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Public Health Concerns of Environmental Exposure Connected with Female Infertility

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Abstract

This study reviewed recent articles on the prevalence and risk exposure of pollutants connected with female sterility. Occupational and regular exposure to metals and other chemicals causes oxidative stress, which causes hormonal imbalance and results in cell membrane damage, cell apoptosis, protein, lipid, and nucleic acid damage, reduced oocyte growth and development, increased mRNA in the anterior pituitary, poor oocyte quality, poor reproductive outcome, damage DNA, embryo fragmentation, implantation failure, abortion, and ovarian cancer. This study revealed an association between environmental contaminants and unexplained infertility, women with unexplained infertility have decreased ovarian sensitivity to gonadotropins, resulting in higher circulating gonadotropin levels, including higher mean serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Aside from the effects of environmental contaminants on female infertility, they may also increase the risk of spontaneous abortion, stillbirths, premature delivery, gestational diabetes mellitus, pregnancy hypertension, preeclampsia, premature rupture of membranes, intrauterine growth restriction, low birth weight, and harm to the growing baby, resulting in foetal abnormality and congenital disabilities. Heavy metal risk exposures should be decreased to a minimum or zero level to treat female infertility.

Keywords: *Fertility, metal mixture, endocrine disruptors, prevalence, endometriosis*

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Introduction

Female infertility is a common condition of the reproductive system that often lead to the failure of a woman to get pregnant after years of regular and unprotected sex and without birth control (Wang *et al.*, 2019; Borght & Wyns, 2018). The WHO defined infertility as the failure of a couple who are active sexually to reproduce within the period of 1 year or more. The WHO reported that over 180 million couples face the costs of infertility/sterility (WHO, 2018). An estimate of 8-15% of couples of childbearing age suffers infertility globally (Sun *et al.*, 2019; Henriques *et al.*, 2019). Another report by WHO posited from 1990 to 2010, the total burden of women sterility from 190 countries is similar in estimated levels and trends (Ma *et al.* 2018).

There are two common types of infertility namely; primary and secondary infertility. Primary infertility/sterility is the inability of a woman to get pregnant after twelve months of sex devoid of birth control methods while secondary infertility is referred to as the inability to conceive after an initial pregnancy. Secondary infertility is a common condition around the globe, usually caused by unsafe abortions, poor maternity care and reproductive tract infections (if left unattended may damage the fallopian tube causing irreversible tubal blockages (Inhorn & Patrizio 2015). Adeoye *et al.* (2018) estimated that 48 million women from South Asia, Sub-Saharan Africa, North Africa, the Middle East, Central Europe and Central Asia suffers the highest.

The causes of infertility include endometriosis, polycystic ovary syndrome, ovulation dysfunction, abnormal uterus or fallopian tube, primary ovarian insufficiency, pelvic adhesions, pelvic inflammatory diseases, tubal blockage, tuboperitoneal abnormalities, myomas distorting the uterine cavity, congenital uterine anomalies, cystic fibrosis and others (Hung *et al.*, 2016; Wang *et al.*, 2019). Environmental contaminant exposure could lead to all these causes mentioned acting as a precursor to causes of female infertility.

Infertility is recognised by WHO as a public health concern globally which has generated into grave health challenge, especially in developing countries. Over 186 million people contend with the problem of infertility globally, with majority from developing countries (Borght and Wyns, 2018). One out of seven women in the western countries suffers from infertility as against one out of four women in the developing countries (Borght and Wyns 2018). The total Infertility rate has been increasing since 1990. A careful investigation of 195 countries from 1990 to 2017 showed that infertility increased by 0.370% per year for females of reproductive age. This was found highest in the Sub-Saharan Africa, North Africa, Central and Eastern Europe, South and Central

Asia, and Middle East regions which may have reached 30% (Mascarenhas *et al.*, 2012). Notably, growing older is accompanied with decrease in fertility rate. A study showed that women of within the ages of 35-39 had the highest prevalence rate while age group within 15-19 had the lowest (Sun *et al.*, 2019).

Effect of Environmental Contaminant on Female Infertility

In females, exposures to environmental toxicants revealed that its effect on the female reproductive functions ends in infertility (Gopinath, 2013). Persistent organochlorine pollutants, increased perfluorochemicals levels, phthalate esters, and intra-uterine exposure to cigarette smoke are environmental factors that causes endometriosis. These factors caused induced oxidative stress, varying hormonal homeostasis, or by changing immune responses (Dai *et al.*, 2018). This review will focus more on endocrine-disrupting chemicals and heavy metals. Environmental chemicals, known as endocrine disruptors, have the capacity to mimic, block or modulate the endocrine system through the interaction with steroidal receptors. Recently, ubiquitous environmental contaminants have been proposed to have a role in the prevalence of endometriosis (Barbosa *et al.*, 2011). Several studies suggested that women occupationally and environmentally exposed to individual heavy metals such as Lead, Mercury, Aluminium, Manganese, Cadmium, Arsenic or mixtures of metals had reduced fertility, high prevalence and incidence rates of menstrual disorders (Osmel and Jose 2020). Growing data shows an association between heavy metals and unexplained infertility. Studies reveal higher levels of heavy metals in urine, hair and blood of women with unexplained infertility than fertile ones (Henriques *et al*., 2019).

i. Endocrine-disrupting chemicals (EDCs) and female reproductive health

An endocrine disruptor is defined as "an exogenous chemical, or blend of chemicals, that can impede with any aspect of hormone action. An estimate of 1000 chemicals is recognised as potential endocrine disruptors (Street *et al*., 2018). Endocrine-disrupting chemicals are chemicals that have the ability to alter or modify the endocrine system of wildlife and humans at ecologically relevant thresholds. There are everyday chemicals that exhibit endocrine-disrupting features in both animals and humans, which result in infertility, improper hormone production, subfertility, menstrual cycle abnormalities, and estrous, anovulation, and early reproductive senescence (Rattan *et al*., 2017). They include plasticisers as bisphenol A, phthalates, flame retardants, industrial chemicals including alkylphenols, heavy metals and dioxins, air pollutants such as polycyclic aromatic hydrocarbons, and pesticides. Smith *et al*., (2013) demonstrated that exposure to propylparaben (PP) a potential endocrine disruptor could lead to reduced ovarian reserve and increased ovarian aging among women.

