HUMAN REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF HEAVY METALS

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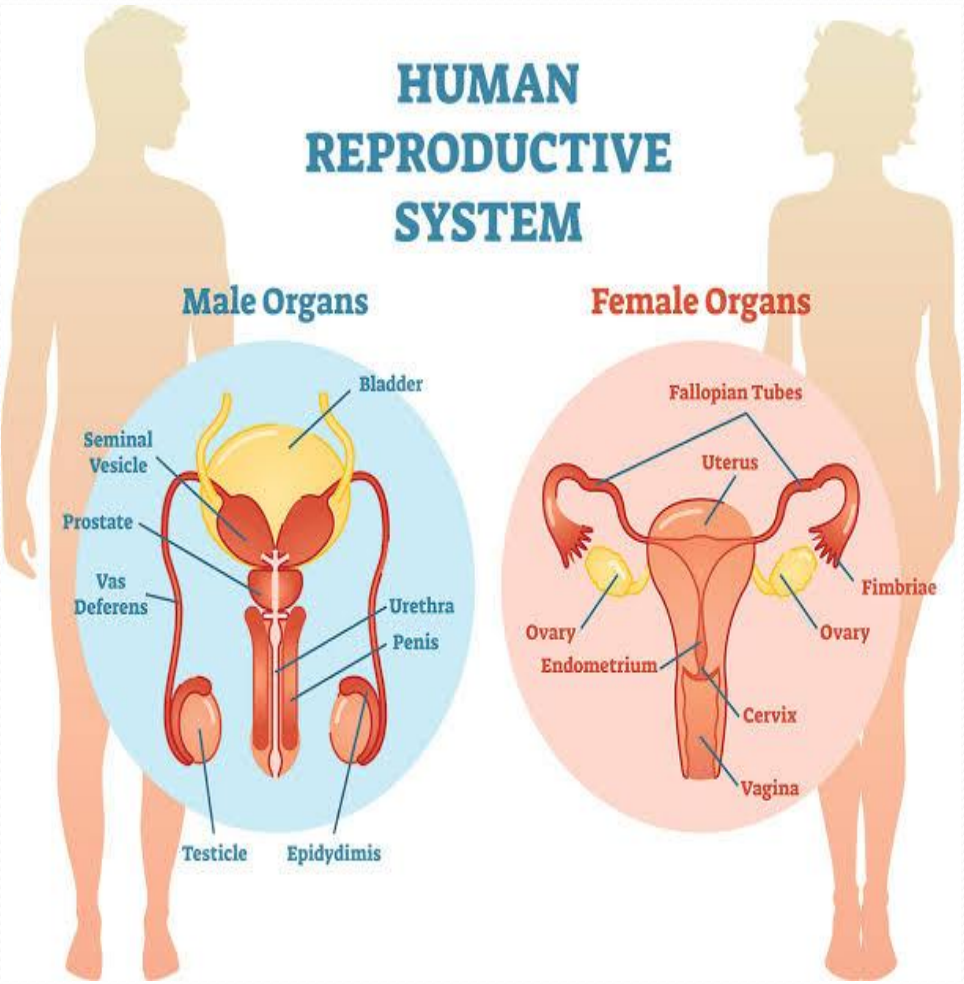
Human reproductive and developmental toxicity of heavy metals

- The field of metal toxicology has received much interest over the past few years. In this volume, the emphasis has been focused on the effects of Heavy Metals on Reproductive System.
- **In this context we considered :**
  - **The Effects of Heavy Metals on Male**
  - **The Effects of Heavy Metals on Female and**
  - **The Effects of Heavy Metals on maternal-offspring (Infants/Children).**
  - **Recommendations**
- For the first two situations - male and female - the primary targets are the gonads, although gonadal effects may also be the result of action of metals on hormonal control. Within the mother-offspring unit, the mutual relationship is a constantly changing one.

