**Review Article**

Indian J Med Res 150, December 2019, pp 532-545
DOI: 10.4103/ijmr.IJMR_1652_17



# Environmental & occupational exposure & female reproductive dysfunction

Sunil Kumar, Anupama Sharma & Chaoba Kshetrimayum

*Division of Reproductive & Cyto-toxicology, ICMR-National Institute of Occupational Health, Ahmedabad, Gujarat, India*

Received November 25, 2017

**All individuals are exposed to certain chemical, physical, biological, environmental as well as occupational factors. The data pertaining to role of these factors on female reproduction are scanty as compared to male. The available data suggest the adverse effects of certain toxicants, *viz*., metals such as lead, cadmium and mercury, pesticides such as bis(4-chlorophenyl)-1,1,1-trichloroethane and organic solvent such as benzene, toluene and ionizing radiation on the female reproductive system affecting directly the organ system or impacting in directly through hormonal impairments, molecular alterations, oxidative stress and DNA methylation impairing fertility as well as pregnancy and its outcomes. Thus, there is a need for awareness and prevention programme about the adverse effects of these factors and deterioration of female reproductive health, pregnancy outcome and offspring development as some of these chemicals might affect the developing foetus at very low doses by endocrine disruptive mechanism.**

**Key words** Environmental - female - fertility - lifestyle factors - metals - miscarriage - occupational - oxidative stress - pregnancy - reproductive impairment

## Introduction

With the advent of industrialization, participation of women in work sectors is increasing, and many of them are in reproductive age. Thus, women are exposed to a variety of chemical, physical, biological and psychosocial factors. Effects of occupational exposure of these factors on the female reproductive system may become apparent in the form of alteration in sex hormone levels, diminished sexual desire and potency, menstrual disorders, early menopause, delayed menarche, ovarian dysfunction, declined fertility and adverse pregnancy outcome. Maternal exposure during pregnancy may interrupt foetal development. Exposure to toxic substances may lead to many wide-ranging effects, *e.g.,* intrauterine growth retardation, foetal and postnatal death, birth defect, preterm birth (PTB), disorders in cognitive development and immunological function.

Environmental deterioration can lead to the elevated risk of human exposure to heavy metals and consequently leading to reproductive disorders[1]. Higher prevalence of birth deficiencies in offspring may be attributed to paternal occupations such as mathematical, physical and computer scientists, photographers and photoprocessors, artists, food service workers, landscapers and groundskeepers, cosmetologists and

hairdressers, office and administrative support workers, sawmill workers, chemical workers, petroleum and gas workers, printers, material moving equipment operators and vehicle operators[2]. Slama and Cordier[3] reviewed the data of chemical and physical factors with respect to pregnancy and its outcome. The highest magnitude of effects was observed due to passive smoking on foetal growth followed by lead on pregnancy-induced hypertension and foetal growth and polychlorinated biphenyls (PCBs) on foetal growth. Effect of atmospheric pollutants on foetal growth and preterm delivery was found to be at a lesser magnitude. They also reported that except for air pollutants, the data on non-persistent compounds are little conclusive. The present review provides information on the effects of environmental and occupational factors on female reproduction and outcome.

## Metals and female reproduction

### *Mercury* (*Hg*)

Mercury is a naturally occurring element and a man-made contaminant of the environment. Olfert[4] reported a significant relationship between exposure to nitrous oxide and spontaneous abortion, reduced fertility among dental personnel. El-Badry *et al*[5] reported that dental staff faced higher odds of spontaneous abortion, pre-eclampsia and infants small for gestational age (SGA), and this might be linked to mercury-induced oxidative stress. Vejrup *et al*[6] found that women in the highest quintile of mercury exposure delivered offspring with 34 g lower birth weight (LBW), risk of SGA offspring as compared to the lowest quintile exposed women. Elemental mercury exposure might be related with a higher prevalence of irregular menstrual cycles but not with miscarriage[7]. Another study reported that the prevalence of abdominal pain and dysmenorrhoea was significantly higher among the mercury exposed workers[8] (Table I).

### *Lead* (*Pb*)

Occupational and environmental lead exposure has been linked to various health issues such as alterations in growth, endocrine function, organ system and effects on reproduction and outcome. Sallmén *et al*[9] reported increased risk of infertility and pregnancy delay among the wives of men occupationally exposed to lead. There are reports on maternal lead exposure and adverse pregnancy outcomes such as delay in pubertal development and growth among the girls who were exposed to environmental lead[10], three-fold higher PTB and four-fold risk of SGA birth among pregnant women with blood lead level ≥10 µg/dl[13]. LBW offsprings of mothers with higher blood lead level, and a negative relationship between cord blood lead levels and birth length[12]. Increased blood lead was shown to be significantly associated with reductions in birth weight, head circumference and crown-heel length[11]. Ahamed *et al*[35] elucidated the possible free radical-mediated mechanism behind PTB due to lead exposure, and lead-induced elevated oxidative stress might be one of the reasons for PTB. Vigeh *et al*[14] found that higher lead level increased the risk of spontaneous abortion. However, low blood lead levels (<5 µg/dl) in early pregnancy may not be a risk factor for spontaneous abortion. Low to moderate lead exposures may elevate the risk of spontaneous abortion which may be dose dependent[15].

### *Cadmium* (*Cd*)

Human are exposed to cadmium by consuming cadmium-contaminated food, inhaling cigarette smoke and during industrial processes such as smelting and electroplating. In cadmium polluted areas significantly higher prevalence of irregular menstrual cycle and dysmenorrhoea in unmarried and sterility in married women have been observed[16]. Rates of queasiness, spontaneous abortion and stillbirth were significantly higher in married women of polluted area during the first two pregnancies. Mothers exposed to cadmium have a high-risk of early delivery, LBW and traces of cadmium are transferred to the next generation through breast milk[18]. Kippler *et al*[36] found sex difference between maternal cadmium exposure and birth size that was apparent in girls. A correlation has been found between cadmium and preeclampsia in exposed women[17]. Low-level exposure to cadmium interferes with the activity of steroid hormones in reproductive organs of both sex and cadmium disrupts steroidogenesis by meddling with the biosynthesis of androgens, oestrogens and progesterone both *in vivo* and *in vitro*, thus, leading to disturbed sex differentiation and altered gametogenesis[19].

### *Arsenic* (*As*)

Arsenic has a semi-metallic property and is the naturally occurring element in the earth's crust and highly toxic in its inorganic trivalent form. Human are exposed to arsenic generally through drinking contaminated water and food. Arsenic exposure might have a negative impact on menarche age[20], and spontaneous abortion, stillbirth and PTB were significantly higher in the arsenic exposed group[21]. Yang *et al*[22] found that arsenic exposure was associated