Endocrine-disrupting chemicals can activate, block, or alter synthesis and degradation of hormone by binding to endocrine receptor, resulting in irregular hormonal signals that could increase or inhibit normal endocrine function (Street *et al*., 2018). EDCs influence hormonal balance and thereby disrupting the function ovarian function, including fertility (Gopinath, 2013). Current studies point to EDC-induced reproductive disorders have been linked with DNA modification (mostly DNA methylation). Investigation by Petro et al., (2012) revealed that human follicular fluid exposed to EDCs and Polychlorinated Biphenyls (PCBs) decreased IVF successes and development of oocyte into embryos of high-quality.

a. Polychlorinated Biphenyls (PCB)

Polychlorinated biphenyls are environmental toxin which often comprise of endocrine disrupting activity. PCBs are stable, lipophilic compounds that build up in the surroundings and in food chains. In females, PCB has been connected with reproductive disorder. In one in vitro study, data showed PCB congeners can lead to an increase in mRNA at 0.01– 100 μM and then reduced peptide levels of gonadotropin releasing hormone (GnRH) in hypothalamic mouse cells and also caused increase apoptosis in hypothalamic GnRH containing cells in a non-monotonic manner (Bell, 2014). Studies has shown that reduced fertility in women and animals is related with exposure to PCB. In women consuming contaminated fish, shorter menstrual cycles and gestation was related with moderate to high PCB exposure (Craig *et al*., 2011; Dallaire *et al*., 2013). Kezios *et al*. (2012) established that mono-ortho and di-ortho exposure to PCB is connected with reduced gestational. Also, PCBs exposure (12.5–50 mg/kg) showed increased apoptosis of cumulus cells, inhibits parthenogenetic activation and maturation of mouse oocytes (Liu *et al.*, 2008), and affects *in vitro* fertilization in females.

b. Bisphenol A (BPA)

BPA is highly produced chemical extensively used in the manufacture of various consumer products such as toilet papers, envelopes, printer ink, processed foods, toys, cell phones, polycarbonate plastics, dental fillings, CDs, DVDs, medical devices, paint, epoxy resin liners of canned foods and thermal receipts (Mínguez-Alarcón and Gaskins, 2017; Rashtian *et al.*, 2019). BPA has endocrine disrupting properties with the capability to impinge on multiple hormonal pathways. It also has the capacity to bind to estrogen receptors and initiate cellular responses similar to those caused by estradiol (Street *et al., 2018)*.

Experimental studies have shown association between BPA and abnormal changes in women reproductive system. Markey *et al.* (2005) exposed female mice utero to BPA via pumps implanted into pregnant dams, the result showed exposure to BPA causes alteration in development of female reproductive organs. Exposure to BPA revealed elevated expression of endometrial ER-α, reduced volume of endometrial lamina propria, decreased progesterone receptor and vaginal weight (Rashtian *et al*., 2019). Hormone synthesis (progesterone and estradiol), mRNA and protein expression of cholesterol side-chain cleavage enzyme (CYP11A), 3β-hydroxysteroid dehydrogenase (HSD), and aromatase (CYP19A1) are also altered by BPA (Mansur *et al*., 2016; Rashtian *et al.*, 2019). Several investigations have found BPA exposure to be connected with women having PCOS. Cross-sectional survey between women suffering from PCOS (n = 71) and those without PCOS that were matched by age and BMI (control group n = 100). The outcome revealed higher BPA level in the blood of women with PCOS than BPA levels in the blood of women without PCOS (Kandaraki *et al*., 2011).

Furthermore, BPA exposure can alter reproductive outcome in infertile women undergoing IVF treatment. Ehrlich *et al*. (2012) associated increased BPA with decreased oocytes retrieved, less mature metaphase II oocytes, less normal fertilized oocytes, reduced serum E2 levels, and tendency of having lower blastocyst formation. Similar study conducted by Mok-Lin *et al.* (2010) reported that 84 women who participated in 112 IVF cycles showed relationship between high urinary BPA and poor ovarian response, which was revealed by less oocytes retrieved per cycle and lower serum E2 levels. Hence, elevated urinary BPA can result to decrease oocyte maturation and reduction in female fertilization. Additionally, frequent loss of pregnancy has been linked to exposure to BPA exposure. A case control study in eastern China, showed higher BPA levels in women with recurring miscarriages than women not exposed to BPA (Shen *et al*., 2015).

c. Triclosan

Triclosan is a lipid emulsifiable phenolic composite with wide spectrum antibacterial characteristics (Mínguez-Alarcón and Gaskins 2017). It is used in personal care products such as toothpaste, air fresheners, anti-bacterial soap, deodorants, surgical scrubs, mouthwash, sanitizers and sutures (Fang *et al*., 2010), and their usage portend their absorption (Yang *et al*., 2015). Triclosan functions as an anti-estrogen or anti-androgen with likely undesirable effects on reproductive outcomes (Mínguez-Alarcón and Gaskins, 2017).
Usage of triclosan has been connected with female infertility and abnormal reproductive effect and reduced ovary weight (Velez *et al*., 2015). Similarly, subcutaneous administration of triclosan (18 and 27 mg/day) into uteri of adult rats result to low number of implantation sites (Crawford and Decatanzaro, 2012). Also, reduced gravid uterine weights were observed when rats were exposed to triclosan (30-600 mg/kg per day) orally, reduced prolactin, estradiol, progesterone and testosterone levels were reported. (Feng *et al*., 2016).