Human reproductive and developmental toxicity of heavy metals



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◆**Effects of heavy metals on Male:**

- Hypophysial gonadotropins, FSH and LH are essential to maintain spermatogenesis. Prolactin may also play an important role, as does the pineal antigonadotropin factor which appears to have a special effect on spermatogenesis during the prepubertal period of sexual development. The release of gonadotropins is regulated by the hypothalamic-gonadotropin- releasing hormone (GNRH). It is conceivable that metals and metal compounds might interfere with the synthesis, release, transport, metabolism and binding of these hormones at their respective receptors.
- Cadmium is known to accumulate in the pituitary gland and in the adrenals. MethyImercury and inorganic mercury are known to accumulate in the central nexvous system and in the hypothalamic area. In the case of lead exposure, a number of reports are available concerning effects on pituitary function.

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- Several metals such as lead, mercury and manganese have been shown to interfere with nervous function at the level of release and action of transmitter. Effects may be anticipated in the case of nervous control of erection and ejaculation. A clinical report indicates interference with ejaculation and erection in lead-poisoned workers.

●Direct effects on male reproductive organs:

- When discussing the effects of metals on male reproductive organs, a number of specific targets must be considered.
- Metals can interfere with the supply of blood nutrients to the gonads by interfering.
- Metals could interfere directly with the endocrine function of Leydig cells and with the different steps of spermatogenesis.
- Metals could inhibit spermatogonial cell divisions or meiosis of spermatocytes.
- They may interfere with either the maturation of spermatozoa, by changing the function of the epididymis, or with the functions of accessory glands.
- Finally, metals may affect spermatozoa directly in the semen, if excreted by the accessory glands.

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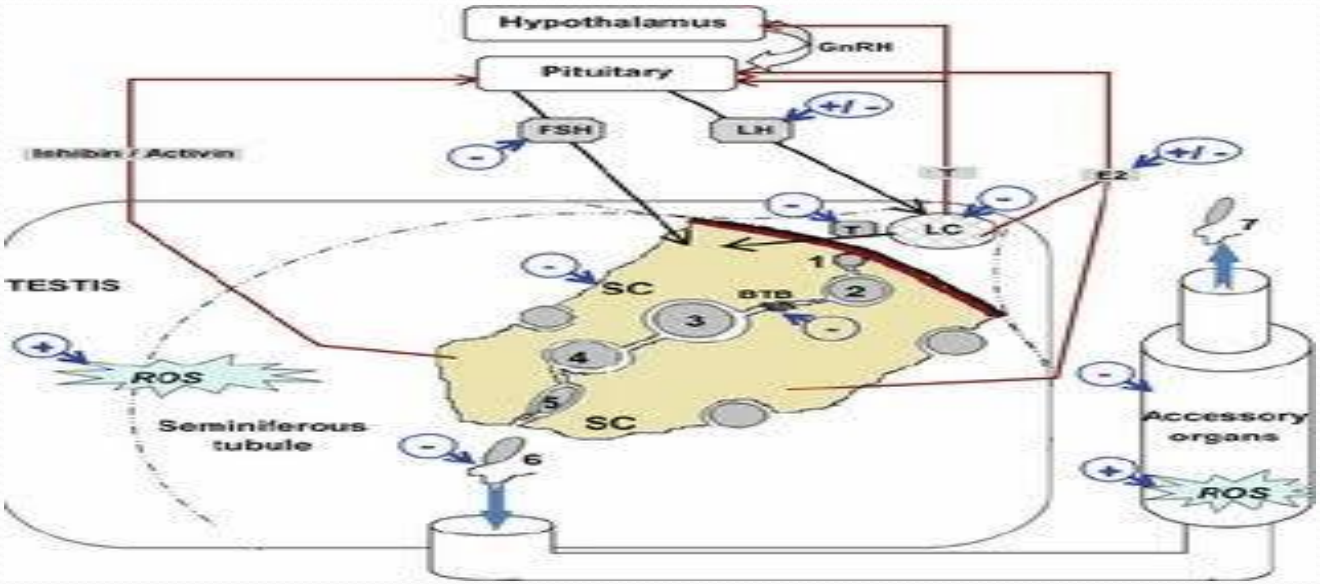

- Effects of Metals on Blood-testis Barrier, Leydig Cells and Testicular Blood Vessels.
- Effects of Metals on Spermatogonia and Primary Spermatocytes primary.
- Effects of Metals on Secondary Spermatocytes, Spermatids, Spermatozoa, and Accessory Glands.
- Effects of Metals on Semen, Fertility and Progeny.

