Y., et al., 1987. Effects of maternal exposure to six heavy metals on fetal development. Bull. Environ. Contam. Toxicol. 38, 580–587.
Tuttle, A.M., Stämpfli, M., Foster, W.G., 2009. Cigarette smoke causes follicle loss in mice ovaries at concentrations representative of human exposure. Hum. Reprod. 24, 1452–1459.
Velde, E.R.T., Pearson, P.L., 2002. The variability of female reproductive ageing. Hum. Reprod. Update 8, 141–154.
Windham, G.C., Lee, D., Mitchell, P., Anderson, M., Petreas, M., Lasley, B., 2005. Exposure to organochlorine compounds and effects on ovarian function. Epidemiology 16, 182–190.
Woodruff, T.J., Zota, A.R., Schwartz, J.M., 2011. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ. Health Perspect. 119, 878–885.
World Health Organization (WHO), 2018. Global Prevalence of Infertility, Infecundity and Childlessness. http://www.who.int/reproductivehealth/topics/infertility/burden/en/.
Wu, H.M., Dan-Tzu, L.T., Wang, M.L., Huang, H.Y., Chyi-Long, L., Wang, H.S., et al., 2012. Lead level in seminal plasma may affect semen quality for men without occupational exposure to lead. Reprod. Biol. Endocrinol. 10, 91.
Wu, M., Yan, C., Xu, J., Wu, W., Li, H., Zhou, X., 2013. Umbilical cord blood mercury levels in China. J. Environ. Sci. 25, 386–392.
Xiao, G., Pan, C., Cai, Y., Lin, H., Fu, Z., 2001. Effect of benzene, toluene, xylene on the semen quality and the function of accessory gonad of exposed workers. Ind. Health 39, 206–210.

Xu, X., Cho, S.I., Sammel, M., You, L., Cui, S., et al., 1998. Association of petrochemical exposure with spontaneous abortion. Occup. Environ. Med. 55, 31–36.
Ye, M., Beach, J., Martin, J.W., Senthilselvan, A., 2017. Pesticide exposures and respiratory health in general populations. J. Environ. Sci. 51, 361–370.
Yucra, S., Gasco, M., Rubio, J., Gonzales, G.F., 2008. Semen quality in peruvian pesticide applicators: association between urinary organophosphate metabolites and semen parameters. Environ. Health 7, 59.
Ziv-Gal, A., Flaws, J.A., 2016. Evidence for bisphenol a-induced female infertility: review (2007-2016). Fertil. Steril. 106, 827–856.