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Occupational and environmental mercury exposure and human reproductive health - a review

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Abstract

Mercury is a toxic heavy metal. Humans are exposed to mercury through several sources including environmental, occupational, contaminated food and water and from mercury-containing dental amalgam. Mercury exposure is known to harm the nervous system profoundly, and have a negative impact on digestive and immune systems, and other organs. To review and discuss the effect of mercury exposure through environmental or occupational routes on human reproduction, pregnancy, and its outcome. Published information about the potential toxic effects of mercury on human reproduction were collected and summarized. Literature was identified by systematic search using relevant keywords. Literature review revealed a number of negative impacts of mercury on human reproduction. These included effects on semen quality, including reduced sperm count, motility, and changes in morphology that may reduce fertility potential. There may also be an effect in changing reproductive hormone levels. Mercury exposure might also affect pregnancy but the data concerning mercury effects on female reproduction are limited except for some data about mercury exposure and poor pregnancy outcomes. Available data indicate that mercury exposure may have a toxicity effect on reproductive potential, especially in males. Prenatal mercury exposure may affect pregnancy or its outcome and this appears to be dependent upon dose, duration, and timing of exposure. Nutritional status of exposed individual might also influence the impact of mercury. (J Turk Ger Gynecol Assoc 2022; 23: 199-210)

Keywords: Mercury, reproduction, fertility potential, semen quality, pregnancy outcome, methyl mercury

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Introduction

It is well known that mercury is a toxic heavy metal. It may be present in different forms, including elemental mercury, or as part of inorganic or organic compounds. Humans are exposed to mercury through both natural and synthetic sources. Sometimes they are subjected to higher quantities of exposure accidently or occupationally. Mercury poisoning might occur through breathing of mercury-contaminated air or consuming contaminated water or food, especially contaminated fish, or accidental exposure to mercury may occur through some occupations or in certain work processes. Accidental exposure may also occur when mercury-containing equipment is damaged. Mercury exposure can cause various health problems in human, and is known to affect child growth in pregnancy or in early life. Furthermore, mercury may also have a toxic impact on the nervous, digestive, and immune systems, and in organs including the lungs, kidneys, skin, and eyes. Mercury metal has been labelled by the WHO as one of the top ten key chemicals with potential public health concern (1).

One of the best known episodes of mercury poisoning occurred in Minamata bay and Niagata, Japan during 1950s, and methyl mercury poisoning happened in Iraq in the 1970s (2). Neurobehavioral deficiency and, in a few cases, clinical signs have been reported for both children and adults with respect to mercury exposure. There are some data on cytogenetic impairment, changes in immune function, and cardiovascular toxicity owing to mercury exposure (3).

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Furthermore, the data on environmental mercury exposure and its influences on human health indicated that mercury has profound cellular, cardiovascular, hematological, renal, pulmonary, immunological, neurological, reproductive, endocrine, and embryonic toxicologic effects (4). Mutter et al. (5) reported that mercury leaching at low doses from dental amalgam used for tooth fillings may be absorbed by various body tissues, contributing to the mercury burden in humans. The debate continues about the consequences of this low-level chronic mercury exposure to the users of dental amalgam on their health or reproduction or impact of occupational mercury exposure to dental professionals while preparing/implanting dental amalgam.

The toxic potential of lead and cadmium on human reproduction has been reviewed (6,7). In this article, we endeavor to assess the effect of mercury exposure on human reproductive health, pregnancy, and its outcome from all of the most likely sources.

Material and Methods

A systematic review of available literature was carried out by searching within a number of databases, including PubMed, Google, PubChem, and Google scholar. These searches were conducted using a number of keywords or key terms, including which were: “mercury exposure and health”, “occupational mercury exposure”, “environmental mercury exposure” and “male human reporoduction”, “female human reproduction”, “pregnancy”, “pregnancy outcome”, “offspring development”, “puberty”, “reproductive hormones”, “reproductive toxic potential”, “erectile dysfunction”, “libido”, “semen quality”, “menstruation cycle”, and “fertility”. A further search was conducted into mercury exposure through dental amalgam and human reproductive health, consumption of fish/seafood with regards to mercury and reproduction, pregnancy or its outcome. More than five hundred articles were identified, and seventy-five relevant articles were incorporated in this review.

The article is divided into three sections: effects of mercury on male reproduction, effects of mercury on female reproduction and effects of mercury on pregnancy or its outcome. The data from the three sections is summarized in Tables 1 and 2 for better and quick appraisal. Some experimental information was also incorporated as and when necessary, either in the absence or scarcity of human data or to provide a better understanding of the mechanism behind reproductive toxicity of mercury. The collection of data and presentation of the information on mercury exposure and human reproduction is depicted in Figure 1.