**Table I.** Metals exposure and female reproduction and pregnancy outcome

| Exposure | Effects |
|---|---|
| | Mercury (Hg) |
| Dental personnel exposed to Hg | Limited evidence of SAb, reduced fertility, congenital abnormalities[4] |
| Maternal exposure to Hg in pregnancy | Offspring with 34 g LBW and increased risk of SGA[6] |
| Dental staff exposed to Hg | SAb, preeclampsia and SGA babies, and this might be due to Hg-induced oxidative stress[5] |
| Elemental Hg exposure | Higher prevalence of irregular menstrual cycles[7] |
| Hg exposure | Abdominal pain, dysmenorrhoea and abnormal menstruation[8] |
| | Lead (Pb) |
| Men occupationally exposed to Pb | Increased risk of infertility and pregnancy delay in wives of men occupationally exposed to Pb[9] |
| Girls exposed to environmental Pb | Delay in pubertal development and growth of girls[10] |
| Prenatal higher blood Pb level | Preterm delivery, lower head circumference and crown-heel length[11] |
| Higher blood and cord Pb level | LBW offsprings of mothers with higher blood Pb and a negative association between cord Pb levels and birth length[12] |
| Pregnant women with blood Pb level ≥10 µg/dl | Three-fold higher risk PTB and four-fold of SGA birth[13] |
| Pb exposure to women | Risk of SAb but blood Pb (<5 µg/dl) not a risk factor for SAb[14] |
| Low to moderate Pb exposure | Risk of SAb[15] |
| | Cadmium (Cd) |
| Women living in Cd polluted area | Abnormal menstrual cycle, dysmenorrhoea in unmarried women and sterility in married women[16] |
| Cd exposure | Associated with preeclampsia[17] |
| Maternal Cd exposure | High-risk of early delivery and LBW[18] |
| Low level Cd exposure | Interferes steroid hormones and disrupts steroidogenesis leading to alter sex differentiation and gametogenesis[19] |
| | Arsenic (As) |
| As-contaminated drinking water | Negative effect on menarcheal age[20]<br>SAb, stillbirth and PTB[21]<br>Non-significant risk of PTB and LBW[22] |
| As exposure during pregnancy | Decreasing gestational age and lower maternal weight gain[23]<br>Six-fold risk of stillbirth, no relation with infant mortality or SAb[24]<br>Increases oxidative stress and inflammation in the placenta[25] |
| | Zinc (Zn) |
| Role of Zn | Normal growth, development, cellular integrity, protein synthesis, nucleic acid metabolism. Beneficial to infant's neurobehavioural development[26] |
| Maternal Zn deficiency | Infertility and embryo/foetal death, intrauterine growth retardation and teratogenesis[27] |
| | Mangnese (Mn) |
| Maternal Mn level | High concentration related with LBW[28] |
| Maternal and cord blood Mn | Birth weight elevated with Mn upto 4.18 µg/dl and reducted at higher levels[29] |
| Mn exposure | Birth weight increased with Mn upto 3.1 µg/l and reducted at higher levels[30] |
| | Chromium (Cr) |
| Female workers exposed to occupational Cr | Increased risk of SAb and threatened abortion[31] |
| Female exposed to Cr during pregnancy | Higher risk of PTB (particularly male offsprings)[33] and LBW (mainly female offsprings)[32] |
| | Vanadium (V) |
| Vanadium exposure through food, water and polluted air | Positive relationship between LBW and maternal urinary V[34] |

SAb, spontaneous abortion; LBW, lower birth weight; SGA, small gestational age; PTB, preterm birth

non-significantly with the risk of PTB and LBW in area with high arsenic contaminated water. Exposure to arsenic (≥200 µg/l) during pregnancy was linked to six-fold risk of stillbirth, but no relationship was found with infant mortality or spontaneous abortion[24]. Kwok *et al*[37] found a small but significant relationship between arsenic exposure and birth defects, whereas other outcomes (stillbirth, LBW, childhood stunting and childhood underweight) were not related. Ahmed *et al*[25] have reported that arsenic can deteriorate immune function which might also be responsible for impairment of foetal and infant health, and maternal exposure to arsenic during pregnancy increases oxidative stress and inflammation in the placenta.

***Trace elements***

It is established that certain metals in trace amounts are essential for the normal growth, development, reproduction and physiological processes. Zinc is an essential element which plays an important role in growth, development, cellular integrity and various biological functions, including nucleic acid metabolism and protein synthesis[26]. Zinc is also involved in cell division, foetal growth and development. The pilot human studies showed the beneficial effect of prenatal zinc supplementation on infant's neurobehavioural development. Uriu-Adams and Keen[27] reported many adverse effects extending from infertility, embryo/foetal death, to intrauterine growth retardation and teratogenesis due to maternal zinc deficiency. About 10 per cent of the human proteome is reported to contain zinc-binding sites[38]. Copper is another important trace element which is necessary for normal biological functions. It plays a role in maintaining normal foetus development in mammals[39]. However, at higher level, it may be a reproductive toxicant.

Manganese is also an essential trace element and important for growth, development and cellular functioning. However, at higher dose, it may have toxic effects on reproductive functions. Eum *et al*[28] mentioned that higher concentration of maternal manganese was linked with LBW. An inverted U-shaped association has been reported between maternal blood manganese level and birth weight[29]. The birth weight was observed to be elevated with manganese levels upto 4.18 µg/dl, whereas a slight reduction occurred at higher manganese levels. Zota *et al*[30] found a non-linear relationship between maternal manganese exposure and birth weight. The birth weight was elevated with manganese levels up to 3.1 µg/l, and then, a small decline was found at higher levels. Xia *et al*[40] observed higher risk of LBW in lowest tertile (≤0.30 µg/g creatinine) as well as highest tertile (≥1.16 µg/g creatinine) manganese level groups. The data suggested that manganese may affect foetal growth by obstructing weight gain.

The data on female reproduction on chromium exposure are scanty as compared to male. The data closely resemble with those reported in experimental studies with respect to Cr(VI) exposure on pregnancy and outcome[41]. Yang *et al*[31] reported increased risk of spontaneous as well as threatened abortion in female workers who were exposed to high-dose of chromium. Mothers who were exposed to higher chromium levels during pregnancy might have higher risk of delivering LBW infants mainly for female offsprings[32] and PTB particularly linked with male infants[33]. Vanadium exposure in human arises through intake of food, water and polluted air, and an association was found between a vanadium exposure and decrease in birth weight[34]. A significant positive trend was found between odds of LBW and vanadium level in maternal urine[34].

**Solvents**

Hooiveld *et al*[42] assessed the risks of reproductive disorders and birth defects in offspring of male painters exposed to organic solvents. Increased risk of congenital malformations was observed in painter's offspring in comparison with carpenter's offspring. The risk of LBW children was slightly higher while other outcomes [TTP (time to pregnancy), spontaneous abortion and PTB] did not show higher risks among painters. Hannigan and Bowen[43] reported that the children whose mothers were exposed to high concentrations of organic solvents during pregnancy had higher risk of pregnancy complications, developmental delays and neurobehavioural difficulties. These implications were found to be more among toluene abusers. Chen *et al*[44] assessed association between birth weight and exposure to benzene and work stress. They found that birth weight was negatively associated with exposure to benzene and work stress (Table II). Protano *et al*[46] found an association between maternal exposure to benzene or early exposure to aromatic solvents and risk of PTB or a decrease in biparietal diameter growth, while no inferences could be drawn with other pregnancy outcomes.

Ekpenyong *et al*[47] studied the effects of gasoline inhalation on menstrual and hormonal profile of female petrol pump workers. The menstrual complaints

among the exposed and unexposed workers were 37.2 and 28.5 per cent, respectively, and duration of exposure was significantly associated with higher menstrual disorders. There were persistent low levels of serum oestradiol and inconsistent levels of other reproductive hormones. Sallmén *et al*[45] investigated fertility potential of women exposed to organic solvents in shoe manufacturing industries. The organic solvents exposure was found to be hazardous for female reproduction, and association could be related to any of the solvents used in shoe manufacturing *i.e.*, n-hexane and its isomers, ethyl acetate, methyl ethyl ketone, toluene, acetone and dichloromethane. Taskinen *et al*[50] found significant delay in conception among formaldehyde-exposed female wood processing workers, whereas no association was observed between dusts, wood dusts, phenols, organic solvents exposure and TTP. Formaldehyde and organic solvents exposure has an increased risk of spontaneous abortion, endometriosis and adverse effect on fertility[50].