d. Parabens

Parabens is a bunch of alkyl esters of p-hydroxybenzoic acid that is utilized as anti-microbial preservatives in cosmetics, personal care products, pharmaceuticals and foods (Rattan *et al.*, 2017; Andersen, 2008; National Toxicology program, 2005). Parabens exposure occurs through ingestion, inhalation, or dermal absorption. Parabens are chemicals that interrupt endocrine functioning, affecting female fertility rate. Studies have described parabens to have binding ability with estrogen receptor, however, rodent toxicity studies described the effects parabens have on female reproductive functioning, as well as reduced ovarian weights and cause changes in histopathology of ovaries (Taxvig *et al*., 2008; Vo *et al*., 2010; Smith *et al*., 2013; Mínguez-Alarcón and Gaskins, 2017). Decreased counts of antral follicle in humans have been connected with elevated levels (87.8–727 μg/L) of propylparaben (Smith *et al*., 2013). A study by Japanese researchers revealed that short menstrual cycles in females were connected to high urinary estrogen equivalent to total and butyl paraben concentrations (Nishihama *et al*., 2016). Furthermore, subcutaneous administration of parabens (6-210 mg/kg) in ovariectomized mice caused increased uterine weight (Lemini *et al*., 2003), also, isobutylparaben (about 4.36 mg/L per day) increased dam uterine weights in rats (Kawaguchi *et al*. 2009). Additionally, in women, high urine

butylparaben were linked with lowered estradiol and reduced estradiol/progesterone ratio (Aker *et al*., 2016; Rattan *et al*., 2017). Exposure to paraben may lead to diminished ovarian reserve, contribute to ovarian aging among women at an infertility clinic and affect pregnancy adversely. Taxvig *et al*. (2008) reported that pregnant rats subcutaneously exposed to parabens showed a decrease in ER-β expression in the ovaries of the female foetus. However, no change was observed in levels of ovarian estradiol or ovarian histopathology (Smith *et al*., 2013). Table 1 summarizes the different endocrine-disrupting chemicals and it effects in female infertility.

Table 1: Endocrine disrupting chemicals effect on females

Endocrine Disruptor	Effect on females	Model	Reference
Polychlorinated biphenyls	i. Increase apoptosis in cells, mRNA and peptide levels of GnRH in the hypothalamic.	Mouse	Bell, 2014.
	ii. Reduced *in vitro* fertilization success rate		
	iii. Decreased development of oocyte into high-quality embryos.		
	iv. Shorten menstrual cycles	Mice	Petro *et al*. 2012
	v. Decrease in gestational length	Women	Craig *et al*. 2011
	vi. Inhibit maturation and activation of oocytes.	Mouse	Liu *et al*. 2014
Parabens	i. Decrease ovarian weights.	-	Mínguez-Alarcón and Gaskins 2017
	ii. Causes changes in histopathology of ovaries.		
	iii. Lowers antral follicle counts.	Human	Smith *et al*. 2013
	iv. Diminish ovarian reserve and contribute to ovarian aging.	women	Nishihama *et al*. 2016
	v. Reduce menstrual cycles	Human	Lemini *et al*. 2003 and
	vi. Increase uterine weight	Mice	Kawaguchi *et al*. 2009
	vii. Decrease ER-β expression in the ovaries	Female fetuses	Taxvig *et al*. 2008
Triclosan	i. Lowered ovarian weight in adult.	Female mice	Fang *et al*. 2015
	ii. Decreased level of sex steroid hormone levels.		
	iii. Reduced estradiol, prolactin, progesterone and testosterone levels.	Adult Rat	Feng *et al*. 2016
Heavy metals	i. Mimic estrogen properties in uterus.	-	Rehman *et al*. 2017
	ii. Interferes with the ovarian steroidogenic pathway at more than one site.		
	iii. Increased uterine weight.	Rats and pregnant dams	Sengupta *et al*. 2015
	iv. Decreased serum estradiol levels.		Rzymski *et al*. 2015
	v. May contribute to unexplained female infertility.	Rat	Weller *et al*. 2017
	vi. Decreased prolactin release	Mice	Maues et al. 2015

ii. Heavy Metals and Female Infertility

The resulting effect of heavy metals on female reproductive health is of a great burden. Human exposures to heavy metals usually happen occupationally, environmentally, or through dietary intake (Ma *et al*., 2018, Amaya *et al*., 2013). Several studies suggested that women occupationally and environmentally exposed to individual heavy metals such as Lead, Mercury, Aluminium, Manganese, Cadmium, Arsenic or mixtures of metals had reduced fertility, high prevalence and incidence rates of menstrual disorders (Osmel and Jose 2020; Maeda et al., 2019, Susko *et al*., 2017; Sengupta *et al*., 2015; Sengupta and Dutta 2018; Henriques *et al*., 2019). Exposure to heavy metals could also be associated with amenorrhoea, Polycystic Ovary Syndrome, premenstrual syndrome, early menopause, dysmenorrhoea (menstrual pain), endometriosis, benign breast disorders and galactorrhoea, these can be related to female infertility (Bjorklund *et al*., 2019).

Heavy metals even at a low level of exposure may have deleterious effects on female fertility (Lee *et al*., 2020; Osmel and Jose 2020). Latest study showed mixtures of heavy metals may affect female fertility. An investigation carried out revealed positive association with self-reported infertility and low level of blood lead and cadmium (Pb = 0.50µg/dL and Cd = 0.26µg/L) after adjusting for confounding factors (odds ratio (OR) for Pb per two-fold increase in blood metal levels = 2.60; 95% confidence interval (95% CI), 1.05–6.41 and OR for cadmium per two-fold increase = 1.84; 95% CI, 1.07–3.15) (Lee *et al*., 2020). Heavy metals even at a low level of exposure may have deleterious effects on female fertility (Osmel and Jose 2020). Growing data shows an association between heavy metals and unexplained infertility. Studies reveal higher levels of heavy metals in urine, hair and blood of women with unexplained infertility than fertile ones (Henriques *et al*., 2019; Altunkaynak *et al*., 2016). Although very few studies have examined the relationship between heavy metal exposures and female fertility outcomes. Heavy metals such as aluminium, lead, manganese, cadmium, mercury and arsenic have reproductive toxicity (Sengupta *et al*., 2015). Studies postulate heavy metal exposure increases the risk of spontaneous abortion, miscarriage, fetal malformation, placental insufficiency, and premature birth (Rzymski *et al*. 2015, Sengupta *et al*., 2015, Susko *et al*., 2017). A study by Quansah *et al*. (2015) found significant association between spontaneous abortion with high levels of As in drinking water and blood Pb levels (As in drinking water OR: 1.98, 95% CI: 1.27, 3.10 and blood Pb levels OR: 1.8, 95% CI: 1.1, 3.1 for every 5µg/dL increase in blood Pb).