Results and Discussion

Both acute and chronic mercury exposure can cause deleterious effects on human health during early life growth and development and there is no known safe dose of mercury exposure reported for human beings. Furthermore, prenatal, and postnatal mercury exposure may occur by different pathways, although bio-accumulation is reported to mostly occur through the aquatic food chain (8). Moreover, mercury exposure has been found to pose substantial health risks to certain occupational groups, such as goldminers and dental personnel, where there may be a greater chance of occupational exposure (9). As has been noted, mercury exposure negatively impacts on human reproductive health, by altering the reproductive as well as the endocrine systems of both sexes. However, the molecular mechanisms behind mercury-linked decline in fertility potential are unclear (10). Furthermore, mercury exposure could damage to Leydig cells, seminiferous tubules, testicular degeneration, and menstrual cycles disorders. Some studies reported spontaneous abortion (SAb) and adverse fertility outcome owing to work-related mercury exposure. They also stated a relationship between inhalation of mercury vapor and poorer reproductive outcome (11). Thus, mercury exposure has the potential to affect reproductive organs and various reproductive endpoints adversely including pregnancy or outcome.

Mercury Exposure and Male Reproductive Health

Numerous experimental studies are available on the effect of mercury on male reproduction. These studies show that mercury is a male reproductive poison, but studies on human male reproduction are few, with inconsistent findings (12). Based upon several published experimental studies, mercury negatively affects male reproductive potential as mercury exposure can deteriorate several male reproductive endpoints, such as sperm quality, motility, normal sperm morphology, testicular injury, sperm DNA damage, and fertility potential (13-17). A few clinical reports are available on the impact of mercury exposure on male reproduction, especially semen quality. One report examined the relationship between blood mercury levels and semen quality parameters in sub-fertile men (18). The sperm concentration, percentage of morphological normal sperm, percentage of normally motile sperm, curvilinear velocity, straight-line velocity, average path velocity, and amplitude of lateral head displacement was reduced in men with higher blood mercury levels, though the alteration was statistically insignificant. Mocevic et al. (12) also studied semen characteristics and reproductive hormones in association with environmental mercury exposure and did not

find any evidence of negative effects of mercury on studied biomarkers of male reproduction in men from Greenland and Europe.

Furthermore, an association between urinary metal levels and sperm DNA impairment was examined. Thirteen metals, arsenic, cadmium, cobalt, chromium, copper, iron, lead, manganese, nickel, molybdenum, selenium, mercury, and zinc were measured in urine samples, and sperm DNA injury was evaluated by comet assay. These authors found that urinary mercury and nickel were associated with elevation of tail length, and urinary manganese was associated with elevation of tail moment. This suggested that environmental exposure to mercury, nickel and manganese might be related to sperm DNA injury (19). Subsequently, Lu et al. (20) also confirmed an association between non-occupational exposure to mercury among reproductive-aged males and DNA methylation in the imprinting gene *H19* in sperm. Furthermore, *in utero* and adult exposure to EDCs is likely to be a modifier of male reproductive health. Mercury may be retained in testicular tissues and pituitary gland causing reduced testicular function, especially spermatogenesis (21). An association between methyl mercury (MeHg), and 2, 2', 4, 4', 5, 5'-hexachlorobiphenyl (CB-153) exposure and sperm quality has been reported. Blood concentrations of MeHg were in the range of 0.11 to 16.59

Table 1. Mercury exposure and male reproduction, semen quality and male mediated reproductive outcome

Sl. No.	Exposure	Effects	Reference
Mercury and semen quality			
1	Blood Hg levels & semen quality in sub-fertile men	Sperm concentration, morphologically normal, motility, curvilinear & straight-line velocity, average path velocity, & amplitude of lateral head displacement, reduced insignificantly with higher blood Hg level	Leung et al. (18)
2	Semen quality, reproductive hormones & environmental Hg exposure	Environmental Hg exposure in Greenlandic & European men with median blood Hg level up to 10 ng mL (-1) not link with hostile effects on male reproductive biomarkers	Mocevic et al. (12)
3	Urinary metal (As, Cd, Cobalt, Cr, Cu, Fe, Pb, Mn, Hg, Ni, Zn, Molybdenum, Selenium) & sperm DNA damage	Urinary Hg & Ni linked with increasing trends of tail length, and Mn linked with tail moment. This advice that environmental exposure to Hg, Mn, & Ni related with sperm DNA damage	Zhou et al. (19)
4	Pre-conceptional Hg exposure & DNA methylation of imprinting genes H19, in human sperm DNA	Environmental Hg exposure related with altered DNA methylation at imprinting gene H19 in sperm, implicating in susceptibility of sperm for environmental insults	Lu et al. (20)
5	Examined an association amid MeHg, and 2, 2', 4, 4', 5, 5'-hexachloro biphenyl (CB-153) exposure, with reverence to sperm quality	No relationship amid MeHg & sperm quality parameters. Men with low MeHg & high CB-153 exposure had slightly higher DFI & fraction of Y-chromosome carrying sperms than men with lower level of these compounds	Rignell-Hydbom et al. (22)
6	Correlated semen quality with hair' Hg level	Hair' Hg level positively linked with sperm concentration, count, & progressive motility. These relations stronger in men with fish consumption. Semen volume & morphology non-significantly related to hair Hg levels	Mínguez-Alarcón et al. (24)
7	Predatory fish usage related with high blood Hg level & semen quality	Linked with lower sperm count & normal morphology. Predatory fish might be al risk factor for higher Hg level that might affect semen quality	Ai et al. (23)
8	Urinary Hg concentrations & semen quality	No positive link amid urinary Hg levels & semen quality, fertility index & quantity of dental amalgam fillings	Hanf et al. (26)
Male mediated reproductive outcome			
9	Male mediated elemental mercury exposure occupationally & reproductive outcomes	No associations demonstrated amid Hg exposure & declined fertility or higher malformations or serious childhood illnesses	Alcser et al. (29)
10	Spontaneous abortions among wives of workers exposed to Hg vapour occupationally	An elevation of SAbs with elevation of Hg in fathers' urine before pregnancy. At high levels above 50 μg/L the SAb risk become doubles	Cordier et al. (30)
11	Reviewed data on parental exposure to metals & SAb	Paternal exposure to Pb or Hg might be related with the risk of SAb	Anttila and Sallmén (31)