Human are also exposed to carbon disulphide ($CS_2$) at work place which is used in the viscose process. Patel *et al*[49] assessed the incidence of miscarriages among wives of $CS_2$-exposed male workers . The incidence of miscarriage was found to be 5.7 and 18.9 per cent among the spouses of workers who were exposed to 1.69 and 12.28 ppm $CS_2$, respectively. Sieja *et al*[48] concluded that reproductive disorders among women exposed to $CS_2$ at the workplace were menstrual disorders, early menopausal age and disturbances in neurohormonal system.

**Phthalates/plasticizers**

Phthalates are chemicals used to soften and elevate the flexibility of plastic. Phthalates have detrimental effects on children's neurodevelopment and attention deficit hyperactivity disorder while the data are inconclusive related to negative effect of phthalates on gestational age and head circumference, but phthalates exposure affect the reproductive hormonal levels *i.e.*, luteinizing hormone (LH), free testosterone, sex hormone-binding globulin and anogenital distance and thyroid function[51]. The phthalate levels in urine were significantly higher in pubertal gynecomastia individuals, girls with thelarche and precocious puberty. Colón *et al*[52] found significantly higher levels of phthalates such as dimethyl, diethyl, dibutyl, and di-(2-ethylhexyl) and its major metabolite mono-(2-ethylhexyl) phthalate in 68 per cent thelarche patients while only one control was found with substantial levels of di-isooctyl phthalate indicating role of plasticizers in thelarche (Table III).

Sathyanarayana *et al*[53] found an inverse association between di-2-ethylhexyl phthalate (DEHP) metabolite concentrations and lower total and free testosterone; this persists regardless of foetal sex. An inverse association between monobutyl phthalate (MBP) concentrations and total and free testosterone levels was also found in women carrying male foetuses. There was no significant relation between prenatal hormone concentrations with infant anogenital outcomes. Women with endometriosis had higher plasma level of DEHP, and 92.6 per cent had detectable level of DEHP and/ormono-ethylhexyl phthalate (MEHP) in the peritoneal fluid[54]. Phthalate metabolites MBP, monobenzyl phthalate (MBzP), mono (3-carboxylpropyl) phthalate and four metabolites of DEHP were found to be higher in urine of women who subsequently delivered PTB[55]. Thomsen *et al*[56] reported that women exposed to MEP

**Table II.** Solvent exposure and female reproduction and pregnancy outcome

| Exposure | Effects |
|---|---|
| Exposure to organic solvents | (*i*) Risk of congenital malformations in offspring of male painters, risk of LBW[42]<br>(*ii*) Pregnancy complications, developmental delays and neurobehavioural difficulties in children whose mother exposed to organic solvents[43]<br>(*iii*) Reduced fertility (female workers in shoe manufacturing)[45] |
| Exposure to benzene and work stress | Decline birth weight[44] |
| Exposure to benzene or aromatic solvents during pregnancy | Higher risk of PTB or a decline in biparietal diameter growth, while no conclusion for other pregnancy outcomes[46] |
| Gasoline inhalation- petrol pump female workers | Increases menstrual disorders[47] |
| Women exposed to $CS_2$ | Menstrual disorders, early menopausal age and disturbances in neurohormonal system[48] |
| Paternal exposure to $CS_2$ | Risk of miscarriages[49] |

$CS_2$, carbon disulphide

**Table III.** Phthalate exposure and female reproduction and pregnancy outcome

| Exposure | Effects |
|---|---|
| Phthalates exposure on reproductive outcomes and children health | (*i*) Affect LH, free testosterone, sex hormone-binding globulin and anogenital distance and thyroid function. (*ii*) Urinery phthalates higher in pubertal gynecomastia individuals, girls with thelarche and precocious puberty[51] |
| Level of phthalates in thelarche and control individuals | High levels of phthalates (dimethyl, diethyl, dibutyl and DEH) and its metabolite mono-(2-ethylhexyl) phthalate in thelarche patients[52] |
| DEHP metabolite, MBP and MEP exposures during pregnancy | Linked with prenatal sex steroid hormone concentrations but sex steroid hormone levels not associated with infant reproductive outcome[53] |
| DEH and its metabolite, MEHP in endometriosis | Women with endometriosis had higher plasma level of DEHP, and 92.6% had detectable level of DEHP and MEHP in the peritoneal fluid[54] |
| Phthalate metabolites MBP, MBzP, mono (3-carboxylpropyl) phthalate and four metabolites of DEH phthalate urinary levels | Higher phthalates urinary concentrations of women who delivered PTB[55] |

MEHP, monoethyl hexyl phthalate; DEHP, di-2-ethylhexyl phthalate; MBP, monobutyl phthalate; DEH, di-2-ethylhexyl; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; LH, luteinizing hormone

but not MBP, MBzP and MEHP were associated with longer TTP. The data suggest adverse effects of some of the phthalates and their metabolites on female reproduction and pregnancy outcome.

**Stress**

Women may face physical and mental stress which may affect reproduction. Hjollund *et al*[57] determined the psychological stress during each menstrual cycle among couples who were first time attempting to concieve. No positive association was found between stress and serum concentration of follicle-stimulating hormone, LH, inhibin B, testosterone or estradiol. It has been reported that maternal mental health in pregnancy can impact on foetal development[58]. The imprinted genes, insulin-like growth factor 2 (IGF2) and H19, are involved in foetal growth, and both are regulated by DNA methylation. These findings suggest that maternal anxiety in pregnancy is related with decreased IGF2/H19 imprinting control region (ICR) DNA methylation in progeny at birth, mainly in female, LBW neonates. ICR DNA methylation may have association with poor maternal mental health and adverse birth outcomes. Earlier, Vrekoussis *et al*[59] have reported that adverse prenatal stimuli, of either maternal or foetal origin, acting on the developing embryo *in utero*, can lead to the developmental disorders. These include PTB, LBW and the development of several adult diseases from the metabolic syndrome to several neurodevelopmental disorders. Women with depression are more likely to have caesarean delivery, preterm labour, anaemia, diabetes, preeclampsia or hypertension[60]. Maternal depression was also associated with adverse foetal outcomes such as foetal abnormalities, foetal growth restriction and foetal death. These studies suggest that maternal depression has adverse effect on mother and foetus.

**Alcohol/caffeine use**

Excess consumption of alcohol during pregnancy by women may be associated with offspring developmental delays and behavioural changes. Ornoy and Ergaz[61] observed that the effect of alcohol on the developing foetus was dose dependent. They reported that after very high chronic doses of alcohol, there were 6-10 per cent chances of developing foetus to have foetal alcoholic syndrome (FAS) as revealed by prenatal and postnatal growth deficit, mental retardation, specific craniofacial dysmorphic features, behavioural changes *etc*. Lower chronic doses of alcohol also have a risk of 'alcoholic effects' demonstrated by slight intellectual impairment, behavioural changes and growth disturbances. Alcohol use during pregnancy is related with health complications that adversely affect the mother and foetus; no level of alcohol intake during pregnancy is reported to be safe[62]. There are inconsistent data on the foetal well-being due to dietary caffeine consumption during pregnancy, especially at levels of 300 mg/day or higher[63]. Although it is difficult to assess the threat of spontaneous abortion with caffeine use, most of the data do not support an elevated risk of adverse fertility, pregnancy or neurodevelopmental consequences with respect to 300 mg/day or less caffeine consumption. Gaskins *et al*[64] investigated the relation between pre-pregnancy caffeine and caffeinated beverage consumption and risk of spontaneous

abortion. They found that coffee consumption at levels ≥4 servings/day was associated with increased risk of spontaneous abortion. The data on caffeine use and female reproduction are inconclusive and needs more studies to confirm the reported findings.

