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LOW LEVEL MERCURY EXPOSURE EFFECTS ON FERTILITY

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Mercury is a toxic heavy metal which is widely present in environment. Mercury can be present in several chemical forms. Mercury is responsible of inducing a variety of clinical presentations. Mercury is a persistent, bio accumulative, toxic pollutant. Mercury has long been recognized as toxic, principally in relation to its effects on humans following acute or prolonged high-level occupational exposures and, in the latter half of the last century, from several environmental incidents. Mercury poisoning is involved in neurological diseases, cardiovascular diseases, collagen diseases, immunological diseases, and even allergies. There is an association between prenatal mercury exposure and the neurological development of the child. Depending on the dose and timing of exposure during gestation, the effects may be severe and immediately obvious, or subtle and delayed. The dose is measured using maternal hair as a biomarker. Prenatal exposure to mercury is associated with loss of IQ points, and a decrease in memory, language, attention, and spatial cognition.

Keywords: mercury, toxicity, oxidative stress, fertility. Recent studies indicate the negative impact of mercury exposure on the fertility, reproductive health and pregnancy evolution. The reproductive effects are present in both men and women.

INTRODUCTION

Mercury is a toxic heavy metal which is widely present in environment. Mercury can be present in several chemical forms. Mercury is responsible of inducing a variety of clinical presentations. Mercury is a persistent, bio accumulative, toxic pollutant. When released into the environment, it accumulates in water laid sediments where it converts into toxic methylmercury and enters the food chain. Mercury contamination is a significant public health and environmental problem because methylmercury easily enters the bloodstream and affects the brain. Due to decades of mercury deposition, mercury contamination in freshwater fish is widespread and significant. Mercury concentrations tend to be higher in larger, older fish and in fish from tea-colored and relatively acidic waters. According to the U.S. Environmental Protection Agency's 2014 National Emissions Inventory report, power plants that burn coal to create electricity are the largest source of emissions; they account for about 42% of all manmade mercury emissions[1].

Once it is released into the atmosphere, mercury can travel hundreds of miles with the wind before being deposited on the earth's surface. Deposition can occur in as little as five to fourteen days after mercury is emitted to the air, or it can take approximately one year – during which time mercury can reside in the air and be transported far around the globe. Once deposited on the ground, mercury can be carried by rain and snowmelt runoff to the state's surface waters. Mercury persists in the environment for long periods by cycling back and forth between the air and soil, all the while changing chemical forms. Atmospheric lifetimes of inorganic elemental mercury are

estimated to be up to two years, while organic methylmercury may stay in the soils for decades. Mercury is never removed from the environment; it is just moved to other locations and eventually buried under soils and sediments. Studies show that mercury deposition rates in New Hampshire, as in the entire Northeast, are higher than in other areas of the country due to the combination of local emissions and transport from upwind sources.

Mercury has long been recognized as toxic, principally in relation to its effects on humans following acute or prolonged high-level occupational exposures and, in the latter half of the last century, from several environmental incidents. Mercury poisoning is involved in neurological diseases, cardiovascular diseases, collagen diseases, immunological diseases, and even allergies. Recently concern has grown about the potential risks to the human population from current background environmental levels which is leading bodies such as the World Health Organization to call for both reduction and elimination of the use of mercury where possible[2].

SOURCES AND RISK OF EXPOSURE

Inhalation is the primary route of entry into the body for elemental mercury, while oral exposure is the primary route for inorganic mercury salts. Dermal penetration is usually not a significant route of exposure to inorganic mercury. There are several ways in which humans may be exposed to mercury. One of the major routes of human exposure is consumption of fish, cooking the fish does not decrease the methylmercury content. Occupation exposure can occur in the form of mercury vapor inhalation from the working environment. Mercury use has been well documented in daily routine products, such as disinfectants, preservatives, diuretics, antiseptics, and many others. Exposure can occur through several routes like oral exposure, inhalation, dental amalgams, and skin exposure from cosmetic products. Natural phenomena of attrition of minerals, volcanoes and human activities like manufacturing of metals, production of chemicals, processing of coal and waste managements have caused environment pollution with Hg[3].

Mercury vapor is a chemically stable gas which can reside in the atmosphere for around one year therefore it is broadly scattered across the globe. Mercury vapor eventually undergoes oxidation and becomes inorganic mercury. Inorganic mercury can combine with water vapor in the atmosphere and eventually travel back to earth in the form of rain resulting in the deposit of inorganic mercury in the soils and bodies of water. At this point the mercury can either be transformed once again into vapor and go back into the atmosphere or it may be converted into insoluble mercury sulfide in bodies of water which accumulates in the sediment and then converted into methylmercury by microorganisms opening a passage for methylmercury to enter the aquatic food chain. Methylmercury is far more toxic than inorganic mercury and organisms need a long time to eliminate it which results in bioaccumulation[3–5].

