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Mini Review

Nickel Toxicity with Reference to Female Reproductive Physiology, Pregnancy and Teratogenesis: A Brief Review

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Abstract: Nickel has been known to adversely affect the female reproductive system and pregnancy, and cause teratogenesis. This review aims to analyse these effects of nickel. The implications of maternal oxidative stress and hormonal perturbations caused due nickel exposure have been discussed. Increased placental permeability, unidirectional foetal exposure through blood and milk leading to defects during organogenesis are analysed, along with post parturition eventualities such as stillbirth and altered sex ratios. Efforts are made to understand the ameliorative effects of selenium and possible future directions of research in the broad area are enumerated.

Keywords: nickel, teratogenesis, toxicity, pregnancy, foetal exposure

1. Introduction

Nickel is known to have mutagenic, immunotoxic, carcinogenic and teratogenic properties [1-3]. Despite heavy metal toxicity being an area of active investigation, not many studies have focused on the reproductive toxicity of metals. A large number of studies have shown that indeed metal ions have detrimental effects on almost all organs, especially the vital organs and nearly all cell types. The toxicity of water-soluble metal ions has been extensively studied on vertebrate model systems including but not limited to zebrafish, mice and rats.

Nickel, in general, is harmful to the reproductive health of lab animals. Nickel exposure is common to people living in and around areas where nickel is mined and/or nickel is used in industries. Our previous review was [4] focused on the consequences of nickel exposure on male reproductive health, besides exploring the general effects of nickel toxicity. In continuation of the same theme, this review explores the effect of nickel exposure on female reproductive health, pregnancy, and subsequent teratogenic effects on the foetus, the maternal body during pregnancy and post parturition. This comprehensive analysis of the reproductive toxicity of nickel in females aims to consolidate our knowledge to provide a firm footing for future work in this area.

2. Effects of nickel exposure on female reproductive physiology

Nickel is a possible stimulator of lipid peroxidation (LPO), as the oxidative degradation of lipid peroxides to more reactive lipid radicals is catalysed by nickel [5]. Possible production of superoxide, hydroxyl radicals, and oxygen from

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hydrogen peroxide reacting with nickel complex of glycyl-L-histidine has been reported [6]. Ascorbic acid is known to protect biomembranes against oxidative degradation by efficiently trapping peroxyl radicals before the beginning of LPO, in human plasma lipids [7].

Nickel causes female reproductive toxicity in more than one way. Various studies have proven that the toxicity of the embryo and foetus may be caused by nickel induced maternal hormonal imbalance, instead of directly affecting fertilization [8]. Various hormones such as prolactin (PRL), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are also altered on nickel exposure. A dose-dependent alteration in the ovarian cycle and decline in the response of progesterone to gonadotrophs along with a dose-dependent decrease in human chorionic gonadotropin (hCG) and dibutyryl-cyclic adenosine monophosphate (db-cAMP) is observed in rat ovary on nickel exposure [9]. Exposure to nickel chloride ($NiCl_2$) in female mice leads to a loss of ovarian and uterine functions besides cytotoxic and histological changes in these organs in the laboratory [10]. A study conducted on granulosa cells acquired from women who underwent in vitro fertilization (aged 23-37 years) revealed a dose-related decline in hCG stimulated progesterone production when exposed to varying concentrations of nickel for 48 hrs (15.6, 31.25, 62.5, 125, 250, 500, 1000 µM Ni) [11]. A decline was observed at 15.625 µM or higher concentration. In order to check the site of action Ni^{2+}, progesterone was produced on stimulation of granulosa cells using 0.1 IU/ml hCG or 1 mM db-cAMP. A significant decline in cell viability was observed at 62.5 µM or higher concentrations of nickel, along with concentration dependent decrease in the amount of progesterone produced at a dose which does not cause a notable cytotoxic effect [11]. The study concluded that Ni^{2+} does not have a cytotoxic effect on progesterone production, the cellular site for Ni^{2+} action is the membrane receptor [9]. It has been experimentally proven that gavage treatment of females with nickel nanoparticles (Ni NPs) (5-45 mg/kg BW) for 18 weeks led to a notable decline in normal pregnancy, birth survival and feeding survival [12]. Damage induced by Ni NPs to ovaries leads to a decrease in ovarian hormones, which in turn leads to an increase in FSH and LH levels in serum, as a result of negative feedback [12]. The treatment of female mice with varying doses of $NiCl_2$ (8 and 18 mg/kg BW) for 30 days led to a drop in body weight in addition to ovary weight in comparison to control. There was a decrease in protein levels of the ovary, increased LPO, a decline in glutathione (GSH) and thioacetamide (TAA) levels, and decreased activity of superoxide dismutase and catalase [10].

Alteration in the growth hormone, the release of insulin [13] as well as inhibition of PRL secretion [14] and increased plasma glucose in female rats could induce foetal hyperglycemia [15] was shown to be caused by nickel ions. Exposure to surplus glucose leads to high incidences of neural tube defects in embryo cultures [16].