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- **Conclusions, based on discussions of the working group:**

1. Metals do accumulate in male reproductive organs such as the testicle and prostate.
2. Animal experiments indicate that certain metals e.g. such as lead and methylmercury can cause toxic injuries and can interfere with male reproductive function.
3. Data on the effects of metal exposure on male reproductive function in man are scarce and insufficient to allow conclusions as to the risk of adverse effects on male reproductively. In the case of lead, data show that toxic exposure interferes with male reproductive function. Effects like hypospermia and impaired fertility have been reported.
4. Genetic effects on male germ cells cannot at present be excluded although no current epidemiological data indicate such effects.
5. Metals, with the possible exception of lead, have not been clearly identified in the scientific literature as environmental agents, such as dibromochloropropane, a-chlorohydrin, that are known to cause adverse effects on male reproductive function.

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- **EFFECTS OF HEAVY METALS ON FEMALE REPRODUCTIVE SYSTEM:**
  - Effects of Metals on Sexual Maturation As indicated previously, sexual maturation is thought to be mediated by the hypothalamus. Cadmium appears to have a different effect than lead in its effect on sexual maturation; the ovaries appear exquisitely sensitive to cadmium toxicity during this period. After sexual maturation, however, the ovary appears relatively resistant to cadmium toxicity. Several investigators have also suggested that mercury may alter hypothalamic function in developing rodents.

- **Effects of Metals on Reproductive Function in the Sexually Mature Female :**
- Hypothalamus - pituitary. Lead, cadmium, mercury and nickel are thought to have an adverse effect on hypothalamic-pituitary function. Lead may affect only developing rather than sexually mature rodents, although one study suggested that ovarian atrophy in sexually mature animals was the result of diminished FSH levels in lead treated animals.

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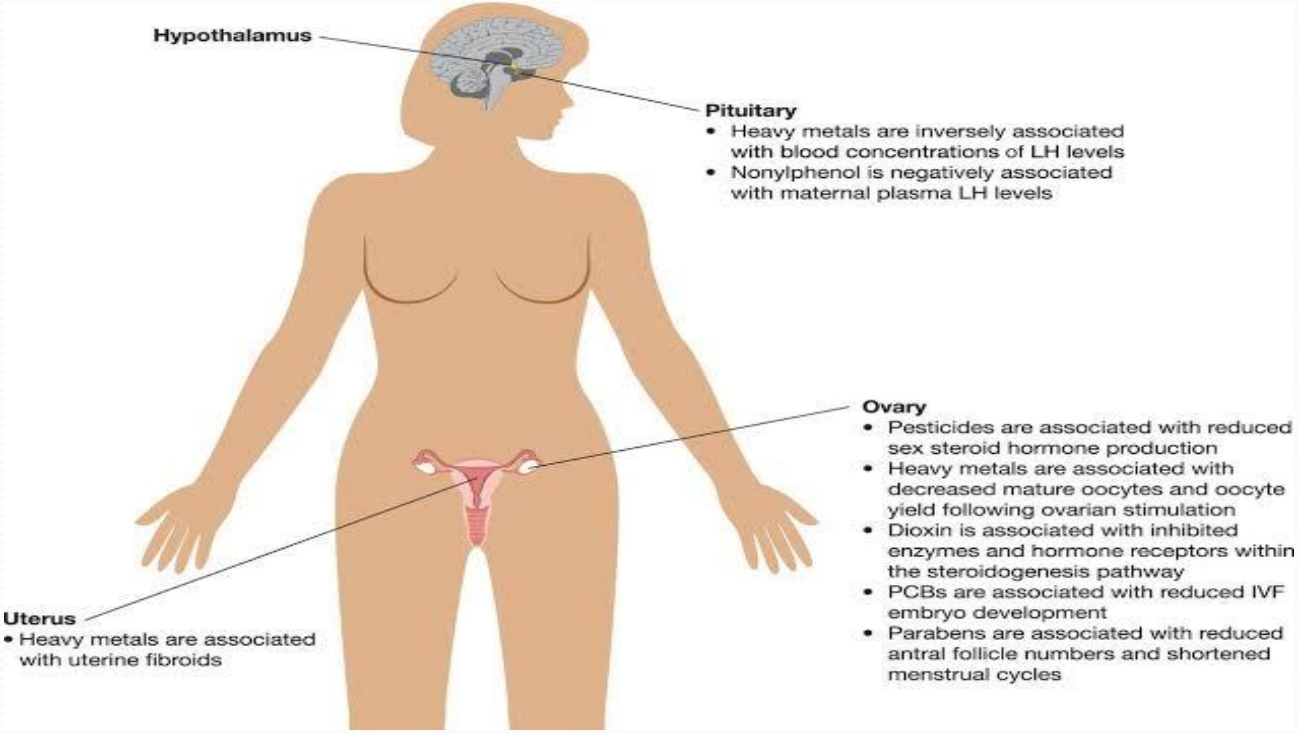
- **Ovary:**