MeHg- Methyl mercury; As-Arsenic; Mn- Manganese; Cd-Cadmium; Cr-Chromium; Cu-Copper, Fe-Iron; Pb-lead; Zn-Zinc; SAb-Spontaneous abortion; DFI- DNA fragmentation index

Table 2. Mercury exposure and Female reproduction

Sl. No.	Exposure	Effects	Reference
Mercury exposure and puberty, menstruation cycle and menopause			
1	Women (dentists & dental assistants) exposed to metallic mercury	A significant, risk amid hair' total mercury labels (TMLs) & reproductive failures. Relation with menstrual disorders was significant	Sikorski et al. (37)
2	Elemental mercury (used in gold mining) on menstrual cycle & miscarriages	Related with occurrence of irregular menstrual cycles but not related to miscarriage	Rodríguez-Villamizar et al. (38)
3	Reproductive risks in female workers exposed to low-level metallic mercury	Low-level long-term Hg exposure brought significantly more dysmenorrhoea, hypomenorrhea at above 0.06 mg/m^3 of Hg level, & below this, menstrual cycles, quantity, duration did not alter significantly. Rates of PTB, SAb, still birth, fetal death, & pregnancy snags in group exposed to 0.06-0.1 mg/m^3 of Hg & control was insignificant	Fu (41)
4	Female workers exposed to Hg vapor	Abdominal pain & dysmenorrhea more in Hg exposed workers	Yang et al. (42)
5	Meta-analysis on the reproductive effects of Hg exposure in female workers	Causes dysfunction of menstrual period, cycle, blood volume, dysmenorrhea & cause hostile outcomes, i.e., pregnancy-induced hypertension, stillbirth, LBW & birth defects	Pan et al. (43)
6	Prenatal Hg exposure & precocious puberty	Prenatal exposure to High doses of Hg related with precocious puberty. Highest risk in children with hostile birth outcomes whose mothers had high RBC-Hg level & cardio-metabolic conditions	Wang et al. (45)
7	Menopause & blood Hg level	Blood Hg was lower significantly in postmenopausal than premenopausal women	Yuk et al. (46)
Mercury exposure and pregnancy and outcome			
8	Mercury exposure in pregnancy	Pregnancy complications & developmental complications in infants	Solan and Lindow (73)
9	Prenatal Hg exposure & newborn anthropometric characteristics	Negative correlation amid blood Hg levels in 1st & 2nd trimesters & birth weight.	Vigeh et al. (47)
10	Assessed association amid exposure to Hg prenatally & birth weight, GST polymorphisms.	Mothers with GSTT1 null genotype, higher maternal blood Hg in late pregnancy linked with risk of LBW. Mothers with GSTM1 & GSTT1 null genotype, maternal & cord blood Hg levels were related with LBW	Lee et al. (48)
11	Prenatal maternal arsenic & Hg exposure & birth outcomes in artisanal & small-scale gold mining (ASGM) subjects.	In ASGM areas, risk of hostile birth outcome elevated with increasing total-As & total-Hg exposure. SAb, stillbirth & PTB significantly linked with elevated total-As, while elevated Hg significantly linked with stillbirth & congenital anomalies	Nyanza et al. (57)
Dental amalgam' mercury exposure and pregnancy outcome			
12	Reproductive history of dentists & dental assistants	No elevated rates of congenital abnormalities or SAb in children of men & women exposed to low v/s high dose of Hg in dental setting	Brodsky et al. (50)
13	Assessed links amid exposure to amalgam fillings & pregnancy outcome	No significant associations amid total teeth with amalgam fillings & early, late PTB, LBW, malformation, or stillbirth babies	Lygre et al. (51)
14	Effect of electro-magnetic fields on the release of Hg from dental amalgam	Dental amalgam fillings pregnant women should limit exposure to electromagnetic fields to prevent effects of Hg to fetuses	Mortazavi and Mortazavi. (52)
15	Dental workers exposed to mercury amalgam, acrylate compounds, solvents, disinfectants & miscarriage.	No strong or dose-response relation detected amid exposure to Hg amalgam, acrylate compounds, solvents, disinfectants & Miscarriage. A slightly more risk of miscarriage with these agents	Lindbohm et al. (53)
16	Exposures to Hg during amalgam preparation.	Women with more Hg exposure were less fertile. The fecundability (chance of conception at each menstrual cycle) of women those prepared 30 or more amalgams/ week have 63% chance of conception than control	Rowland et al. (54)

