Subacute Exposure to a Mixture of Tributyltin plus Mercury Impairs Reproductive Axis Function, Exacerbating Premature Ovarian Insufficiency Features and Reducing Fertility in Female Rats.

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ABSTRACT.

Tributyltin (TBT) and mercury (Hg) are known endocrine-disrupting chemicals (EDCs), which individually cause reproductive complications. However, the reproductive consequences of exposure to a mixture of TBT plus Hg are not well known. We hypothesized that exposure to a mixture of TBT plus Hg alters the function of hypothalamic-pituitary-gonadal (HPG) axis components. Adult female rats were exposed daily for 15 days to the following doses:1-CON rats (vehicle, ethanol 0.4%, by gavage, saline solution 0.9% by im, n=5), 2-TBT rats (100 ng/kg/day, by gavage, n=5), 3-Hg rats (first dose 4.6 mg/kg, and subsequent doses of 0.07 mg/kg/day, im, n=5) and 4-TBT+Hg (similar dose/exposure from TBT and Hg groups, n=5). Chemical accumulation in serum and organs, morphology, hormone levels, inflammation, fibrosis, and protein expression of reproductive organs were assessed. Irregular estrous cycles, showing less time in the proestrous phase and longer cycle length were observed in TBT-Hg rats compared with CON rats ($p < 0.05$). Increases in tin and Hg levels were found in the serum, hypothalamus, pituitary, ovary, and uterus of TBT-Hg rats compared with CON rats ($p < 0.05$). TBT-Hg rats showed an increase in gonadotropin-releasing hormone (GnRH) protein expression and serum follicle-stimulating hormone (FSH) levels and, a reduction in luteinizing hormone (LH) levels compared with CON rats ($p < 0.05$). Reduction in ovarian reserve, antral follicles, corpora lutea (CL) number, and estrogen levels, with increases in atretic and cystic follicles, were also found, suggesting that TBT-Hg exposure exacerbated premature ovarian insufficiency (POI) features compared with CON rats ($p < 0.05$). Further, in TBT-Hg rats, there was an increase in ovarian mast cell number, IL6 (inflammation marker), FSH receptor protein expression, and collagen deposition compared with CON rats ($p < 0.05$). In the uterus, apoptosis, reduction in uterine glands, and glycogen levels were observed in TBT-Hg rats compared with the CON rats ($p <0.05$). Reduction in litters and pups/litters for 90 days were found in TBT-Hg rats, suggesting impairment in fertility compared with the CON rats ($p < 0.05$). Collectively, these data suggest that TBT plus Hg exposure leads to HPG axis abnormalities, exacerbating POI features and reducing in fertility of female rats.

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