Methylmercury was released in a large ocean bay called Minimata Bay and around 200–600 tons was discharged into the bay over a period of 16 years (1952–1968)[5]. This resulted in bioaccumulation to a high extent in the local fish population with lethal levels of MeHg that eventually ended up being passed to the fish consuming local population[6]. This disaster revealed that the neurotoxicological effects on fetal development from pregnant women ingesting Hg-contaminated fish could be especially severe. This finding and as well as research over decades on the process of Hg bioaccumulation and biomagnification in marine life has led to today's about pregnant women limiting their consumption of fish like tuna, swordfish.

PHARMACOKINETICS

ELEMENTAL MERCURY

Elemental (HgO) exists as liquid metal and can vaporize at room temperature due to high vapor pressure. After inhalation, mercury vapor is rapidly absorbed, 80%, in the lungs and distributes to all tissue in the body due to its high lipid solubility. Once its inside cells it oxidizes into inorganic mercury by tissue and erythrocyte catalase. A significant amount of mercury vapor can cross the blood brain barrier and through the placenta, where it lodges in the fetal brain, before it is oxidized by erythrocytes into mercuric mercury, although not so quickly as to prevent considerable uptake by the central nervous system while still in the metallic form. This results in a higher neuro and developmental toxicity in comparison to inorganic salts that cross less rapidly[4, 7]. In addition to the brain, elemental mercury is also deposited in various other sites where it may be associated with

these organs dysfunctions such as the thyroid, breast, myocardium, kidneys, lungs, liver, pancreas, testes, and the prostate. It is also known to have the ability to bind on sites on the surface of T cells where it forms sulfhydryl groups and influence their function[7].

Inorganic mercury has a poor absorption rate when ingested and its absorption rate ranges from between 7% to 15% depending on the inorganic mercury that has been ingested and the highest concentrations of inorganic mercury are found in the kidney. A large amount of the body burden resides in the proximal convoluted tubule in is conjugated with metallothionein[4, 7]. The uptake of mercury salts in the kidney happens in two ways: from luminal membranes in the proximal tube in the form of cystine S-conjugates, or through the basolateral membrane through organic anion transporters[8]. Inorganic mercury has a half-life of 2 months and Is eliminated through feces and urine. This form of mercury cannot cross the blood-brain barrier but does accumulate in the placenta, amniotic fluid, and fetal tissues[4, 7].

METHYLMERCURY

Organic mercury undergoes pulmonary absorption and is well absorbed when ingested, only small amounts are absorbed through the skin[9]. When methylmercury is ingested 95% of it is absorbed and distributed throughout all the tissue in the body within 4 days when equilibrium between the body tissue and the blood occurs; the maximum accumulation in the brain is reached within 5 to 6 days. 10% of the absorbed mercury is distributed in the brain and about 5% remains in the blood where it builds up in erythrocytes in which the concentration Is 20 times higher than that found in plasma. Up to 80% of volatile methylmercury compounds such as methylmercury chloride vapor can be absorbed. Dermal absorption of methylmercury has been absorbed but there is lack of data on the subject. The half-life of methylmercury in the blood is from 49 to 164 days while its half-life in the brain is even longer than that[4, 5, 7].

Methylmercury can easily cross the blood-brain barrier and the placenta because methylmercury forms complexes with cystine, thiol containing molecules, which mimics methionine which crosses these barriers through the neutral amino acid carrier. There is enough time for methylmercury to cross these barriers since organic mercury has a slow metabolism rate. A great degree of accumulation of ionic mercury in body tissues and the brain occurs as methylmercury is metabolized into inorganic mercury and it has been found that accumulation also occurs in fetal umbilical cords in which the levels of methylmercury in the cord blood is higher than that in maternal blood. Methylmercury readily accumulates in hair thus hair mercury concentrations are a good indicator of exposure; blood to hair ratio is 1:250 in humans[4, 5].

Methylmercury is metabolized into inorganic mercury in the liver and kidneys. The inorganic form enters an oxidation-reduction cycle in the red blood cells, liver, and lungs which results in the formation of the divalent cation (hg++). About 1% of the methylmercury remaining in the gastrointestinal tract is converted into inorganic mercury per day by the intestinal flora. The excretory half-life of methyl mercury in man is about 70 days and around 90% of methylmercury is excreted through feces while 10% is excreted through urine and the degree of elimination depends on the body burden. It has been shown that lactating women have a significantly shorter excretion period in comparison to non-lactating women and about 20% of methyl mercury is excreted in breast milk, with the actual amount varying with severity of exposure[5, 7].