Table 2. Continued

Sl. No.	Exposure	Effects	Reference
17	Pregnant dental professionals	Suffered with higher odds of developing spontaneous abortion, pre-eclampsia, and babies smaller for gestational age and this may be connected to oxidative stress induced by mercury	El-Badry et al. (40)
Sea food/fish intake related mercury exposure and outcome			
18	Birth' anthropometry, placental wt. & gestational length & Hg	Prenatal Hg exposure by seafood may be related with lower placental & fetal growth	Murcia et al. (49)
19	Consumption of seafood in pregnancy	Hg exposure is undesirably related with birth weight. Seafood usage in pregnancy not to be avoided but find at what level Hg exposure might exceed the risk of seafood	Vejrup et al. (58)
20	Maternal seafood consumption	Maternal seafood intake linked with Hg level. No association amid Hg level & fetal growth, except negative relation with biparietal diameter	Drouillet-Pinard et al. (59)
21	MeHg level & fish consumption	Blood MeHg level significantly more in infertile than pregnant women & consistent with fish consumption	Lei et al. (60)
22	Mercury exposure level	No evidence of impairment with total Hg exposure if mother ate fish in pregnancy	Hibbeln et al. (61)
23	Pregnant women receive two messages with fish usage	Fish usages positively related with hair' Hg levels. Equated with women deliver at term, women who delivered prior to 35 weeks likely to have Hg hair at or more the 90th percentile (> or =0.55 microg/g)	Xue et al. (62)
24	Hg exposure & birth outcome	About 15.7% of subjects had PTB & 8.1% delivered LBW. Lower hair Hg exposure (lowest tertile < 2.34 μg/g), related with LBW while no link amid hair Hg & PTB	Baldewsingh et al. (44)
25	Total hair mercury (HHg) level as a pointer of fish usage & MeHg exposure	Birth weight considerably different among groups but not exhibit a consistent pattern with fish usage	Marques et al. (63)
26	Blood Hg in pregnant women on birth outcomes & compared with those who ate fish or not	No links amid maternal blood Hg & head circumference, birth weight, or crown-heel length & PTB. When compared into fish-eaters or not, no relations except a negative link with birthweight in non-fish-eaters. Moderate Hg level not linked with anthropometric variable, LBW or PTB risk. Fish usage may be protective	Taylor et al. (64)
27	Moderate fish intakes	Linked with improvements in metabolic health of children, while high maternal Hg exposure linked with hostile metabolic profile	Stratakis et al. (67)
28	Methyl mercury exposure from fish & sea mammals' consumption	Inorganic Hg in aquatic sediments methylated by microorganisms & stored in aquatic food. Fish users do not reveal hostile effects. Even, some tests show beneficial impacts	Clarkson and Strain (65)
29	Reviewed data on maternal exposure to MeHg & health of fetuses, neonates, children	Prenatal exposure to MeHg linked with LBW, & negative link with birth length. Hostile effect on anthropometric variables, cognitive or physical growth	Saavedra et al. (66)

LBW: Low birth weight, PTB: Pre-term birth, MeHg: Methyl mercury

μg/L and serum concentrations of CB-153 were in the range of 37 to 1,460 ng/g of lipid. No relationship was found between MeHg and any of the male-related endpoints examined. These authors noted that men with lower MeHg and higher CB-153 levels had slightly, but insignificantly, higher DNA fragmentation index and more Y-chromosome carrying sperms compared with men with lower levels of both compounds (22).

It has been reported that men consuming predatory fish had higher blood mercury concentration, which was related with poorer sperm count with normal morphology (23). Thus, consumption of predatory fish might be a crucial risk factor for deterioration of semen quality (23). In addition, Mínguez-Alarcón et al. (24) correlated semen quality with hair mercury concentration in males. They reported that the median hair mercury concentration was 0.72 ppm (range 0.03 to 8.01ppm) and 30% of their subjects had hair mercury concentrations >1 ppm. Hair mercury concentration was positively correlated with sperm concentration, count, and progressive motility.