**Tobacco smoking/chewing**

Shiverick and Salafia[65] reviewed the effects of constituents of tobacco and smoking on ovarian, uterine and placental tissues. They reported an adverse effect of smoking on ovarian function which was dose dependent, whereas more reversible effects were seen in implantation and ongoing pregnancy. Smoking may alter fertility potential through effects on uterine-fallopian tube functions that mediate gamete and conceptus transport. The increased miscarriage rate among mothers who smoke may be related to direct effects of nicotine, cadmium and polycyclic aromatic hydrocarbons (PAHs) on trophoblastic invasion and proliferation[65]. Sapra *et al*[66] reported that female smoking elevated TTP while links with male smoking were ambiguous. Detrimental effects of prenatal tobacco smoking on foetal growth and infant weight have been reported, and one of the mechanisms behind this association is variation in epigenetic programming[67]. Maternal smoking was observed to be inversely related with insulin-like growth factor II differentially methylated region (IGF2DMR) methylation in newborns, which might be one of the mechanisms through which smoking affect foetal growth. Salama *et al*[68] evaluated the effects of environmental tobacco smoke exposure during pregnancy on neonates. The percentage of full-term babies in non-exposed women was 72 per cent as compared to 67 per cent in exposed group. The weight of newborn was significantly reduced, and neuron-specific enolase (NSE) and soluble E-cadherin (sE-cadherin) were significantly increased in exposed group. The increased morbidity in the neonates of the exposed group could be attributed to cessation of breast feeding and increased NSE.

England *et al*[69] reported that mean birth weight was reduced by 39 and 190 g in snuff users and smokers, respectively. Further, snuff usage was related with elevated to the risk of PTB and preeclampsia. Baba *et al*[70] suggested that snuff users and smokers in early pregnancy elevated risks of SGA births, and smoking cessation in early pregnancy was linked with a larger reduction in risk than smoking cessation at later in pregnancy (Table IV).

Consumption of smokeless tobacco in pregnant women showed three-fold higher risk of stillbirth and a two- to three-fold elevated risk in LBW babies[71]. England *et al*[72] reported that using smokeless tobacco was not significantly related with PTB, hypertension or placental abruption while the mean weight of infants

**Table IV.** Personnel habits and female reproduction and pregnancy outcome

| Exposure | Effects |
|---|---|
| Prenatal very high doses of alcohol | 6-10% of developing foetus have risk of FAS[61] |
| Alcohol during pregnancy | Adversely affect mother and foetus; women consume excess alcohol are at risk for a child with FAS[62] |
| Tobacco and smoking | Adverse effect on ovarian function and reversible effects on implantation and ongoing pregnancy. Modify fertility affecting uterine-fallopian tube functions. Miscarriage due to effects of nicotine, Cd and PAHs on trophoblast[65] |
| Female smoking | Elevates TTP while links with male smoking are ambiguous[66] |
| Prenatal tobacco smoking | Toxic effects of prenatal tobacco smoking on foetal growth and infant weight[67] |
| ETS exposure during pregnancy | Risk of SGA and LBW among neonates[68] |
| Snuff uses during pregnancy | Reduced birth weight 39 g in snuff users and risk of preterm delivery and preeclampsia[69] |
| Snuff uses during early pregnancy | Risks of SGA births[70] |
| Smokeless tobacco use in pregnancy | 3-fold increased risk of stillbirth and 2-3 fold risk of LBW[71] |
| Prenatal smokeless tobacco use | Birth weight reduced 78 g while no association with PTB, hypertension or placental abruption of smokeless tobacco users[72] |
| Betel quid chewing during pregnancy | Adverse birth outcomes were five times higher[73] |
| Maternal areca nut chewing during pregnancy | Associated with birth weight loss, birth length reduction. Enhanced risk of LBW with simultaneous use of betel quid, cigarette and alcohol[74] |

FAS, foetal alcoholic syndrome; TTP, time to pregnancy; ETS, environmental tobacco smoke; PAHs, polycyclic aromatic hydrocarbons

born to smokeless tobacco users was lesser by 78 g. Yang *et al*[73] reported that maternal betel quid chewing and maternal age have adverse effect on birth outcomes. After adjusting for maternal age, adverse birth outcome was five times higher in betel quid-chewing women. They also reported that maternal areca nut chewing was significantly associated with birth weight loss and length reduction. The chances of male newborn rate were significantly lower among aboriginal women with a habit of betel quid chewing during pregnancy. Women using this substance showed 2.4-fold higher risk of LBW and 3.6-fold risk of full-term LBW[74] (Table IV).

**Pesticides and agrochemicals**

Some of the pesticides especially organochlorine have adverse effects on human health including reproduction which depend on the dose, duration and route of exposure. Heeren *et al*[75] reported that infants with birth defects were seven times more likely to be born to mother exposed to chemicals used in gardens and fields and were nearly twice to be born to mothers who were involved in dipping livestock used to prevent ticks. They were 6.5 times more likely to be born to mother who were using plastic containers (formerly contained pesticides) for water (Table V). Thakur *et al*[76] reported significantly higher adverse pregnancy outcomes such as spontaneous abortion (20.6/1000 live births) and premature births (6.7/1000 live births) were in the areas affected by heavy metal and pesticide pollution. Petrelli *et al*[77] found the ratio of abortions/pregnancies for pesticide applicators to be 0.27 and 0.07 for food retailers. Odd ratio for spontaneous abortion after adjusting for the age of wife and smoking habit of parents was 3.8-fold higher in the multiple logistic regression model and 7.6-fold with interaction effects'model than control (Table V). Certain pesticide exposure among men or women have higher risk of sperm abnormalities, decreased fertility, increased spontaneous abortion, deficit of male children, birth defects or foetal growth retardation[78]. Rogan and Chen[79] mentioned that exposure to bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT) might cause PTB retracting the benefit of lowering infant mortality from malaria at the doses that would be needed in malaria control. Salazar-García *et al*[80] also found an elevated risk of birth defects related with high occupational exposure to DDT. Bastos *et al*[81] reported higher levels of a metabolite of DDT (p,p'-DDE) in 100 per cent infertile women. A relationship between the decreased fecundability ratio and pesticide exposure has also been reported[82]. Parental occupation in agriculture might escalate the risk of congenital malformations such as birthmarks in the form of haemangioma, orofacial cleft and nervous system impairment and musculoskeletal defects.

**Table V.** Pesticides and female reproduction and pregnancy outcome

| Exposure | Effects |
|---|---|
| Exposure to agricultural chemicals | Birth defects seven times in offsprings of mother exposed to chemicals used in gardens and fields and twice to born to mothers involved in dipping livestock to prevent ticks and 6.5 times to born to mother using plastic containers (past used for pesticide) for water[75] |
| Water pollution due to heavy metals and high pesticide consumption | Spontaneous abortion (SAb), PTB and still births higher in area affected by heavy metal and pesticide pollution[76] |
| Pesticide applicators wives | SAb 3.8 times greater in multiple logistic regression model and 7.6 times with interaction effects' model[77] |
| Men or women exposed to pesticides | Risk for sperm abnormalities, decreased fertility, deficit of male children, SAb, birth defects or foetal growth retardation[78] |
| Exposure to DDT | DDT quantities that needed in malaria control might cause PTB[79]<br>Risk of birth defects with paternal exposure to DDT[80] |
| DDT exposure | p,p'-DDE detected in 100% infertile women[81] |
| Employment in agriculture | Employment in agriculture on TTP unequivocal; most studies suggest a connection between decreased fecundability ratio and pesticide exposure[82] |
| High level of organochlorines | Menstrual disorders and SAbs, and prolonged TTP, reduced birth weight, skewed sex ratio, altered age of sexual development[83] |
| Fungicide applicators spouses | Risk for miscarriages, foetal loss in the spouses of applicators[84] |

DDT, bis(4-chlorophenyl)-1,1,1-trichloroethane; DDE, dichlorodiphenyldichloroethylene

Organochlorines are predominant pollutants in humans and effects such as deterioration of semen quality, testicular cancer, menstrual cycle impairments, spontaneous abortions, and extended TTP, tilted sex ratio, reduced birth weight and altered age of sexual development are associated with higher concentrations of organochlorines[83]. Garry *et al*[84] found a significant increase in the risk for miscarriages and/or foetal loss and lower number of male children born in the spouses of applicators who used fungicides. The overall data suggest a need for awareness programme among workers about potential adverse effect of some of the pesticides on fertility and pregnancy outcome.