CLINICAL MANIFESTATIONS

ELEMENTAL MERCURY

Mercury vapor that is inhaled in high concentrations results in interstitial pneumonitis and acute corrosive bronchitis[4, 7]. Within a few hours of exposure, the patients typically experience having a cough with fever, shortness of breath, headache and muscle aches. The patients develop interstitial pneumonitis with bilateral infiltrates, a non-cardiogenic edema, and acute respiratory distress within a few days. Chest x-rays show diffuse, patchy changes of pulmonary edema, which usually clear but may progress to interstitial fibrosis, pulmonary granulomas, and bronchiectasis[10, 11]. In Chronic exposure to mercury vapor the major effects are apparent on the central nervous system. At first the effects may not be apparent and early sings are non-specific and is known as asthenic-vegetative syndrome or micro-mercurialism. To diagnose this neurasthenic symptom must be present and at least three of various clinical findings. The triad of tremors, gingivitis, and erethism is the major manifestation of chronic mercury poisoning through inhalation. Isolated instances of proteinuria and

nephrotic syndrome may occur in persons who undergo chronic exposure. It is good to note that mercury release from dental amalgam is too low to cause any significant toxicity[4, 7].

INORGANIC MERCURY

The toxicity of mercury salts depends on their solubility. In general, mercurous compounds are less toxic than mercuric compounds because they are less soluble in water, and oral exposure to mercury salts is generally considered to be of greater acute health effects than of mercury vapor[12]. The proximal tubule is the primary site of uptake and accumulation of mercuric species within the kidney[13,14]. There are several characteristics that make the kidney in general and the proximal tubules specifically highly susceptible to mercury. These characteristics include having a high rate of renal blood flow and glomerular filtration, having a high number of plasma membrane transport systems on the renal epithelial cells that lead to intracellular accumulation of chemicals, countercurrent flow and some other concentrating mechanisms that are involved in the formation of urine, because of the high requirements for ATP for transport and other processes, the kidneys especially susceptible to injury from chemicals or certain pathological states that inhibit mitochondrial function and energy metabolism[14]. On the other hand, a low exposure to inorganic mercury can also result in a rare immunologic glomerular disease[4]. Chronic poisoning with mercury salts is rare, but it may result in both renal tubular necrosis and autoimmune glomerulonephritis. A person may also develop a hypersensitivity reaction to mercury which includes asthma, dermatitis, and disruption of NK cells[7, 12]. Chronic inorganic mercury toxicity can also cause acrodynia which is a hypersensitivity reaction. It has been documented that African women who have been using skin lightning creams that contain ammoniated mercury eventually develop nephrotic syndrome[5]. Mercury containing lightening creams act to lighten the skin by replacing the copper required for tyrosinase activity and by inhibiting melanin in melanocytes[15].

METHYLMERCURY

There have been several mechanisms that have been proposed to explain how mercury neurons and these include: protein inhibition, disruption of mitochondrial functions, disruption of neurotransmitters, effects on ion exchange in neurons, and the destruction of the structural framework of neurons. Clinical manifestation can be seen in the forms of paresthesia, ataxia, neurasthenia, vision and hearing loss, spasticity, and tremors. Symptoms may keep progressing to coma and eventually death[4, 5, 7]. Numerous studies have also suggested other mechanisms of Hg toxicity such as induction of oxidative stress, damage of Ca homeostasis, and changes in glutamate homeostasis.

Methylmercury has a high affinity for the anionic form of thiol (-SH) which is responsible for most of its toxicological effect[16]. Methylmercury forms bonds with sulfhydryl groups throughout the body, therefore it can potentially interfere with the function of any cellular or subcellular structure[7]. Such interaction plays an important role in methylmercury induced oxidative stress and neurotoxicity[17]. Brain uptake of methylmercury is specifically linked to its binding of L-cysteine and its transfer via the neutral amino acid carrier site and this is probably the result of molecular mimicry; the L-cysteine-mercury complex has been found to mimic that of L-methionine[18].