Lead and cadmium are well documented to produce direct ovarian toxicity. Although differential follicular counts have not been performed, it is expected that the effects will be manifested on the growing and preovulatory follicles.



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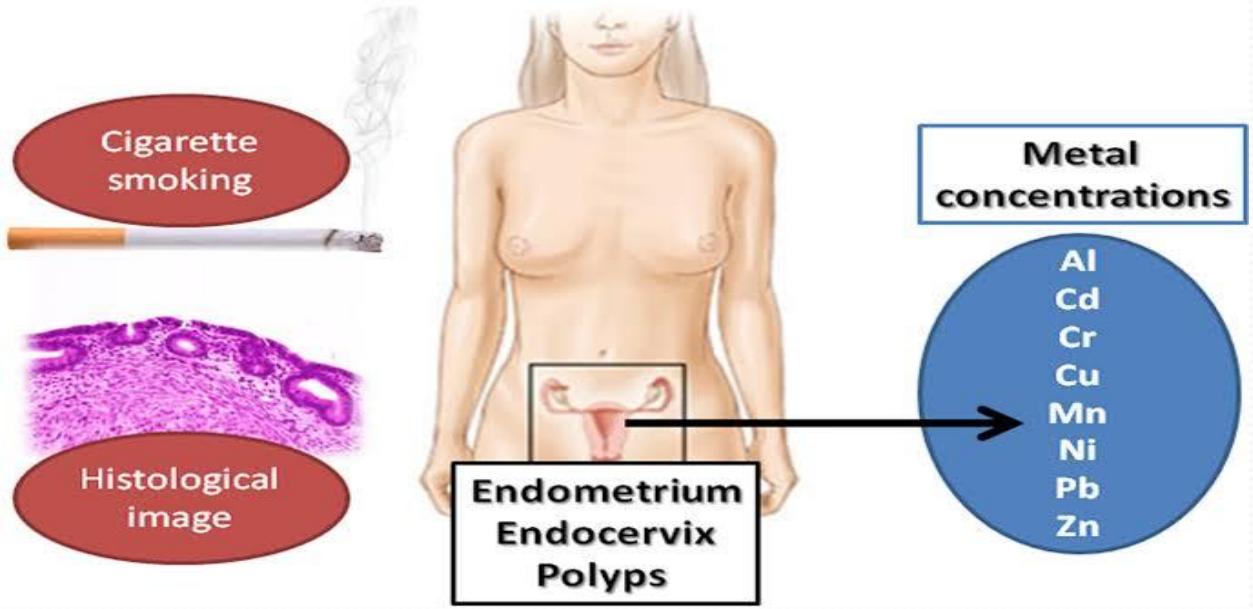
- **Uterus:**

At the present time lead, copper, nickel and cadmium appear to alter the function of the uterus. The effect of lead appears to be specific for estrogen receptors, altering endometrial response to ovarian estrogen creating an endometrial environment hostile to preimplantation embryos.The effect of cadmium on the uterus appears subtle.