Furthermore, men in the highest quartile of mercury hair concentration had 50, 46 and 31% more sperm concentration, count, and progressive motility, respectively, compared to men with the lowest mercury quartile. These relationships were stronger in men whose fish consumption was above the study population median level. Seminal volume and sperm morphology were not related to hair mercury levels. These data showed that occurrence of MeHg exposure through fish consumption may be a significant dietary source of mercury exposure, amongst other heavy metals, that may have an impact on semen quality. It was suggested that additional research is required to elucidate the complex relationship between Hg exposure through fish consumption, and impacts on male reproduction (24). Moreover, processed meat consumption had a negative impact on sperm morphology, while fish consumption was connected positively with sperm count and normal morphology. Likewise, consumption of fish in place of other meats, mostly processed red meats, might have a beneficial effect on semen quality. Thus, the role of nutrition (fish intake) might play some role in prevention of deterioration of semen quality, even though consumption of fish has been linked to mercury exposure in some studies (25). Mercury levels in urine and ejaculate were measured in the partners of women undergoing infertility treatment who were also assessed for the number of dental amalgam fillings. No positive association was identified in regard of partner urinary mercury *concentration* and *semen* quality. Similarly, no association was found between fertility index and the quantity of dental amalgam fillings (26).

Both the experimental and human studies with higher exposure to certain metals usually support a negative effect of some heavy metals, especially cadmium, mercury, lead, and arsenic, on human reproductive outcomes, while data on the impact of lower, environmentally-realistic exposure to these metals on male reproduction are limited. The effects of low-level exposure were strongest for lead, cadmium, and mercury, and to a lesser extent for arsenic (27). Further, it has been reported that moderate- to low-level lead exposure worsens certain reproductive parameters in humans, and cadmium exposure reduces serum testosterone levels and prostate function. Despite the negative effects of manganese, mercury, arsenic, and chromium on semen quality parameters, there is less evidence concerning the effect of these contaminants on serum hormone changes (28). Based upon the data available, there appears to be relatively good evidence of the adverse impact of mercury on human male reproduction, especially semen quality, but more research is required on

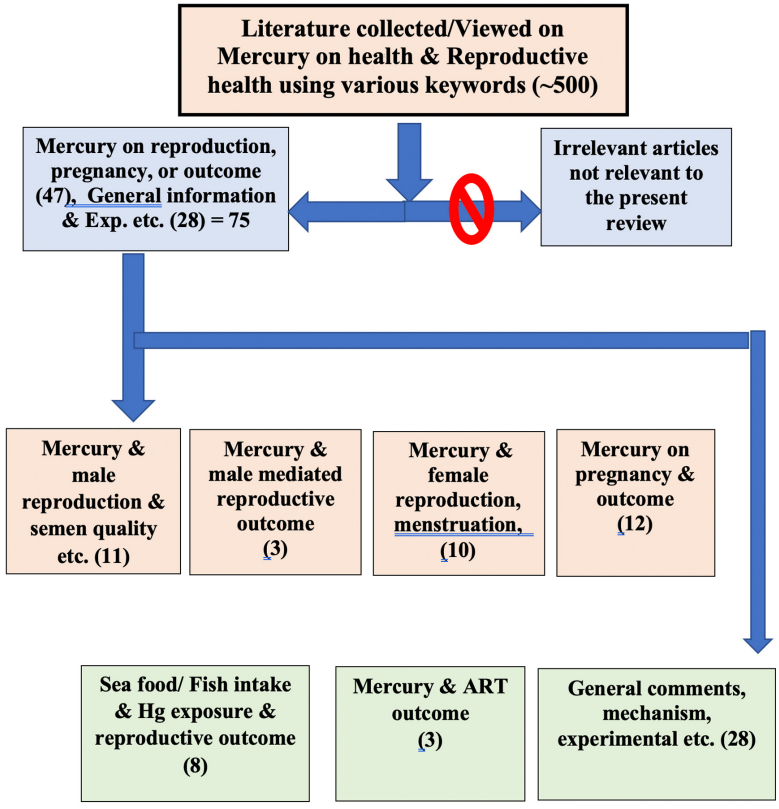

Figure 1. Flow diagram of literature collection on mercury and reproduction or outcome

ART: Assisted reproductive

the role of consumption of fish with regards to semen quality, despite the known association between fish consumption and increased retained mercury levels.

Mercury and Male-mediated Reproductive and Pregnancy Outcomes

There is relatively good evidence of the effects of mercury exposure on male reproductive function and reproductive organs. This may also impact male-mediated pregnancy outcome. The association between male workers exposed to elemental mercury and reproductive outcomes was investigated. All the study subjects worked for a minimum period of four months at a plant using elemental mercury. No links were reported between mercury exposure and diminished fertility, increased rates of major birth deformities or serious childhood illness in offspring but a limitation of this study was the lack of long-term recall of data concerning reproductive outcomes (29). Another study reported an association between male worker exposure to mercury vapor and rates of SAb in partners. There was a correlation between urinary mercury levels in the fathers' urine prior to pregnancy and SAb rate. Mercury concentrations at or above 50 μg/L of urine increased the risk of SAb two-fold (30). A review also stated that paternal exposure to lead or mercury might be related to the risk of SAb (31). More data are needed on the effect of mercury on human male reproduction or male mediated impact on pregnancy and outcome.