Furthermore, women with unexplained infertility have decreased ovarian sensitivity to gonadotropins, resulting in higher circulating gonadotropin levels, including higher mean serum FSH and luteinizing hormone (LH) levels (Lei *et al*., 2015). Asides from heavy metals effects on infertility in females, exposure to heavy metals could also increase the risk of suffering spontaneous abortion, stillbirths, premature delivery, gestational diabetes mellitus, pregnancy hypertension, preeclampsia, premature rupture of membranes, intrauterine growth restriction, low birth weight, harm the growing baby leading to foetal abnormality and congenital disabilities such as cleft lip/palate and other pregnancy complications in pregnant women (Osmel and Jose 2020; Cheng *et al*., 2017; Maeda et al., 2019; Itai *et al*., 2004; Kumar, 2018; Yorifuji *et al*., 2017).

i. Lead (Pb) effect on female reproduction

Lead is a heavy metal that is both harmful to human and animal's health. Industrial activities like burning of fossil fuel, mining, production of lead-acid batteries, pigments, paints and various manufacturing processes contribute greatly to Pb increase in the environment (Rehman *et al*., 2017). The effect of Pb could result in impairment of the female reproductive system to function properly.

To establish the correlation between heavy metals and female infertility, the Pb level in 33 infertile women and 32 fertile women were compared. Endometrial samples were collected at 20–24 days of the menstrual cycle by endometrial biopsies, and Pb concentrations in the endometrium were then measured. It was discovered that Pb was 15% in endometrial samples of infertile women, but only 3% in endometrial samples of fertile women. Thus, it was revealed that Pb exposure level could induce reproductive toxicity and result in women becoming infertile.

New studies also have shown that lead could be harmful even at its low threshold exposures. In a study, Chang *et al*. (2006) compared women with blood Pb level ≤2.5 µg/dL and women with blood lead level >2.5 µg/dL, the result revealed that infertile women had greater blood Pb level than controls (3.55 vs 2.78 µg/dL). Thus, Pb was associated with a threefold elevated risk for infertility, after adjusting for various confounding factors. These findings suggest an important role of even low blood lead level in the risk of infertility in women (Chang *et al*., 2006). An investigation performed by Rahman *et al*. (2013) on blood Pb levels in females with unexplained infertility ranging from 18-40 years revealed the mean blood level of lead was significantly higher in

case group than that in control group (130.0±45.2 vs. 78.3±36.4µg/L, ($p<0.001$).

A study by Tang and Zhu (2003) reported that female workers exposed to Pb were found to have significant elevated blood lead level than in control resulting in polymenorrhea, prolonged and abnormal menstruations and hypermenorrhea. Likewise, another survey conducted in women undergoing IVF treatments in Taranto, Italy, an environment recognised as heavy metal contaminated area, by industrial processes found decreased number of mature oocytes retrieved, significant rise of follicular fluid concentration of several heavy metals, including Pb in women from Taranto. Additionally, recent study by Lee *et al.* (2019) revealed that lead exposure was positively connected with elevated serum FSH concentrations ($\beta = 2.929$, $p = 0.019$) in postmenopausal women. High levels of serum FSH could indicate poor ovarian function. Therefore, lead exposure result in decrease female fertility via reduced oocytes number, menstrual cycle disturbances, delayed conception time, changing hormonal production, circulation, affecting pregnancy, low gestational weight, premature birth and miscarriages (Kumar 2018; Lee *et al*., 2020).

ii. **Mercury (Hg) effect on female reproduction**

Mercury has been identified as a neurotoxicant as well as immunotoxic and designated by the WHO as one of the ten most dangerous chemicals to public health (Bjørklund *et al*., 2017). Methyl mercury exposure even at low level can have a reproductive toxicity. A study carried out by Maeda et al. (2019) showed significant link of infertility with elevated mercury and reduced selenium levels. Females with higher Hg level were found to have decrease luteinizing hormone (LH), estradiol, progesterone and prolactin levels (Henriques *et al*., 2019). Methyl mercury (at exposures as low as 1 mM for 2 h) also decreased prolactin release (Maues *et al.*, 2015).

Occupational exposure to mercury may lead to decline fecundity. As reported by Wright *et al.* (2015) dental care professionals who carry out procedures that exposed them to Hg showed reduced fertility (fecundability ratio (FR): 0.63, 95% CI: 0.42, 0.96). Mercury is also responsible for irregular menstruation, severe dysmenorrhea, spontaneous abortion and fetal birth defects (Ma *et al*., 2018; Liu *et al*., 2008). In a case control study in Hong Kong, Choy *et al.* (2002) found that blood Hg concentrations in women with unexplained infertility were significantly higher than those in women with normal fertility

iii. Manganese (Mn) effect on female reproduction

Manganese is a trace element that is a major component of life, usually needed for normal physiology and is commonly found in food. However, information or data to link the possible effect of Manganese and infertility is limited. Places such as dried battery cell factories and mines are potential places for occupational exposure to manganese.