Overall Conclusions:

1. Lead, cadmium and mercury have definite multiple adverse effects along the mature hypothalamic-pituitary-ovarian-uterine axis in experimental animals. In addition, cadmium, mercury, selenium and arsenic appear to alter the development of the reproductive system in experimental animals.
2. In spite of the adverse effects along the hypothalamic-pituitary-ovarian-uterine axis, and for the developing reproductive system noted above, there remain large gaps in our knowledge of the sensitivity of the female reproductive system to metals.
3. At the present time, it is not possible to rank the relative sensitivity of reproductive endpoints along the hypothalamic-pituitary-ovarian-uterine axis, or the developing female reproductive system. Because of this, it is necessary to consider all of these endpoints in studies exploring the reproductive toxicity of metals.

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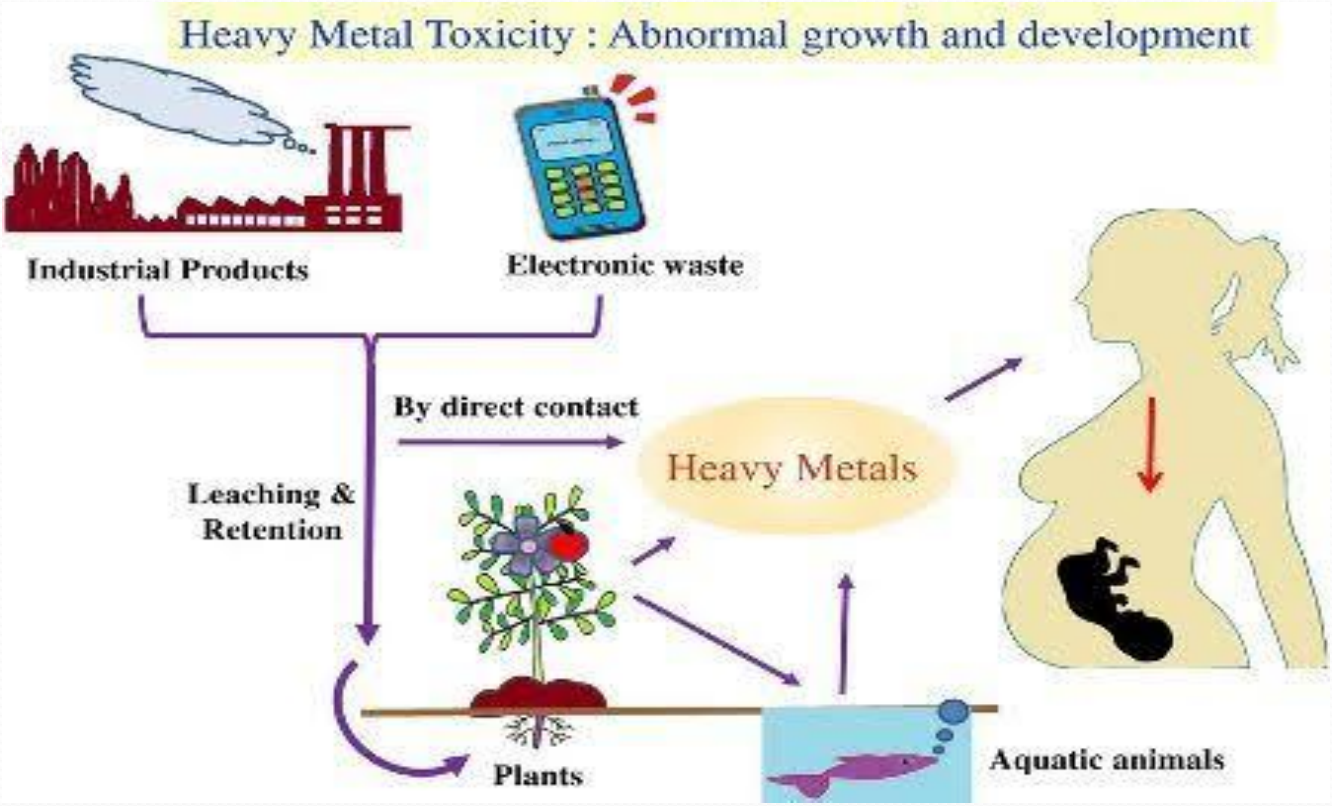
- **EFFECTS ON CHILDREN AND PREGNANT WOMEN:**

Heavy metals like arsenic (As), cadmium (Cd), lead (Pb) and mercury (Hg),The exposure to these heavy metals during pregnancy are believed to have adverse effects on the mother and the fetus.