**Air pollutants**

Exposure to indoor air pollution due to burning of biomass fuel is a common major source of domestic pollution in low- and middle-income countries. Tielsch *et al*[85] assessed the health outcomes in early infancy due to exposure to biomass fuel and second-hand tobacco smoke (SHTS). Exposure to biomass fuel was found to be related with a 34 per cent increased incidence of respiratory illness, 49 per cent increased risk of LBW and 21 per cent increased risk of six-month infant mortality. Further, 45 and 30 per cent higher risks of underweight and stunting growth, respectively at six months among exposed infants were also reported. Ballester *et al*[86] mentioned that the prenatal exposure to traffic-related air pollution might also be associated with declined foetal growth. Exposure to traffic-generated air pollution during pregnancy increases the risk of preeclampsia and PTB[87]. The exposure to air pollutants was found to be related with LBW and PTB and mechanisms of air pollutants affecting foetus health are not fully established[88].

**Perfluoroalkyl and polyfluoroalkyl substances (PFASs)**

Perfluoroalkyl substances have been reported to be associated with alterations in menstrual cycle and fecundity. Lum *et al*[89] found an association between two perfluoroalkyl substances and variations in menstrual cycle length and diminished fecundity. Louis *et al*[90] assessed polyfluoroalkyl substances (PFASs) and pregnancy loss. Seven PFASs were quantified, and no significantly elevated levels of PFASs were found suggesting no association with pregnancy loss.

Perfluorooctanoic acid (PFOA) has applications in several industrial and consumer products. Wu *et al*[91] evaluated the exposure of women to PFOA and the potential hazards to neonates in an electronic waste recycling area. The PFOA concentration was higher in maternal serum from electronic waste recycling area. Maternal PFOA concentrations were significantly different between normal births and adverse birth outcomes *i.e*., premature delivery, term LBW and stillbirths. Kristensen *et al*[92] reported that daughters exposed to greater levels of PFOA *in utero* had 5.3 months delay in age of menarche compared with reference group of lower PFOA.

**Ionizing radiation**

It is established that exposure to ionizing radiation may have adverse effects on human reproduction that depend on dose, duration, intensity and frequency of radiation exposure. Ogilvy-Stuart and Shalet[93] reported that the response of the ovary to radiation exposure varied with age, dose and duration. An ovarian exposure to a dose of 4 Gy may cause 30 per cent of sterility in young women, but 100 per cent sterility occurs in women above 40 yr of age (Table VI). Based on experimental data, it has been suggested that ionizing radiation can induce DNA damage in the germ cells which can bring harmful effects in progeny, including miscarriage, LBW and congenital abnormalities[94]. However, no clear-cutproofs of such effects are seen in epidemiological studies.

A few reports are also available with regard to non-ionizing radiation and female reproductive health with inconsistent findings. Larsen *et al*[95] reported that high-frequency electromagnetic radiation was associated with LBW, but only for male newborns, and other outcomes were non-significant. Goldhaber *et al*[96] evaluated the risk of miscarriage among women who were using visual display terminals during the first trimester and found no significant risk for birth defects. Positive findings might be due to unmeasured factors such as poor ergonomic conditions or job stress. Lerman *et al*[97] found that exposure to short waves was associated with a significantly increased congenital malformations and LBW (Table VI). The available studies pointed out that ionizing radiation have harmful effect on reproduction, and more epidemiological studies are needed on non-ionizing radiation.

**Shift and night work**

Chau *et al*[98] reviewed data on the impact of night work on women's reproductive health. A diverse relationship exists between circadian rhythms and reproductive hormones, and this in turn may affect the women reproductive health. However, the impact of night work on female reproduction is inconclusive.

**Table VI.** Radiations and female reproduction and pregnancy outcome

| Exposure | Effects |
|---|---|
| Ionizing radiation | An ovarian exposure to 4 Gy may cause a 30% sterility in young women, 100% sterility in over 40 yr women[93] |
| Ionizing radiation | Induce DNA damage in germ cells, harmful effects in progeny, miscarriage, lower birth weight (LBW) and congenital abnormalities based on experimental data. No proofs of such effects in epidemiological studies[94] |
| High frequency electromagnetic radiation | Associated with LBW, but only for male newborns, other outcomes were statistically nonsignificant[95] |
| Women using visual display terminals in I$^{st}$ trimester | No significant elevated risk for birth defects and positive findings might be due to unmeasured factors *i.e.*, poor ergonomic conditions, job stress[96] |
| Exposure to shortwaves in women | Increased congenital malformations and LBW[97] |

Night shift work may elevate menstrual cycle disorder and endometriosis, but evidence is preliminary[99]. Albert-Sabater *et al*[100] found that nursing staff on the rotating shift did not demonstrate elevated risk of menstrual disorders. Night shift work led to a 50 per cent increase in risk of endometriosis and working more than half of shifts job at night doubled the risk[101].

There are certain other occupations that may be accountable for the adverse effects on female reproduction. Bello *et al*[102] reported the median TTP in administrative workers, domestic workers and teachers as 4, 12 and 3 months, respectively. After adjusting confounders, domestic workers had a significantly lower per-cycle probability of conception as compared to administrative workers. The effect of e-waste recycling exposure on birth outcomes has been studied[103]. Significantly elevated rates of stillbirth, LBW and lower APGAR (Appearance, Pulse, Grimace, Activity, Respiration) scores and birth weight were observed in exposed area births with higher cord blood lead level in neonates.

## Conclusion

It is well established that certain chemical exposures during pregnancy may have a profound impact on reproductive health. Some organochlorine chemicals such as di-chloro-diphenyl trichloromethane; metals such as lead, mercury; industrial pollutants such as dioxin, organic solvents, radiations and lifestyle-associated factors *i.e.*, tobacco smoking (active and passive) and excessive intake of alcohol had adverse effect on pregnancy and outcome[104]. The existing data support that working women have an elevated risk of undesirable reproductive outcomes, even though the data are inconclusive. Epidemiological studies are needed to find out the effects of those reproductive toxicants which have been proved to be toxic in animal models[104]. There is a need to educate the childbearing women to avoid exposure to the reproductive risk factors and increase the awareness among employers to take appropriate measures to reduce the workplace exposure.

***Financial support & sponsorship*:** The first author (SK) acknowledges the Indian Council of Medical Research (ICMR), Department of Science & Technology (DST), Department of Biotechnology (DBT), New Delhi, for financial assistance in the form of Ad-hoc research grants with respect to occupational, environmental, lifestyle factors and reproductive health.