Overexposure to manganese chloride cause grave fertility abnormalities, developmental toxicity, neurotoxicity, and immunotoxicity. In rats, manganese exposure may likely reduce the number of follicles in the ovaries and induced persistent corpora lutea (Sengupta *et al.*, 2015). Pine *et al*. (2005) as well reported that rats exposed to Mn for 4 or 13 weeks showed a progressive and significant decrease in hypothalamic dopamine (DA), while prolactin and pituitary transcription factor-1 messenger RNA (Pit-1 mRNA) levels increased in response to Manganese exposure.

iv. Aluminium (Al) effect on female reproduction

Aluminium is categorized as toxic heavy metal that has no biological function in living organisms (Miska-Schramm 2016). There are limited studies associated with aluminium and its effects on female reproduction. However, a few data suggest that aluminium exposure inhibit reproductive function in female rats. Wang *et al*. (2012) examined the effects of aluminium exposure on the reproductive function in female rats. The results showed decrease levels of estrogen, progesterone, FSH, and LH. Whereas increased testosterone level in the low and medium dose groups ($P<0.05$). Similarly, Miska-Schramm *et al*. (2016) studied the effect of aluminium exposure on reproductive ability in the bank vole. The results reveals that in females treated with 3 mg/l Al, had increased uterus weight higher than control ($p < 0.05$).

v. Cadmium (Cd) effect on female reproduction

Environmental exposures to cadmium can lead to hormonal imbalance in females. Studies demonstrated Cd has estrogen-like effect, which can act as an endocrine disruptor strongly affecting the female reproductive organ in diverse ways. Cd at nanomolar level shows xenoestrogenic activities by persuading cell growth and motivating prolactin excretion from anterior pituitary cells in an estrogen receptor-dependent manner. As well, Cd acted as an effective xenoestrogen that can play a significant role in the causation of various pathologies of the anterior pituitary and estrogen-responsive tissues that represent a risk to human health (Kumar and Sharma 2019). It was also speculated that Cd may cause unexplained infertility. A case-control study showed that the levels of FSH were significantly positively correlated with Cd concentrations in women's serum (Gallagher *et al*., 2010).

Rats exposed to cadmium oxide dusts had increased duration of the estrous cycle, decreased pre-ovulatory luteinizing hormone levels in blood, and inhibited ovulation (Sengupta *et al*., 2015). Cd exposure to rodents resulted in a down regulation of pituitary hormones including gonadotropins, prolactin (PRL), adrenocorticotropin hormone, growth hormone, and thyroid-stimulating hormone (Miler *et al*., 2010). According to Sengupta, Cadmium exposure up regulated the progesterone receptors and affects production of progesterone and testosterone in proestrous rats and pregnant dams, therefore, cadmium interferes with the ovarian steroidogenic pathway at more than one site (Sengupta *et al*., 2015). An investigation carried out by Weller *et al*. to evaluate the effects of cadmium exposure on female infertility parameters in mice, showed that exposure to cadmium was associated with significantly decreased serum levels of estradiol. Outcome of the study reveals that cadmium might contribute to unexplained female infertility (Weller *et al*., 2017). Long term Cd exposure at environmental levels is also allied with high serum FSH in US women aged 42–60 years. Also, Zheng *et al*. (2015), disclosed increase in Cd levels is linked with a 21 % increase in early follicular phase estradiol levels (each 1 µg/L). Another study by Zhang *et al*. (2004) evaluated the possible effects of environmental Cd exposure on pregnancy outcome, fetal growth and development. A higher cord blood Cd (>0.40µg/L) level was associated with a 2.24cm decline in neonatal birth height as compared to a lower cord blood Cd level (≤0.40µg/L). They concluded that environmental Cd exposure significantly reduces neonatal birth height. Equally, Wang *et al*. (2019) observed that maternal Cd exposure during middle gestational period increases the risk of small for gestational age infants in contrast to Cd exposure during early gestational stage. In addition, Lee *et al.* examined the correlation between self-reported infertility and heavy metals (blood Pb and Cd) levels in US women. They compared the metal levels in infertile women and pregnant women. The result revealed low blood lead and cadmium levels were positively linked with self-reported infertility (blood lead = 0.50µg/dL and blood cadmium = 0.26µg/L). The result suggests that even low level of blood Cd and Pb may be harmful to female fertility in women aged 20-39ys (Lee *et al*., 2020).

Cadmium exposure can also exert harmful effect on ovaries, placenta and uterus of females. Kumar and Sharma revealed that Cd exposure could either increases or inhibits the biosynthesis of progesterone, a hormone that is certainly linked with normal ovarian cyclicity and pregnancy maintenance Thus, Cd exposure was found to have an impact on ovarian and reproductive tract morphology, and extremely low doses were stated to stimulate ovarian luteal progesterone biosynthesis while high doses prevented it (Kumar and Sharma 2019). In another study, increased uterine wet weight, as well as endometrial thickness and endometrial stromal thickness, were observed in a group of rats during 3 days of exposure to 0.8 mg kg-1 Cd in intraperitoneal injections (Rzymski *et al*., 2015). Also, Cd has been seen to mimic estrogen properties in uterus and female offspring experienced an earlier commencement of puberty and rise in the epithelial area and the number of terminal end buds in the mammary gland (Rehman *et al.*, 2017). Additionally, experimental data has revealed that exposure to cadmium affects female fertility by altering pituitary function, ovulation, steroidogenesis, and fertilization (Lee *et al*., 2020). A study found Cd to also reduce the production of human chorionic gonadotropin and inhibited placental transmission of nutrients and oxygen to the fetus. Both the detection rate and exposure level of Cd in endometrial samples showed obvious differences between infertile and normal women (Tanrıkut *et al.*, 2014). **Prevalence of Female Infertility**

Infertility is a common medical problem that affects couples in developed countries. In Canada, total rate of fertility in Canada since 2009 has been reducing, for instance, from 1.68 to 1.54 children per woman in 2016 (Provencher *et al*., 2018). The National Survey of Family Growth (NSFG) report from 2015-2017 estimates 8.8% of married women aged 15–49 years in the US are infertile, 13.1% of women aged 15-49 have impaired fecundity and 16.2% of married women with impaired fecundity defined as the inability to conceive and carry a baby to term. Among females in Britain, the estimated prevalence of infertility was 12.5% (Datta *et al.*, 2016). Also, in Canada it was estimated that the prevalence of infertility among women aged 18-44 was 16% for heterosexual couples and China 1–18% (Meng *et al.*, 2015). Infertility in developed countries is associated with factors such as endometriosis, Chlamydia trachomatis infection and pelvic surgery as well as obesity,

chemotherapy and some long-term chronic medical conditions (Bhattacharya *et al.*, 2009). Also, infertility rate varies within countries and among countries.