Impact of Mercury Exposure on Female Reproduction

Several studies are available concerning the adverse impact of mercury exposure on female reproductive health, on pregnancy and outcome in various animal species (32-36). Some clinical reports have been published about mercury exposure and female reproduction, as well as on pregnancy or outcome. A study in female dentists and dental assistants, who have a high risk of occupational exposure to mercury in dental amalgam, had significantly higher total hair mercury levels (TMLs). There was a notable, positive correlation between hair TMLs and the incidence of reproductive failure. Furthermore, there was a significant correlation between scalp hair TMLs and the manifestation of menstrual cycle illnesses (37). The effect of exposure to elemental mercury, used in gold mining, on menstrual cycle and miscarriages was evaluated among female inhabitants of gold mining areas in Colombia. A putative association was reported between elemental mercury exposure and the occurrence of menstrual cycles disorders, but no association was found with miscarriage (38). Similarly, the relationship between menstrual disorders in Tanzanian women involved in artisanal and small-scale gold mining (ASGM) was examined. This study reported that women workers exposed to mercury had a higher risk of menstrual disorders (39). Pregnant dental staff have been reported to be a greater risk of developing SAb and pre-eclampsia and giving birth to babies smaller for gestational age and it was suggested that this may be related to oxidative stress induced by mercury (40).

The reproductive risks of low-level exposure to metallic mercury in female workers was investigated and it was noted that longer duration of exposure caused dysmenorrhoea, and the incidence was dose dependent. At a mercury concentration over 0.06 mg/m^3, occurrence of hypomenorrhea significantly increased, while at a concentration <0.06 mg/m^3, menstrual cycles, flow quantity and length of flow did not alter significantly. Differences in occurrences of preterm delivery, SAb, fetal demise, still birth, and difficulties in pregnancy amid the group exposed to 0.06-0.1 mg/m^3 of mercury compared to the control group were not significant (41). Later, a retrospective study in female workers exposed to mercury vapor and non-exposed workers in food processing units showed the mercury level in the air of workplace was from 0.001-0.200 mg/m^3. The manifestation of abdominal pain and dysmenorrhea was significantly greater in the exposed workers (42). Furthermore, a meta-analysis showed that work-related mercury exposure could led to dysfunction in the menstrual period, menstrual cycle length, menstrual blood quantity, and dysmenorrhea among female workers and caused adverse reproductive outcomes, such as pregnancy-induced hypertension, stillbirth, low birth weights (LBW) and birth defects (43). A study assessed the association between mercury exposure, LBW (<2,500 g) and occurrence of preterm birth (PTB). About 15.7% of subjects delivered PTBs and 8.1% subjects delivered a LBW child. Lower mercury exposure, as in the group with the lowest tertile of hair mercury (<2.34 μg/g), was significantly related with LBW; this relationship was independent of maternal age, ethnicity, household income, and village location, while no relationship was found between hair mercury concentration and PTB (44).

In a very recent *in utero* mercury exposure study, prenatal exposure to high doses of mercury was related with an increased risk of precocious puberty, which was reinforced by concomitant maternal impaired cardiometabolic conditions and worse birth outcomes. The maximum risk of precocious puberty was noted amongst children who had poorer birth outcomes and their mothers had high erythrocyte mercury levels, together with impaired cardiometabolic conditions (45). Furthermore, a report indicated that mercury concentration in blood was significantly lower in postmenopausal women when compared to premenopausal women (46). These studies suggest that mercury exposure

related to menstruation dysfunction should be investigated further as there is uncertainty over the relationship between mercury exposure and the changes in age at menarche, puberty, and menopause.

Impact of Mercury Exposure on Pregnancy and Outcome

Some reports are available on maternal occupational/environmental exposure to mercury on pregnancy and outcome. Recently, a notable negative association between blood mercury concentration in the first and second trimesters and low birth weight (LBW) babies was observed (47). These authors suggested that pregnant and reproductive age women must avoid mercury exposure, even at low doses, as it has a potential severe negative effect on fetal development. Lee et al. (48) analyzed the relationship between prenatal mercury exposure birth weight and the influence of mercury exposure on *GST* polymorphisms. The geometric average concentration of mercury in the mothers' blood in late gestation and cord blood were 3.30 and 5.53 μg/L, respectively. For mothers with the *GSTT1* null genotype, a higher mercury level in maternal blood in late pregnancy was related with an elevated risk of LBW. For mothers having *GSTM1* and *GSTT1* null genotype, maternal and cord blood mercury was related to LBW. This suggested that mercury interaction with *GSTT1* and *GSTM1* polymorphisms might have some role in lowering birth weight (48). Furthermore, the effect of mercury exposure with neonatal auxology, placental weight, and gestational duration length in women exposed to mercury was assessed in terms of dietary seafood and it was found that prenatal mercury exposure may be associated with lower placental weight and poorer fetal progression (49).