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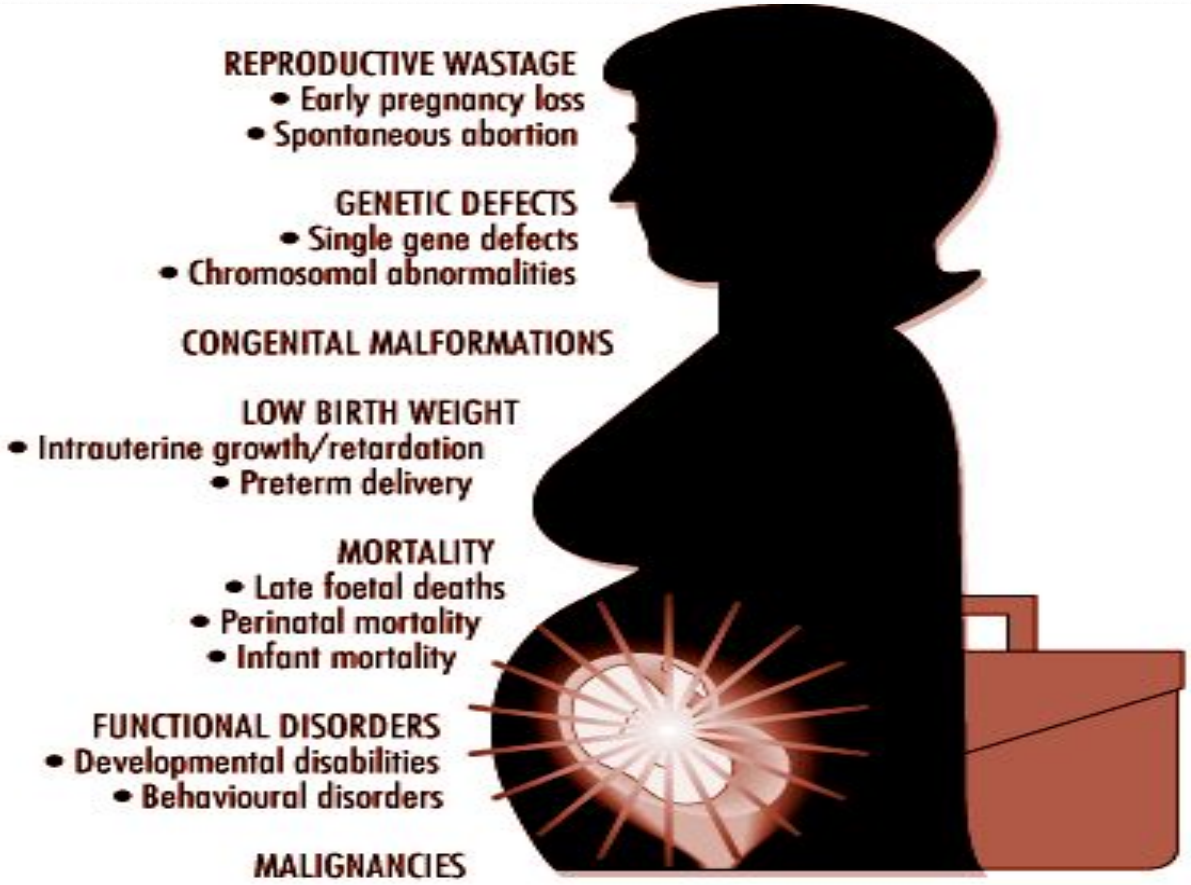
- Placenta cannot prevent the passage of toxins like thalidomide or mercury which subsequently accumulate in fetal tissues.



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- The heavy metals are key toxicants that are well-documented to cross the placenta and to accumulate in fetal tissues with subsequent deleterious effects . This particular group of heavy metals have been shown to alter the delicate maternal-fetal balance, hence causing long-term damage to the newborns.
- Prenatal mercury exposure, measured through samples of cord blood, is associated with ADHD symptoms in children.
- Aluminum accumulates in immune cells of the brain. This may provoke an inflammatory immune response that ultimately affects neurological function and behavior.