***Conflicts of Interest*:** None.

## References

1. Rzymski P, Tomczyk K, Rzymski P, Poniedziałek B, Opala T, Wilczak M. Impact of heavy metals on the female reproductive system. *Ann Agric Environ Med* 2015; *22* : 259-64.
2. Desrosiers TA, Herring AH, Shapira SK, Hooiveld M, Luben TJ, Herdt-Losavio ML, *et al.* Paternal occupation and birth defects: Findings from the national birth defects prevention study. *Occup Environ Med* 2012; *69* : 534-42.
3. Slama R, Cordier S. Impact of chemical and physical environmental factors on the course and outcome of pregnancy. *J Gynecol Obstet Biol Reprod (Paris)* 2013; *42* : 413-44.
4. Olfert SM. Reproductive outcomes among dental personnel: A review of selected exposures. *J Can Dent Assoc* 2006; *72* : 821-5.
5. El-Badry A, Rezk M, El-Sayed H. Mercury-induced oxidative stress may adversely affect pregnancy outcome among dental staff: A cohort study. *Int J Occup Environ Med* 2018; *9* : 113-9.
6. Vejrup K, Brantsæter AL, Knutsen HK, Magnus P, Alexander J, Kvalem HE, *et al.* Prenatal mercury exposure and infant birth weight in the Norwegian mother and child cohort study. *Public Health Nutr* 2014; *17* : 2071-80.

7. Rodríguez-Villamizar LA, Jaimes DC, Manquián-Tejos A, Sánchez LH. Human mercury exposure and irregular menstrual cycles in relation to artisanal gold mining in Colombia. *Biomedica* 2015; *35* : 38-45.
8. Yang JM, Chen QY, Jiang XZ. Effects of metallic mercury on the perimenstrual symptoms and menstrual outcomes of exposed workers. *Am J Ind Med* 2002; *42* : 403-9.
9. Sallmén M, Lindbohm ML, Anttila A, Taskinen H, Hemminki K. Time to pregnancy among the wives of men occupationally exposed to lead. *Epidemiology* 2000; *11* : 141-7.
10. Selevan SG, Rice DC, Hogan KA, Euling SY, Pfahles-Hutchens A, Bethel J, *et al.* Blood lead concentration and delayed puberty in girls. *N Engl J Med* 2003; *348* : 1527-36.
11. Taylor CM, Golding J, Emond AM. Adverse effects of maternal lead levels on birth outcomes in the ALSPAC study: A prospective birth cohort study. *BJOG* 2015; *122* : 322-8.
12. Xie X, Ding G, Cui C, Chen L, Gao Y, Zhou Y, *et al.* The effects of low-level prenatal lead exposure on birth outcomes. *Environ Pollut* 2013; *175* : 30-4.
13. Jelliffe-Pawlowski LL, Miles SQ, Courtney JG, Materna B, Charlton V. Effect of magnitude and timing of maternal pregnancy blood lead (Pb) levels on birth outcomes. *J Perinatol* 2006; *26* : 154-62.
14. Vigeh M, Yokoyama K, Kitamura F, Afshinrokh M, Beygi A, Niroomanesh S. Early pregnancy blood lead and spontaneous abortion. *Women Health* 2010; *50* : 756-66.
15. Hertz-Picciotto I. The evidence that lead increases the risk for spontaneous abortion. *Am J Ind Med* 2000; *38* : 300-9.
16. Wu SY, Tian J, Wang MZ, Pan BJ, Lü HD, Wang ZM, *et al.* The effect of cadmium pollution on reproductive health in females. *Zhonghua Liu Xing Bing Xue Za Zhi* 2004; *25* : 852-5.
17. Pollack AZ, Ranasinghe S, Sjaarda LA, Mumford SL. Cadmium and reproductive health in women: A systematic review of the epidemiologic evidence. *Curr Environ Health Rep* 2014; *1* : 172-84.
18. Nishijo M, Nakagawa H, Honda R, Tanebe K, Saito S, Teranishi H, *et al.* Effects of maternal exposure to cadmium on pregnancy outcome and breast milk. *Occup Environ Med* 2002; *59* : 394-6.
19. Georgescu B, Georgescu C, Dărăban S, Bouaru A, Paşcalău S. Heavy metals acting as endocrine disrupters. *Anim Sci Biotechnol* 2011; *44* : 89-93.
20. Sen J, Chaudhuri AB. Effect of arsenic on the onset of menarcheal age. *Bull Environ Contam Toxicol* 2007; *79* : 293-6.
21. Ahmad SA, Sayed MH, Barua S, Khan MH, Faruquee MH, Jalil A, *et al.* Arsenic in drinking water and pregnancy outcomes. *Environ Health Perspect* 2001; *109* : 629-31.
22. Yang CY, Chang CC, Tsai SS, Chuang HY, Ho CK, Wu TN. Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in Northeastern Taiwan. *Environ Res* 2003; *91* : 29-34.
23. Kile ML, Cardenas A, Rodrigues E, Mazumdar M, Dobson C, Golam M, *et al.* Estimating effects of arsenic exposure during pregnancy on perinatal outcomes in a Bangladeshi cohort. *Epidemiology* 2016; *27* : 173-81.
24. von Ehrenstein OS, Guha Mazumder DN, Hira-Smith M, Ghosh N, Yuan Y, Windham G, *et al.* Pregnancy outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. *Am J Epidemiol* 2006; *163* : 662-9.
25. Ahmed S, Mahabbat-e Khoda S, Rekha RS, Gardner RM, Ameer SS, Moore S, *et al.* Arsenic-associated oxidative stress, inflammation, and immune disruption in human placenta and cord blood. *Environ Health Perspect* 2011; *119* : 258-64.
26. Favier M, Hininger-Favier I. Zinc and pregnancy. *Gynecol Obstet Fertil* 2005; *33* : 253-8.
27. Uriu-Adams JY, Keen CL. Zinc and reproduction: Effects of zinc deficiency on prenatal and early postnatal development. *Birth Defects Res B Dev ReprodToxicol* 2010; *89* : 313-25.
28. Eum JH, Cheong HK, Ha EH, Ha M, Kim Y, Hong YC, *et al.* Maternal blood manganese level and birth weight: A MOCEH birth cohort study. *Environ Health* 2014; *13* : 31.
29. Chen L, Ding G, Gao Y, Wang P, Shi R, Huang H, *et al.* Manganese concentrations in maternal-infant blood and birth weight. *Environ Sci Pollut Res Int* 2014; *21* : 6170-5.
30. Zota AR, Ettinger AS, Bouchard M, Amarasiriwardena CJ, Schwartz J, Hu H, *et al.* Maternal blood manganese levels and infant birth weight. *Epidemiology* 2009; *20* : 367-73.
31. Yang Y, Liu H, Xiang XH, Liu FY. Outline of occupational chromium poisoning in China. *Bull Environ Contam Toxicol* 2013; *90* : 742-9.
32. Pan X, Hu J, Xia W, Zhang B, Liu W, Zhang C, *et al.* Prenatal chromium exposure and risk of preterm birth: A cohort study in Hubei, China. *Sci Rep* 2017; *7* : 3048.
33. Xia W, Hu J, Zhang B, Li Y, Wise JP Sr., Bassig BA, *et al.* A case-control study of maternal exposure to chromium and infant low birth weight in China. *Chemosphere* 2016; *144* : 1484-9.
34. Jiang M, Li Y, Zhang B, Zhou A, Zheng T, Qian Z, *et al.* A nested case-control study of prenatal vanadium exposure and low birthweight. *Hum Reprod* 2016; *31* : 2135-41.
35. Ahamed M, Mehrotra PK, Kumar P, Siddiqui MK. Placental lead-induced oxidative stress and preterm delivery. *Environ Toxicol Pharmacol* 2009; *27* : 70-4.
36. Kippler M, Tofail F, Gardner R, Rahman A, Hamadani JD, Bottai M, *et al.* Maternal cadmium exposure during pregnancy and size at birth: A prospective cohort study. *Environ Health Perspect* 2012; *120* : 284-9.
37. Kwok RK, Kaufmann RB, Jakariya M. Arsenic in drinking-water and reproductive health outcomes: A study of participants in the Bangladesh integrated nutrition programme. *J Health Popul Nutr* 2006; *24* : 190-205.
38. Kaur K, Gupta R, Saraf SA, Saraf SK. Zinc. The metal of life. *Compr Rev Food Sci Food Saf* 2014; *13* : 358-76.