Methylmercury can overcome the cell's natural protective mechanisms which are given by glutathione, metallothioneins, and the heat shock protein which results in the generation of reactive oxygen species (ROS)[16, 18]. A disruption in calcium and glutamate homeostasis also contributes to this[16]. Increased intracellular Ca^{2+} levels are associated with the generation of oxidative stress and neurotoxicity[17]. Astrocytic glutamate transport impairment by methylmercury can lead to an overproduction of ROS because increased glutamate concentrations in the synaptic cleft can result in a hyperactivation of N-methyl D-aspartate (NMDA) type glutamate receptors and this results in an increase in intracellular Na^{+} and Ca^{2+}, and this is associated with generation of ROS[16]. The most important health effect from exposure to methylmercury is its neurotoxicity. Methylmercury accumulates in the brain and is incorporated into the mitochondria, endoplasmic reticulum, Golgi apparatus, nuclear envelopes, and lysosomes. It can also be found in myelin sheaths of nerve fibers where it results in demyelination. The cerebellar cortex seems the be prominently affected with the granule cells being more affected than purkinje cells while the glial cells are typically sparred any direct damage[4]. Prenatal exposure resulted in microcephaly, cerebropalsy, seizures, and mental retardation[18].

Methyl mercury has been associated with reduction in Natural Killer cell activity as well as an imbalance in Th2 to Th1 ratios favoring

autoimmunity[7,12]. Certain autoimmune disease may manifest such as IBD, lupus. Rheumatoid arthritis, or multiple sclerosis. The immunotoxin effects of mercury compounds have been demonstrated many times over in animal models but at present day there is no evidence that suggest that mercury may induce frank autoimmune disease in humans[19].

PRENATAL MERCURY POISONING

The neurodevelopmental effects of mercury poisoning on the fetus are associated with maternal exposure. Fish and other sea forms are an essential component to a healthy diet. Some benefits to consumption of fish in pregnant woman is the presence of relatively high concentrations of ω-3 polyunsaturated fatty acids which are not commonly found in other foods as well as certain proteins which are essential for the development of the fetal brain[20]. The drawback of eating seafood is that many fish species organic mercury at high concentrations due to bioaccumulation which can cause adverse developmental effects on the fetus. The best evidence of the toxic effects on the fetus comes from the Minamata bay incident and Iraq poison grain disaster[20–22]. In Iraq in 1972, bread made from grain that has been treated with a methylmercurial fungicide poisoned 6,530 people[18].

There is an association between prenatal mercury exposure and the neurological development of the child. Depending on the dose and timing of exposure during gestation, the effects may be severe and immediately obvious, or subtle and delayed. The dose is measured using maternal hair as a biomarker. Prenatal exposure to mercury is associated with loss of IQ points, and a decrease in memory, language, attention, and spatial cognition[20, 21]. Prenatal methylmercury exposure might contribute to elevated blood pressure levels for teenage boys[21]. A study on very low-level prenatal exposure and behaviors in children has found that there was no statistical significance between mean prenatal mercury concentration and increase in behavior problems scores. The same study has found that a two-fold increase in mercury levels at around 16 weeks of gestation was associated with the development of anxiety[22].

Mercury exposure has a negative impact in fertility. This effect is caused by the hormonal imbalance, especially in female. After exposure the release of LH-luteinizing hormone is inhibit, due to the changes in progesteron/oestrogen ratio. Mercury can induce the prolactin secretion which will inhibit galactopoiesis. Mercury can act like an endocrine disruptor. Mercury exposure was correlated with premenstrual syndrome, amenorrhea, endometriosis, polycystic ovary syndrome. Newborns are more susceptible to the lowlevel mercury concentrations because of very permissive blood-brain barrier. Pediatric population present a higher rate of gastrointestinal absorption of mercury. The excretion mechanism are not well develop. The exposure of the mother during the early period of gestation can cause the accumulation of mercury in the amniotic fluid and adversely affect the normal development of the central nervous system. The main clinical sign is the children's cognitive acquisitions. Low level exposure to mercury will reduce the semen quality and induce the hormonal imbalance. Exposure to the mercury vapor was associated with the accumulation of this toxic in the testicles. After exposure, the level of testosterone can decrease and need for some various therapeutic approaches might be necessary. Inorganic mercury and methylmercury can be excreted in breastmilk[23–26].

CONCLUSIONS

Recent studies indicate the negative impact of mercury exposure on the fertility, reproductive health and pregnancy evolution. The reproductive effects are present in both men and women. Mercury reduced the sperm quality, reduced the movement of sperm, decreased the volume of spermatic fluid. Numerous researches show that the mercury act like an endocrine disruptor, especially on the progesterone/estrogen ratio. Exposure to low level exposure was correlated with a high incidence of dysmenorrhea, premenstrual syndrome, endometriosis, changes in lactation process. Some studies suggest that the poisoning can induce spontaneous abortions, congenital malformations and alter the neurological normal development.

These findings create the perspective to reduce the exposure of general population to mercury by initiating public health measure to protect the human being in front of a very persistent and accumulating toxic.

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