In developing and under developed countries, child bearing is a means of preserving a family's lineage and also guarantees some form of economic security, in the sense that parents will rely on their children for support when aging. Therefore, most couples are under undue pressure to procreate (Kaadaaga *et al.*, 2014). Hence, female infertility and low birth rate are important public health issues with profound social, psychological, and economic consequences. The prevalence of infertility in female is much higher in developing countries than developed countries. The prevalence rate of infertility in developed countries ranges from10-15% while in the SSA infertility prevalence rate has been notable high ranging from 10-30%. Study reveals that 17 out of the 30 SSA countries studied, shows high rates of fertility decline indicative of fertility transition (Sneeringer, 2009). Also, WHO demographic studies have identified that Sub-Saharan Africa countries has over 30% of women aged 25 - 49 years that suffer from secondary infertility (WHO, 2004). According to repeated cross-national surveys, infertility in female is also prevalence in Central, West, and Southern Africa compared to low rates observed in East and North Africa.

Countries in Central African such as Angola, Central African Republic, Equatorial Guinea, Gabon and Mozambique have high rate of primary and secondary female infertility. Also, in countries like Zimbabwe, secondary infertility rate accounts for 62% for women between the age of 25 and 49 years which is more than half of all reproductive aged women (Inhorn and Patrizio, 2015; Mascarenhas *et al.*, 2012; Nachtigall 2006; Rutstein and Iqbal 2004).

The high prevalent rates of female infertility in SSA may be as a result of high exposure to environmental contaminants (heavy meals) and untreated Reproductive Tract Infections (RTIs) in the region. Bede-Ojimadu *et al.* (2018) revealed that heavy metal exposure levels among Sub-Saharan African were generally higher than people in developed countries. In developed nations, blood lead levels of the populace have continued to decrease over the years following regulatory bans on leaded gasoline and reduction in lead content of consumer goods such as paints. On the contrary, reports from Sub-Saharan African indicate that blood lead level in this population have remained elevated despite an official phase-out of leaded-gasoline in these countries (Bede-Ojimadu *et al.*, 2018). Out of 33% of women worldwide, 85% of women in SSA with infertility problems have their diagnosis attributed to infections, (Inhorn and Patrizio 2015: Mascarenhas *et al.*, 2012). Table 2 summarize the prevalence of female infertility in several countries.

Table 2: Prevalence of female infertility in developed and developing nations

Country	Age Group of females	Prevalence	Authors
USA	15-49	8.80%	NSFG 2017
UK	16-74	12.50%	Datta *et al.*, 2016
Canada	18-44	11.5% – 15.5%	Bushnik *et al.*, 2012
Germany	18-45	8.91%	Ziller *et al.*, 2015
China	20-49	15.50%	Zhou *et al.*, 2018
Northern china	-	13.09%	Cong *et al.*, 2016
France	15-44	14.10%	Thonneau *et al.*, 1991
Turkey	15-44	3.93%	Sun *et al.*, 2019
Norway	50-69	1.80%	Rostad *et al.*, 2006
Scotland	31-50	19.30%	Bhattacharya *et al.*, 2009
Russia	18-45	16.7	Philippov *et al.*, 1998
Spain	30-49	17.58%	Cabrera-Leon *et al.*, 2015
	25-44	18.60%	Karmaus and Juul, 1999
North Italy	25-44	26.20%	Karmaus and Juul, 1999
South Italy	25-44	14.80%	Karmaus and Juul, 1999
Australia	15-50	18.40%	Dick *et al.*, 2003
New Zealand	21-38	26.00%	Roode *et al.* 2015
Ghana	-	11.80%	Osei 2014
Cameroon	15-49	24.60%	Larsen, 2003
Tanzania	20-44	6.90%	Larsen, 2003
South Africa	21-41	8-12%	Dyer *et al.* 2002
Nigeria	20-29	59.30%	Mohammed-D *et al.*2019
North west	17-47	15.70%	Panti and Sununu 2014
South South	34	58.90%	Odunvbun *et al.*2018
South Western	15-55	17%-50.5%	Sule *et al.* 2008
Benin	22-44	13%	Larsen 2000
Burkina xFaso	-	10.40%	Eric *et al.* 2016
	15-49	13.40%	Rutstein and Iqbal 2004
Burundi	20-44	8%	Larsen 2000
Malawi	15-34	7.40%	Barden-O'Fallon, 2005
Central African republic	15-49	33.20%	Larsen 2003
Chad	15-49	9.60%	Rutstein and Iqbal 2004
Comoros	20-24	21%	Larsen 2000
Côte D'Ivoire	19-43	14%	Dia *et al.*, 2017
	20-44	19%	Larsen 2000
Gabon	15-54	3.0% - 22.4%	Schrijvers *et al.*, 1991
	15 -49	28.30%	Larsen 2003
Kenya	-	11.90%	Kimani and olenja , 2001
	20-24	16%	Larsen 2000
Madagascar	15-49	13%	Rutstein and Iqbal 2004
	20-24	21%	Larsen 2000
Liberia	20-24	18%	Larsen 2000
Namibia	20-24	22%	Larsen 2000
Mali	15-49	10.40%	Hess *et al.*, 2018
Mozambique	20-24	23%	Larsen 2000
Senegal	15-49	12.30%	Rutstein and Iqbal 2004
Niger	15-49	10%	Rutstein and Iqbal 2004
Togo	15-49	23.50%	Rutstein and Iqbal 2004