A few reports on the effect of workplace mercury exposure while preparing and implanting of dental amalgam and pregnancy outcome are available. Brodsky et al. (50) collected the reproductive history of dental professionals, both male and female and including dentists and dental assistants._Their data showed no difference in the rates of SAb or congenital deformities in the children of both men and women when comparing those exposed to low versus high doses of mercury in a dental setting (50). In addition, the association between mercury exposure through dental amalgam fillings in pregnancy and birth outcome was investigated using logistic regression modeling, with variables including mother's age, body mass index, parity, education, smoking and alcohol intake during pregnancy. No significant relationship was found between the number of amalgam fillings and early or late preterm delivery, LBW, malformation, or stillbirth (51). There is some suggestion that exposure to electromagnetic fields may increase the discharge of mercury from dental amalgam and this led to the suggestion that pregnant women with amalgam fillings should avoid exposure to electromagnetic fields to minimize the toxic impact of mercury on their fetus (52). Furthermore, no robust correlation or constant dose-response association was found between exposure to chemical agents, including mercury amalgam, acrylate compounds, solvents and disinfectants, and the risk of miscarriage among dental workers. A slightly increased hazard of miscarriage was noted with acrylate compounds, solvents, mercury amalgam, and disinfectants (53). In addition, women with higher work-place mercury exposure were reported to be less fertile than non-exposed women. The fecundity, defined as the possibility of conception at each menstrual cycle, of women working in dental practice who prepared ≥30 amalgams per week and who had five or above poor mercury hygiene issues have 63% fecundity compared to unexposed women after controlling for covariates (54).

Inorganic mercury vapor exposure and reproductive outcomes were studied and a higher occurrence of contrary reproductive outcomes, particularly congenital anomalies, was reported amongst women who were exposed to inorganic mercury at or considerably lower than 0.6 mg/m^3, while no significant alterations in the miscarriage or stillbirth rates were observed between exposed and control groups (55). A higher miscarriages and stillbirth rate was observed in women who were exposed to five different heavy metals including mercury, lead, arsenic, chromium, and cadmium (56). Recently, a relationship between prenatal maternal mercury and arsenic exposure and adverse birth consequences was examined among ASGM subjects in Tanzania. In ASGM zones, the relative risk of poorer birth outcome was elevated with increasing total arsenic and total mercury exposure. Occurrence of SAb, stillbirth and PTB were significantly linked with elevated total arsenic levels, whereas elevated total mercury level was significantly related with stillbirth and congenital anomalies (57).

In addition, seafood consumption during pregnancy has been positively related with birth weight, while exposure to mercury was negatively linked with birth weight. Thus, seafood usage in pregnancy need not be avoided, but more data on the specific mercury exposure limits is needed to clarify at what level of mercury exposure poses adverse risk and reduce the advantages of seafood usage (58). However, maternal seafood consumption was linked with significantly higher levels of mercury. There was no relationship between mercury concentration and fetal growth, with the exception of a negative relationship with the biparietal diameter in offspring. A positive relationship was found between seafood consumption and fetal progress in women with higher BMIs, which remained after adjustment for mercury level. Nevertheless, seafood consumption was related to mercury contamination, but the contamination was

low. No consistent relationship was found between mercury level and fetal growth (59). Furthermore, blood MeHg level was significantly increased in infertile women compared to pregnant women and persistent with fish usage frequency. Compared to the reference blood MeHg concentration of <5.8 μg/L, the higher blood MeHg concentration (≥5.8 μg/L) found in infertile women was related to a 3.35 and 4.42-folds of risk associated with fish consumption of 1-2 meals/week or >3 meals/week, respectively (60). Moreover, there was no evidence of neonatal impairment related with mercury exposure due to consumption of fish during pregnancy and women should be confident that consuming fish during pregnancy is advantageous for their unborn child (61). These studies highlighted the positive role of fish consumption on reproductive outcome but that there is a risk of mercury exposure, depending on the source of dietary fish, which may impair fetal development. Hence, both risk and benefit should be considered with the consumption of fish in pregnancy.