39. Michaluk A, Kochman K. Involvement of copper in female reproduction. *Reprod Biol* 2007; *7* : 193-205.
40. Xia W, Zhou Y, Zheng T, Zhang B, Bassig BA, Li Y, *et al.* Maternal urinary manganese and risk of low birth weight: A case-control study. *BMC Public Health* 2016; *16* : 142.
41. Remy LL, Byers V, Clay T. Reproductive outcomes after non-occupational exposure to hexavalent chromium, Willits California, 1983-2014. *Environ Health* 2017; *16* : 18.
42. Hooiveld M, Haveman W, Roskes K, Bretveld R, Burstyn I, Roeleveld N. Adverse reproductive outcomes among male painters with occupational exposure to organic solvents. *Occup Environ Med* 2006; *63* : 538-44.
43. Hannigan JH, Bowen SE. Reproductive toxicology and teratology of abused toluene. *Syst Biol Reprod Med* 2010; *56* : 184-200.
44. Chen D, Cho SI, Chen C, Wang X, Damokosh AI, Ryan L, *et al.* Exposure to benzene, occupational stress, and reduced birth weight. *Occup Environ Med* 2000; *57* : 661-7.
45. Sallmén M, Neto M, Mayan ON. Reduced fertility among shoe manufacturing workers. *Occup Environ Med* 2008; *65* : 518-24.
46. Protano C, Scalise T, Orsi GB, Vitali M. A systematic review of benzene exposure during pregnancy and adverse outcomes on intrauterine development and birth: Still far from scientific evidence. *Ann Ig* 2012; *24* : 451-63.
47. Ekpenyong CE, Davies K, Daniel N. Effects of gasoline inhalation on menstrual characteristics and the hormonal profile of female petrol pump workers. *J Environ Prot* 2013; *4* : 65-73.
48. Sieja K, von Mach-Szczypiński J, von Mach-Szczypiński J. Health effect of chronic exposure to carbon disulfide ($CS_2$) on women employed in viscose industry. *Med Pr* 2018; *69* : 329-35.
49. Patel KG, Yadav PC, Pandya CB, Saiyed HN. Male exposure mediated adverse reproductive outcomes in carbon disulphide exposed rayon workers. *J Environ Biol* 2004; *25* : 413-8.
50. Taskinen HK, Kyyrönen P, Sallmén M, Virtanen SV, Liukkonen TA, Huida O, *et al.* Reduced fertility among female wood workers exposed to formaldehyde. *Am J Ind Med* 1999; *36* : 206-12.
51. Jurewicz J, Hanke W. Exposure to phthalates: Reproductive outcome and children health. A review of epidemiological studies. *Int J Occup Med Environ Health* 2011; *24* : 115-41.
52. Colón I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ Health Perspect* 2000; *108* : 895-900.
53. Sathyanarayana S, Barrett E, Butts S, Wang C, Swan SH. Phthalate exposure and reproductive hormone concentrations in pregnancy. *Reproduction* 2014; *147* : 401-9.
54. Cobellis L, Latini G, De Felice C, Razzi S, Paris I, Ruggieri F, *et al.* High plasma concentrations of di-(2-ethylhexyl)-phthalate in women with endometriosis. *Hum Reprod* 2003; *18* : 1512-5.
55. Meeker JD, Hu H, Cantonwine DE, Lamadrid-Figueroa H, Calafat AM, Ettinger AS, *et al.* Urinary phthalate metabolites in relation to preterm birth in Mexico city. *Environ Health Perspect* 2009; *117* : 1587-92.
56. Thomsen AM, Riis AH, Olsen J, Jönsson BAG, Lindh CH, Hjollund NH, *et al.* Female exposure to phthalates and time to pregnancy: A first pregnancy planner study. *Hum Reprod* 2017; *32* : 232-8.
57. Hjollund NH, Bonde JP, Henriksen TB, Giwercman A, Olsen J; Danish First Pregnancy Planner Study Team. Reproductive effects of male psychologic stress. *Epidemiology* 2004; *15* : 21-7.
58. Mansell T, Novakovic B, Meyer B, Rzehak P, Vuillermin P, Ponsonby AL, *et al.* The effects of maternal anxiety during pregnancy on IGF2/H19 methylation in cord blood. *Transl Psychiatry* 2016; *6* : e765.
59. Vrekoussis T, Kalantaridou SN, Mastorakos G, Zoumakis E, Makrigiannakis A, Syrrou M, *et al.* The role of stress in female reproduction and pregnancy: An update. *Ann N Y Acad Sci* 2010; *1205* : 69-75.
60. Bansil P, Kuklina EV, Meikle SF, Posner SF, Kourtis AP, Ellington SR, *et al.* Maternal and fetal outcomes among women with depression. *J Womens Health (Larchmt)* 2010; *19* : 329-34.
61. Ornoy A, Ergaz Z. Alcohol abuse in pregnant women: Effects on the fetus and newborn, mode of action and maternal treatment. *Int J Environ Res Public Health* 2010; *7* : 364-79.
62. Centers for Disease Control and Prevention. Alcohol consumption among women who are pregnant or who might become pregnant – United States, 2002. *MMWR Morb Mortal Wkly Rep* 2004; *53* : 1178-81.
63. Morgan S, Koren G, Bozzo P. Is caffeine consumption safe during pregnancy? *Can Fam Physician* 2013; *59* : 361-2.
64. Gaskins AJ, Rich-Edwards JW, Williams PL, Toth TL, Missmer SA, Chavarro JE. Pre-pregnancy caffeine and caffeinated beverage intake and risk of spontaneous abortion. *Eur J Nutr* 2018; *57* : 107-17.
65. Shiverick KT, Salafia C. Cigarette smoking and pregnancy I: Ovarian, uterine and placental effects. *Placenta* 1999; *20* : 265-72.
66. Sapra KJ, Barr DB, Maisog JM, Sundaram R, Buck Louis GM. Time-to-pregnancy associated with couples' use of tobacco products. *Nicotine Tob Res* 2016; *18* : 2154-61.
67. Bouwland-Both MI, van Mil NH, Tolhoek CP, Stolk L, Eilers PH, Verbiest MM, *et al.* Prenatal parental tobacco smoking, gene specific DNA methylation, and newborns size: The generation R study. *Clin Epigenetics* 2015; *7* : 83.
68. Salama RH, Abdel-Aal Del D, EshraDKh, Nagieb S, Arief AF. Clinical and biochemical effects of environmental tobacco smoking on pregnancy outcome. *Indian J Clin Biochem* 2013; *28* : 368-73.
69. England LJ, Levine RJ, Mills JL, Klebanoff MA, Yu KF, Cnattingius S. Adverse pregnancy outcomes in snuff users. *Am J Obstet Gynecol* 2003; *189* : 939-43.

70. Baba S, Wikström AK, Stephansson O, Cnattingius S. Changes in snuff and smoking habits in Swedish pregnant women and risk for small for gestational age births. *BJOG* 2013; *120* : 456-62.

71. Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. *Respirology* 2003; *8* : 419-31.

72. England LJ, Kim SY, Shapiro-Mendoza CK, Wilson HG, Kendrick JS, Satten GA, *et al.* Effects of maternal smokeless tobacco use on selected pregnancy outcomes in Alaska Native women: A case-control study. *Acta Obstet Gynecol Scand* 2013; *92* : 648-55.

73. Yang MJ, Chung TC, Yang MJ, Hsu TY, Ko YC. Betel quid chewing and risk of adverse birth outcomes among aborigines in Eastern Taiwan. *J Toxicol Environ Health A* 2001; *64* : 465-72.

74. Yang MS, Lee CH, Chang SJ, Chung TC, Tsai EM, Ko AMJ, *et al*. The effect of maternal betel quid exposure during pregnancy on adverse birth outcomes among aborigines in Taiwan. *Drug Alcohol Depend* 2008; *95* : 134-9.

75. Heeren GA, Tyler J, Mandeya A. Agricultural chemical exposures and birth defects in the Eastern Cape province, South Africa: A case-control study. *Environ Health* 2003; *2* : 11.

76. Thakur JS, Prinja S, Singh D, Rajwanshi A, Prasad R, Parwana HK, *et al.* Adverse reproductive and child health outcomes among people living near highly toxic waste water drains in Punjab, India. *J Epidemiol Community Health* 2010; *64* : 148-54.

77. Petrelli G, Figà-Talamanca I, Tropeano R, Tangucci M, Cini C, Aquilani S, *et al*. Reproductive male-mediated risk: Spontaneous abortion among wives of pesticide applicators. *Eur J Epidemiol* 2000; *16* : 391-3.

78. Frazier LM. Reproductive disorders associated with pesticide exposure. *J Agromedicine* 2007; *12* : 27-37.

79. Rogan WJ, Chen A. Health risks and benefits of bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT). *Lancet* 2005; *366* : 763-73.

80. Salazar-García F, Gallardo-Díaz E, Cerón-Mireles P, Loomis D, Borja-Aburto VH. Reproductive effects of occupational DDT exposure among male malaria control workers. *Environ Health Perspect* 2004; *112* : 542-7.

81. Bastos AMX, Souza Mdo CBD, Almeida Filho GLD, Krauss TM, Pavesi T, Silva LED, *et al.* Organochlorine compound levels in fertile and infertile women from Rio de Janeiro, Brazil. *Arq Bras Endocrinol Metabol* 2013; *57* : 346-53.

82. Hanke W, Jurewicz J. The risk of adverse reproductive and developmental disorders due to occupational pesticide exposure: An overview of current epidemiological evidence. *Int J Occup Med Environ Health* 2004; *17* : 223-43.

83. Toft G, Hagmar L, Giwercman A, Bonde JP. Epidemiological evidence on reproductive effects of persistent organochlorines in humans. *Reprod Toxicol* 2004; *19* : 5-26.

84. Garry VF, Harkins M, Lyubimov A, Erickson L, Long L. Reproductive outcomes in the women of the red River Valley of the North. I. The spouses of pesticide applicators: Pregnancy loss, age at menarche, and exposures to pesticides. *J Toxicol Environ Health A* 2002; *65* : 769-86.

85. Tielsch JM, Katz J, Thulasiraj RD, Coles CL, Sheeladevi S, Yanik EL, *et al.* Exposure to indoor biomass fuel and tobacco smoke and risk of adverse reproductive outcomes, mortality, respiratory morbidity and growth among newborn infants in South India. *Int J Epidemiol* 2009; *38* : 1351-63.

86. Ballester F, Estarlich M, Iñiguez C, Llop S, Ramón R, Esplugues A, *et al.* Air pollution exposure during pregnancy and reduced birth size: A prospective birth cohort study in Valencia, Spain. *Environ Health* 2010; *9* : 6.

87. Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the South Coast air basin of California. *Environ Health Perspect* 2009; *117* : 1773-9.

88. Lee BE, Park HS, Kim YJ, Park EA, Hong YC, Ha EH. Air pollution exposure and health effects in fetus. *J Prev Med Public Health* 2004; *37* : 291-9.

89. Lum KJ, Sundaram R, Barr DB, Louis TA, Buck Louis GM. Perfluoroalkyl chemicals, menstrual cycle length, and fecundity: Findings from a prospective pregnancy study. *Epidemiology* 2017; *28* : 90-8.

90. Louis GM, Sapra KJ, Barr DB, Lu Z, Sundaram R. Preconception perfluoroalkyl and polyfluoroalkyl substances and incident pregnancy loss, LIFE study. *Reprod Toxicol* 2016; *65* : 11-7.

91. Wu K, Xu X, Peng L, Liu J, Guo Y, Huo X. Association between maternal exposure to perfluorooctanoic acid (PFOA) from electronic waste recycling and neonatal health outcomes. *Environ Int* 2012; *48* : 1-8.

92. Kristensen SL, Ramlau-Hansen CH, Ernst E, Olsen SF, Bonde JP, Vested A, *et al.* Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction. *Hum Reprod* 2013; *28* : 3337-48.

93. Ogilvy-Stuart AL, Shalet SM. Effect of radiation on the human reproductive system. *Environ Health Perspect* 1993; *101* (Suppl 2) : 109-16.

94. Jacquet P. Sensitivity of germ cells and embryos to ionizing radiation. *J Biol Regul Homeost Agents* 2004; *18* : 106-14.

95. Larsen AI, Olsen J, Svane O. Gender-specific reproductive outcome and exposure to high-frequency electromagnetic radiation among physiotherapists. *Scand J Work Environ Health* 1991; *17* : 324-9.

96. 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.

97. Lerman Y, Jacubovich R, Green MS. Pregnancy outcome following exposure to shortwaves among female physiotherapists in Israel. *Am J Ind Med* 2001; *39* : 499-504.

98. Chau YM, West S, Mapedzahama V. Night work and the reproductive health of women: An integrated literature review. *J Midwifery Womens Health* 2014; *59* : 113-26.

99. Fernandez RC, Marino JL, Varcoe TJ, Davis S, Moran LJ, Rumbold AR, *et al.* Fixed or rotating night shift work undertaken by women: Implications for fertility and miscarriage. *Semin Reprod Med* 2016; *34* : 74-82.

100. Albert-Sabater JA, Martínez JM, Baste V, Moen BE, Ronda-Perez E. Comparison of menstrual disorders in hospital nursing staff according to shift work pattern. *J Clin Nurs* 2016; *25* : 3291-9.

101. Marino JL, Holt VL, Chen C, Davis S. Shift work, hCLOCK T3111C polymorphism, and endometriosis risk. *Epidemiology* 2008; *19* : 477-84.

102. Bello B, Heederik D, Kielkowski D, Wilson K. Increased time-to-pregnancy is associated with domestic work in South Africa. *Reprod Health* 2016; *13* : 106.

103. Xu X, Yang H, Chen A, Zhou Y, Wu K, Liu J, *et al.* Birth outcomes related to informal e-waste recycling in Guiyu, China. *Reprod Toxicol* 2012; *33* : 94-8.

104. Kumar S. Occupational, environmental and lifestyle factors associated with spontaneous abortion. *Reprod Sci* 2011; *18* : 915-30.

*For correspondence*: Dr Sunil Kumar, Division of Reproductive & Cyto-toxicology, ICMR-National Institute of Occupational Health, Meghani Nagar, Ahmedabad 380 016, Gujarat, India
e-mail: sunilnioh@gmail.com