Workers exposed to nickel showed an increase in spontaneous abortions [17]. Alteration in cell shape and distribution of microtubule, as well as a decrease in the number of cadherins and β-catenins along the surface in human ovarian granulosa cells is induced by nickel exposure [9].

Pituitaries of pregnant rats show higher uptake of nickel as compared to non-pregnant rats, as nickel hinders PRL release from the pituitary and it may be a mediator for the hypothalamus/pituitary axis disruption [11].

Dietary intake of nickel results in major accumulation in the kidney, some of it is accumulated in the liver, and some of it is retained in skin and fur (to be removed through its active metabolism) [18].

There is a noticeable accumulation of metal in the kidney of rats on the intramuscular administration [19]. It has been observed that intrarenal injections of nickel subsulphide result in renal carcinomas [20] whereas nickel carbonate induces protein-deoxyribonucleic acid (DNA) cross-links in rat kidneys in vivo [21], and in cultured mammalian cells [19] in rats. Experiments on zebrafish kept on varying concentrations of nickel in diet (116 µg Ni/g diet) for 80 days, showed a significant decrease in the number of eggs spawned per female. It was 65% less compared to the animal on the controlled diet (3.5 µg Ni/g diet) [22]. The effects of nickel on the female system are summarised in Figure 1.

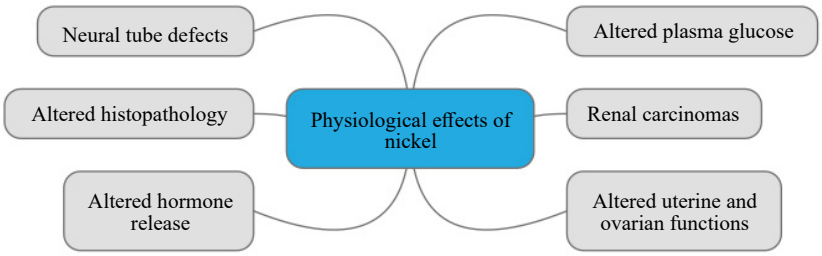

Figure 1. The physiological effects of nickel on the female system

3. Effects of nickel exposure on pregnancy

Syncytiotrophoblast and the foetal endothelium are two layers of the human placenta, which allow the transport of ions through it [23]. The accessible characteristic of the tissue layers in the middle of maternal and foetal blood limits the movement of hydrophilic molecules by the placenta [24]. Transport function and cellular integrity are affected by exposure of the placenta to heavy metals [25].

On treatment with nickel, enhanced permeability of potassium ions was observed, suggesting that nickel affects placental permeability [26]. On increasing the dose of nickel, foetal metal retention did not increase, which shows placental shielding counter to nickel loading, which may be due to the reaction of nickel with histidine residues of syncytiotrophoblast [27]. Autoradiograph of foetus and placentas on the 19th day of gestation has shown localization of Ni^{2+} in the foetal urinary bladder, basal laminae and yolk sac [19]. The surplus nickel in the basal lamina may localise as a nickel-albumin complex since albumin is a chief transport protein for serum nickel [20]. Placental transfer from mother to foetus is in one direction and leads to the accumulation of nickel in the kidney. The damaging effect of nickel is seen in the foetal kidney, which retains the highest concentrations of nickel.

Tumours of the kidney and pituitary occur in foetuses on the transplacental transfer of nickel [28]. Nickel is known to cross the placenta and reach an embryo during the first week of gestation [13, 29]. Embryotoxicity and teratogenicity of nickel are a result of the direct embryo-damaging effect and cytotoxic effect on the placenta. Altered embryonic development is due to the mutagenicity of nickel [30, 31].

In rats, post parturition, the offspring are more vulnerable during nursing since nickel is secreted in milk [32], which results in a major loss of pups. Increased mortality before the weaning period may be a result of physiological disturbance caused by nickel consumed via milk. Altered milk quality and decline in milk production occur on high exposure to $NiCl_2$ [32]. Exposure to high levels of nickel may adversely affect reproduction. Investigations have revealed an increase in embryo mortality and impaired foetal growth on exposure of pregnant rats to $NiCl_2$ and nickel sulphide.

It can thus be inferred, that toxicity of nickel on the human placenta is mediated by reactive oxygen species (ROS) [26]. Nickel induced peroxidative changes in the human placenta may lead to a decline in the viability of the placenta, toxicity of the embryo and altered permeability [33]. LPO is known to affect placental nutrient permeability leading to changes in histopathology of reproductive organs and foetal toxicity.

In the treatment of rats with increasing concentrations of nickel sulfate, an increase in the rate of intrauterine foetal mortality has been reported [34].