Furthermore, pregnant mothers are usually given two different messages about the consumption of fish: 1) unsaturated fatty acids and protein consumption through fish are assumed to be advantageous; and 2) pollutants, such as MeHg, found in some fish might be hazardous. Fish intake was positively linked with hair mercury levels. Compared to women who delivered at term, women those delivered <35 weeks of gestation were more likely to have hair mercury levels ≥90th percentile (0.55 microg/g), after adjusting for maternal features and fish consumption (62). Furthermore, birth weights may be a good indicator of maternal health matters connected with nutrition and environmental pollutants. Hair mercury (HHg) level was examined as a marker of fish consumption and exposure to MeHg in mothers or newborns. Birth weight varied considerably among different groups and there was no consistent pattern with fish consumption nor HHg (63). The impact of blood mercury concentration in pregnant women on birth outcomes was evaluated and stratified by mothers who ate or did not eat fish. No significant relationship was found between maternal blood mercury and neonatal head circumference, birthweight, crown-heel length when analyzed by adjusted linear regression. Similarly, no increased odds of LBW or preterm delivery was observed. When this model was assessed by reference to the presence or absence of fish consumption, there was only a significant negative relationship for birthweight in non-fish-eaters. Moderate mercury level exposure during pregnancy was not connected with changes in neonatal anthropometry, or the odds of LBW or PTB and fish consumption might actually have a protective role on birthweight (64).

Clarkson and Strain (65) reported that a major source of human exposure to MeHg occurred usually from eating fish and sea mammals. Inorganic mercury is present in aquatic sediments, where it is methylated by microorganisms, and then enters the aquatic food chain. However, epidemiological studies among fish consumers from the Seychelles Islands have shown no negative effects. In contrast, the results of the few tests that were conducted in prenatally exposed offspring indicate advantageous outcomes (65). Very recently, the clinical consequences of MeHg exposure during pregnancy on fetuses, neonates, and child health were reviewed. It was reported that MeHg exposure during prenatal development was related with LBW, and one study described a negative relationship with birth length. The data are evidence of a clear negative effect of maternal MeHg exposure on anthropometric variables, cognitive or physical growth in children. Furthermore, mercury poisoning might sometimes be lessened by vital nutrients present in the maternal diet (66). A recent report indicated that moderate fish consumption, consistent with current health recommendations during pregnancy, was related to improvement in the metabolic health of offspring, while higher maternal mercury exposure was related with an unfavorable metabolic profile in children (67). Thus, an appropriate balance should be maintained in consumption of fish during pregnancy.

Finally, there are some data on the effects of mercury exposure and assisted reproductive outcome. The data on toxic agents in follicular fluid (FF) and in vitro fertilization outcomes indicated poorer IVF outcomes in couples exposed to certain reproductive toxins compared to couples not subjected to such exposure (68). HHg concentrations were not connected to ovarian stimulation outcomes (highest estradiol concentration, total or mature oocyte yields), embryo quality, fertilization frequency, clinical pregnancy, or live birth rate after IVF procedures (69). Very recently, it was reported that FF mercury level was related with a lower probability of biochemical pregnancy or live birth rate, and higher FF lead concentration was related to a lower probability of live birth. These data suggest that avoidance of exposure to mercury and lead might lead to improved IVF success rates (70). However, more data are required on this aspect. Hanna et al. (71) investigated methylation changes related to exposure to pollutants in women going through IVF and reported that DNA methylation was altered at several CpG sites related to exposure to mercury, lead and bisphenol A (BPA), offering candidates to be examined by utilizing a larger sample size.

The data on impact of mercury exposure on reproduction clearly suggests that mercury exposure, particularly exposure to MeHg, has deleterious effects on human reproduction, especially semen quality, menstruation, and pregnancy outcome. Additional data are needed on other reproductive endpoints to draw further inferences. A recent review based upon experimental data showed that testis and ovary are specifically sensitive to lead, cadmium, and mercury. In ovaries, toxic effects of lead, cadmium, or mercury diminished

follicular growth, led to the manifestation of follicular atresia, deterioration of the corpus luteum, and alterations in menstrual cycle. In testes, exposure to these heavy metals included changes in seminiferous tubules, testicular stroma, reduction of sperm count, viability and motility, and increased aberrant sperm morphology (72). Mercury exposure during pregnancy has been reported to be linked with pregnancy problems and impaired development in infants (73). Moreover, mercury exposure may have a substantial impact on several stages of reproduction, from prior to conception until maturation of organs and endocrine systems or even the healthy development of children (74). Tan et al. (75) reviewed the endocrine properties of mercury in humans and wildlife and reported five main mercury-related mechanisms within the endocrine system: 1) accumulation in the endocrine system; 2) precise cytotoxicity in endocrine tissues; 3) variations in hormone concentrations; 4) interactions with sex hormones; and 5) up-regulation or down-regulation of enzymes in the steroidogenesis pathway.

Conclusion

Based upon the data available, there is strong evidence that mercury exposure may have a deleterious impact on reproductive health of both sexes. Therefore, an adequate preventive strategy should be adopted to stop or significantly reduce mercury exposure for all populations. There is also a need for more data concerning various aspects of human reproduction and mercury exposure to substantiate the available data.

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