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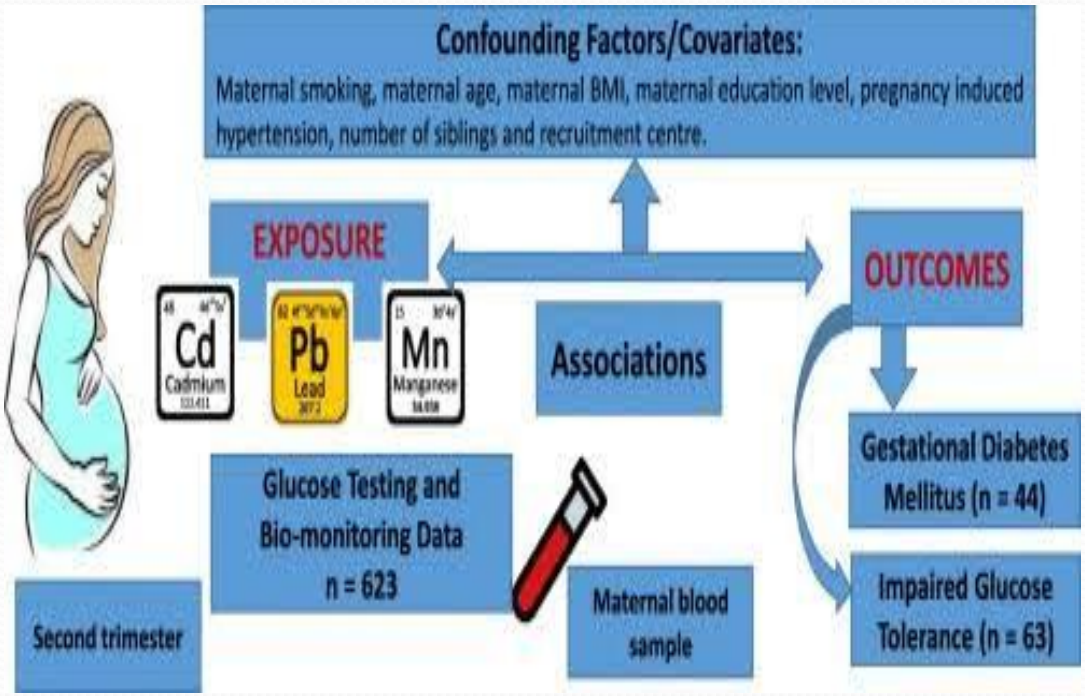
- Mercury content in ambient air is linked to an increased prevalence of autism in children. Even low levels of mercury are harmful to the developing brain and have been associated with learning disabilities.
- Heavy metals displace essential minerals such as zinc and iron that are required for neurotransmitter production. Heavy metals induce oxidative stress, which reduces neuronal plasticity and impairs learning and behavior.



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- **Recommendations, based on discussions of the working group:**

1. Identify areas for further. Study (e.g., molecular biology, biochemistry, endocrinology, and male reproductive physiology, etc.) and further develop improved and validated testing methods to assess male reproductive toxicity
2. Special efforts should be made to develop procedures in order to facilitate the cooperation of workers and people subject to metal exposure to take part in studies and to provide semen samples. Procedures should also be worked out to enhance investigator and management cooperation. Comprehensive studies in humans should also be well designed and should include:

Metal levels in semen and blood.

- **Fertility.**
- **Teratology.**
- **Possible biopsy.**
- **Semenanalysis.**
- **Statistical analysis.**