4. Teratogenic effects of nickel

Nickel administration results in foetal malformations during organogenesis and effects are dose-dependent. There is a decline in the number of live pups in addition to a drop in the body weight of foetuses in pregnant rats and mice [35]. Exposure to nickel in males leads to fewer pregnancies and increased pre-implantation deaths [36]. On the other hand, exposure to nickel in both sexes leads to an increase in pup mortality and the amount of runt pups [37].

Nickel treatment altered the sex ratio as only a small number of pups were male. This effect is seen when nickel is administered to either parent.

Increased frequency of stillborn and abnormal foetuses along with decreased implantation frequency in early embryogenesis is also observed on nickel treatment. Intravenous injection of nickel acetate in pregnant hamsters on the eighth day of gestation shows an increase in the percentage of resorbed foetuses [38] whereas nickel carbonyl exposure resulted in ocular anomalies in the progeny [39] thus implicating nickel toxicity in the development of the eye.

Studies have revealed that exposure to $NiCl_2$ in pregnant mice (7^{th}-11^{th} day of gestation) resulted in developmental malformations [40]. The teratogenic effects of nickel are summarised in Figure 2.

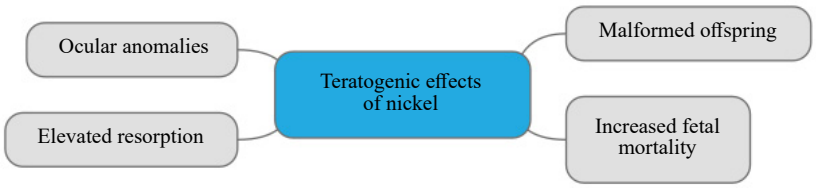

Figure 2. Summary of teratogenic effects of nickel

5. Protection studies to minimise and ameliorate nickel toxicity to the foetus by selenium

Various studies are being carried out to investigate the potential of agents which can minimize the toxicity of nickel to the foetus.

Moderate supplementation of selenium has advantageous effects on the reproduction of experimental animals. Nickel is known to have oxidative properties [41], while selenium plays a key role in the antioxidant system of animal tissue [42]. Nickel exposure on supplementation with selenium aids in the synthesis of glutathione peroxidase [42], an enzyme that catalyses the reaction of reduced GSH with hydrogen peroxides and organic peroxides [43]. When dietary levels of selenium are low, growing pups become more prone to oxidative damage caused by nickel or other trace elements. The defects might be prevented by subtoxic supplementation of selenium. This contributes to protection in developing pups during nickel exposure. This could be explained in two possible ways: selenium, as an antioxidant, could protect the pup tissues from oxidative stress or it could participate in chelating nickel, thereby preventing toxic effects. Various symptoms observed in pups that died before weaning resemble those seen in selenium deficiency, which could possibly be induced by nickel [18]. Still, extensive research is required to clearly understand the underlying mechanism of nickel-selenium interaction.

6. Conclusion and further line of research

Nickel is known to adversely affect female reproductive physiology, developmental biology, fetal growth, and lactation [1, 2, 32, 35, 44]. Other than the obvious ROS mediated DNA damage to the oocyte and the oxidative stress produced in the ovaries, nickel has been shown to decrease litter size [35] and influence sex ratio and teratogenesis, possibly by causing ROS mediated changes to DNA.

Whether nickel is involved in the sex chromosome disjunction has not been studied, however, interference of nickel with the hormone balance is well documented [11, 13, 14, 45]. Nickel has been shown to influence PRL, LH, FSH and gonadotropins, and their crosstalk. Nickel has been shown to lower the levels of testosterone in males [46, 47], however, studies on how the testosterone levels in females are affected if at all are conspicuously absent. Nickel is known to be secreted in milk and therefore children of lactating mothers exposed to nickel may be at extra risk since, besides environmental exposure, these children would be exposed to an extra dose of nickel in milk. Nickel has further been shown to influence placental permeability [13, 29], which is indispensable for normal placental functioning [11].

Further research in this area includes the development and validation of better cellular model systems which can provide physiologically meaningful information with reference to female reproductive biology. The effect of

heavy metals in general and nickel in particular on the menstrual cycle needs to be understood at a greater depth. Another important and emerging area of research is identifying junctures where heavy metals act in the hormonal synchronization of the menstrual cycle, pregnancy, foetal development, birth and lactation. It has not escaped our notice that such studies on both animal models and humans will generate large data sets, and suitable programming softwares need to be developed to handle the acquired data to obtain and extract biologically meaningful information.

Nickel mediated DNA damage in the placenta has not been documented, however, it is reasonable to presume that nickel will be producing oxidative damage and oxidative DNA breakage in the placenta [48]. Interestingly, the gestational date of exposure and/or time of exposure post conception also seems to affect the fate of the fetus in experimental animals [34, 38-40]. This area seems to be largely unexplored and could possibly lead to insights into the molecular mechanisms of fetal nickel toxicity.

Conflict of interest

There is no conflict of interest for this study.

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