	20-44	5%	Larsen 2000
Zambia	15-49	14.50%	Rutstein and Iqbal 2004
Uganda	15-49	10.40%	Rutstein and Iqbal 2004
Zimbabwe		10.96%	Rutstein and Iqbal 2004
Morocco	15-49	19.20%	Rutstein and Iqbal 2004
Iran	18-45	17.30%	Kazemijaliseh *et al.* 2015
	20-49	4.73%	Mirzaei *et al.* 2018
Peru	15-44	3.60%	Sun *et al.* 2019
India	25-29	8.90%	Katole and Saoji 2019
	-	14.20%	Kumar 2007
Pakistani	-	7 .5%	Shaheen *et al.*, 2010
Sudan	16-46	42.80%	Elhussein *et al.* 2019

Oxidative Stress Implication in Female Infertility

Oxidative stress (OS) takes place when the generation of reactive oxygen species (ROS) and other radical species overrules the scavenging capability of antioxidants, either by excess production of ROS or inadequate availability of antioxidants (Krajcir *et al.*, 2008; Agarwal *et al*., 2012). Oxidative stress induces infertility in females through various mechanisms. Recent studies reveal that the disproportion between ROS and antioxidants could result to etiopathogenesis of pregnancy, endometriosis, polycystic ovarian disease, hydatidiform mole, tubal factor infertility and unexplained infertility (Agarwal *et al*. 2012; Merve and Elmas 2016; Diamanti-Kandarakis *et al.*, 2017; Wojsiat 2017; Adeoye *et al*., 2018; Banerjee and Bhattacharya 2019). Excessive production of ROS may overwhelm the antioxidant defenses of follicular fluid, resulting in oocyte damage, reduced fertilization capacity, and precipitous pathologies affecting female reproduction.(Agarwal *et al.*, 2005; Adeoye *et al.*, 2018).

Oxidative stress induced hormonal imbalance may lead to damage cell membrane, cause cell apoptosis, damage proteins, lipid and nucleic acid, reduced growth and development of oocytes , increase mRNA in anterior pituitary, reduce follicular development and growth, poor oocytes quality, poor reproductive outcome, damage DNA, embryo fragmentation, implantation failure, abortion, ovarian aging and steroidogenesis, folliculogenesis, impaired placentation, congenital abnormalities and formation of numerous developmental abnormalities (Krajcir *et al*., 2008; Miler *et al.*, 2010; Merve and Elmas 2016; Adeoye *et al*., 2018; Engwa *et al.*, 2019). Thus, increasing studies indicate oxidative stress is one of the main causes of infertility in females (Agarwal *et al.*, 2005; Ruder *et al*., 2009; Andriyas and Lal 2013; Banerjee and Bhattacharya 2019). Additionally, OS is implicated in the pathophysiology of pre-eclampsia and retards embryo development which damagingly modify fertilization capabilities, development of embryo and freely induced birth defects (Tranquilli *et al.*, 2004). Oxidative stress can as well adversely affect the success of assisted fertility including IVF/ICSI and in-vitro maturation (Krajcir *et al*., 2008).

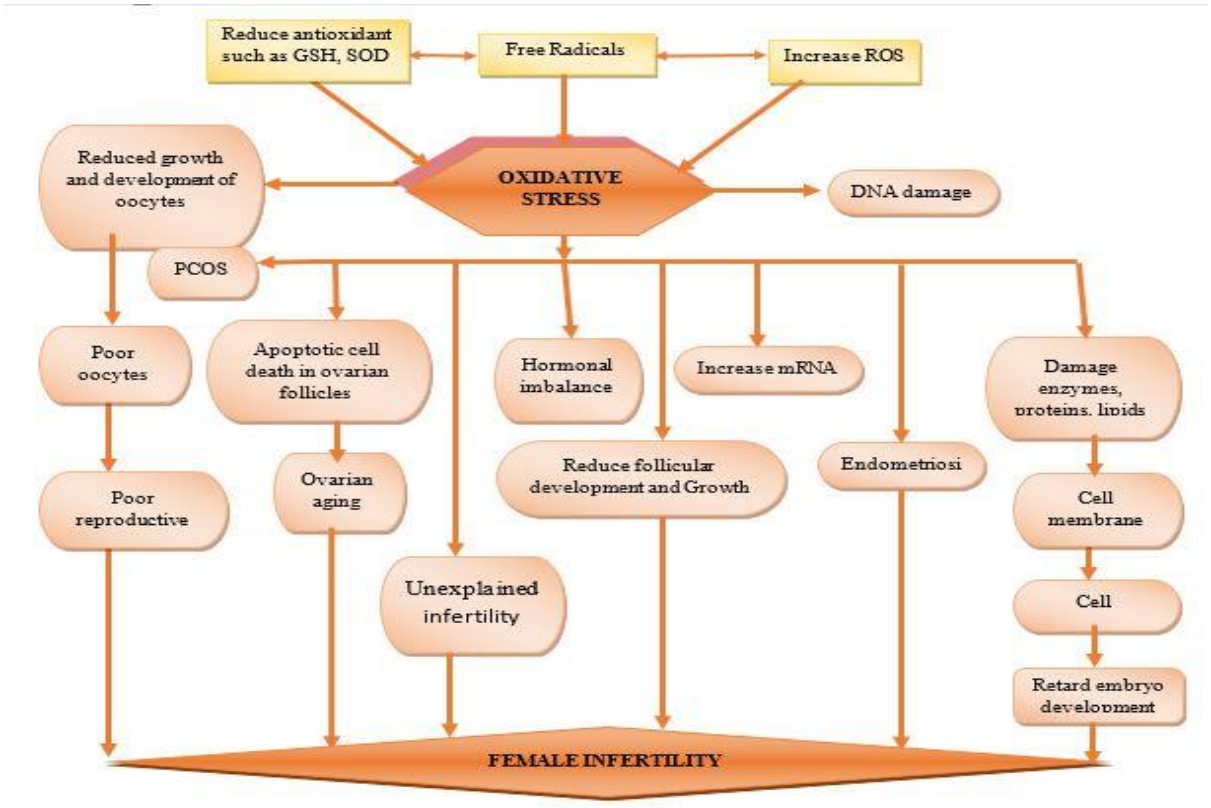

Figure 1: Effects of Oxidative Stress on female reproductive system

Other Factors affecting female infertility

Parameters such as age, obstetrical, reproductive history, nutrition, exercise, psychological stress, smoking and drinking alcohol patterns, menstruation, BMI index, lifestyle and environmental factors are considered to be the major risk factors leading to infertility (Zhou *et al.*, 2018, Cong *et al.*, 2016).