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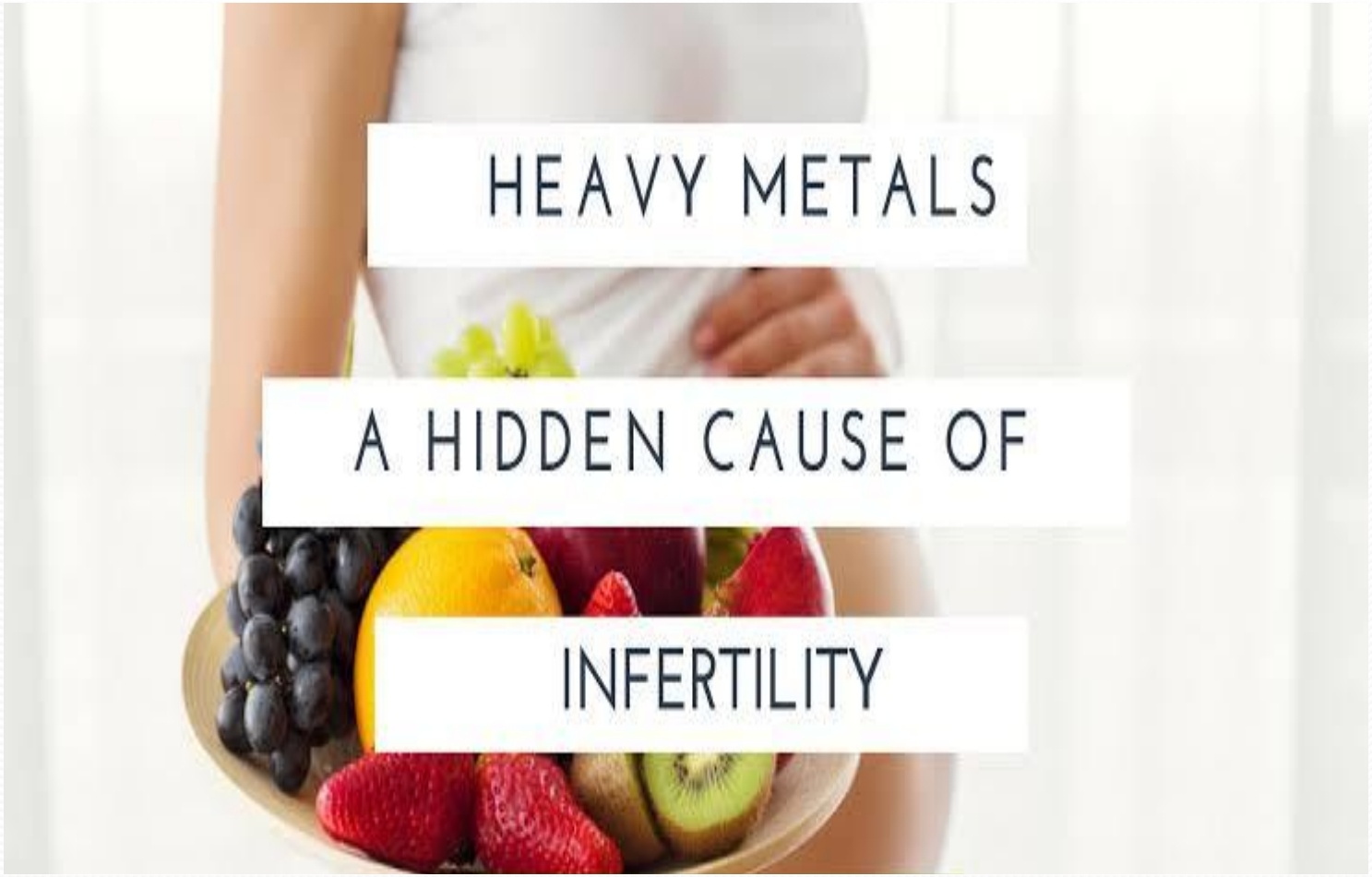

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3. Additional directed epidemiological studies of exposed populations are needed to develop an understanding of human hazard and evaluate risk.
4. An International Clearinghouse for reproductive toxins for occupational, environmental or accidental exposures needs to be established to collect and evaluate worldwide data on reproductive toxicity.

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5. Worldwide educational programs should be developed to Increase the awareness of health scientists and physicians to the potential for reproductive hazards.
6. Specific focused studies of occupationally exposed populations to measure early unrecognized pregnancy loss should be encouraged to evaluate the utility of this promising technique.
7. Regional differences in human and domestic animal reproductive endpoints with respect to exogenous food/or water contamination should be explored. This technique has been helpful in exploring environmental factors in carcinogenesis and in lead toxicity and may prove useful in reproductive toxicology. Metals with increasing industrial use and environmental contamination should be flagged for characterization of effects on the female reproductive system (e.g., aluminum, cobalt, iron, lead, molybdenum, tungsten and vanadium).

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