i. Hyperprolactinemia

Hyperprolactinemia occurs when the pituitary gland overproduces prolactin hormone in the blood. A study of 1607 female patients with medically treated hyperprolactinemia, showed prolactin hinders gonadotrophin secretion resulting in anovulation (Borght and Wyns, 2018).

ii. Infection

Infectious agents have diverse modes of fecundity impairment. They can cause pelvic inflammatory disease and tubal Obstruction in females. Epidemiological figures suggest correlation between a past Chlamydia trachomatis infection and subfertility in women (Karinen *et al.*, 2004). WHO estimated that the prevalence of Chlamydia trachomatis infections among

adult females in 2005 was 4%–6% in all regions of the world, except the WHO Eastern Mediterranean and South-East Asia regions, where prevalence was below 2% (Mascarenhas *et al*., 2012). Also, WHO, (2008), recorded the highest incidence of gonorrhoea to be in the Western Pacific Region (42.0 million cases), South-East Asia Region (25.4 million) and Africa Region (21.1 million).3.4 million cases of gonorrhoea were estimated in the European Region (53 countries). Neisseria gonorrhoea is a pathogen that affects the fallopian tube (Mitchell and Prabhu, 2013). Thus, the female reproductive system is negatively affected by infections.

iii. Stress and Depression

Stress and other psychological factors have a strong impact on reproductive cycles (Gopinath, 2013). According to a study illustrated in a nurse population, working longer hours (over 40 h/week) is linked with increased time to conceive, suggesting an association of fatigue or stress with decreased fertility (Gaskin *et al*., 2015). Impaired fertility might lead to depression in women trying to get pregnant; also it is likely that a history of depression could affect fecundity (Crawford *et al.*, 2017).

iv. Systemic disease

It is commonly deemed that severe systemic disease, for example, sepsis or severe renal disease will thwart embryonic implantation. Diseases such as unstable diabetes, poorly managed celiac disease which is five times more common in females involved in unexplained infertility or recurring miscarriage than in the general population. The existence of thyroid antibodies in a woman with normal thyroid function is said to be connected with difficulty to conceive, recurring implantation failure of embryos and early pregnancy loss, potentially due to an unrecognized thyroid hormone deficiency or an autoimmune cause (Borght and Wyns, 2018).

v. Lifestyle-related factors

Lifestyle factors, such as regular exercise, frequent sexual intercourse, 2-3 times per week starting shortly after menses and following a healthy diet, could also help in achieving pregnancy (Borght and Wyns, 2018). Contrary, calorie restriction and extreme exercise may lead to a decrease in the regularity of ovulation, amenorrhea and poor endometrial development (Hart *et al.*, 2016).

vi. Cigarette smoking

Cigarette smoking has a known effect on female fertility. Crawford *et al.* (2017) reported likely difficulty staying pregnant in females who had ever smoked at least 100 cigarettes., Each phase of reproductive function, embryo transport, folliculogenesis, endometrial angiogenesis, steroidogenesis, endometrial receptivity, uterine blood flow and uterine myometrium are impaired in cigarette smoking females, as the smoke consists heavy metals, nitrosamines, polycyclic hydrocarbons and aromatic amines (Dechanet *et al.*, 2011).

vii. Marijuana and Alcohol intake

Marijuana consumption in females' distorts menstrual cycle and decreased number of oocytes retrieved during in vitro fertilization. The probable mechanisms of action through which alcohol may impair fertility include an alcohol associated rise in estrogens leading to reduced FSH secretion and impaired ovulation (Borght and Wyns, 2018).

viii. BMI

Smurthwaite and Bagheri, (2017) stated that 21% of women in the globe are categorized as obese according to their body mass index (BMI). A recent study revealed that prolonged duration of infertility, age of females and BMI enhanced the generation of stress hormones and decreased antioxidant activity which augmented the risk of infertility (Alam *et al.*, 2019). Data have also proven that women with higher BMI were more likely to have a delayed pregnancy or to be infertile (Meng *et al*., 2015; Bhattacharya *et al*., 2009; Wise *et al.*, 2013). Cong *et al.*, analysed the association between BMI values of women at childbearing age and the incidence of infertility and it was concluded that women with moderate BMI had the lowest incidence of infertility, and the overweight group was second. Underweight and obese women had high incidences of infertility, and the incidence of infertility was highest in the obesity group (Cong *et al.*, 2016). Similarly, Borght and Wyns, stated women who are overweight are less likely to ovulate and to conceive spontaneously even after infertility care (Borght and Wyns, 2018). Moreover, a study carried out by Kumar revealed the success rate of IVF was about 31.8 per cent, and BMI was significantly reduced in females with positive outcome (Kumar *et al*., 2018).

Conclusion

Female infertility is a key public health problem with profound social, psychological, and economic consequences. The prevalence of female infertility is much higher in developing countries than in developed countries. Occupational or environmental exposure to heavy metals such as lead, mercury, aluminium, manganese, cadmium and/or mixtures of metals had reduced fertility, induced oxidative stress, cause high prevalence and incidence rates of menstrual disorders. Heavy metal exposure has also been related to polycystic ovary syndrome, premenstrual syndrome, dysmenorrhoea (menstrual pain), amenorrhoea, early menopause, endometriosis, benign breast disorders and galactorrhoea, often associated with female infertility. In Sub Saharan Africa, the levels of heavy metal exposure among people were found to be higher than people in developed countries. This may be a contributory factor to the high prevalence of female infertility in this region. Thus, to manage female infertility exposures to heavy metal and other environmental toxicants should be eliminated, mostly in SSA.

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