UDC: 618.111 -6 15.009-06-92

CHEMICALS AS A RISK FACTOR FOR REPRODUCTIVE FUNCTION DISORDERS IN WOMEN

Mavlonova G.Sh., Tokhirov Zh. Ya.
Bukhara Medical University named after Abu Ali Ibn Sina. Uzbekistan.

Annotation. Study of the effect of titanium dioxide nanoparticles when administered orally on the morphofunctional state of the liver of rats**.**
Keywords: itanium dioxide, liver, Ki-67, CD68, p53.

Relevance. In Uzbekistan, a list of chemical substances harmful to human reproductive health has been approved - reprotoxicants, included in the document approved by the Chief State Sanitary Doctor of the Uzbekistan on July 29, 2009, “UzR 2.2.2008-05. Guidelines for hygienic assessment of factors." [1,2,3,4,5,6,7]. Reproductive toxicants (reprotoxicants) are chemical, physical or biological agents that have a harmful effect on the reproductive processes, regardless of gender. In the European Union, according to Directive 92/32/EEC, the concept of “toxic for reproduction” is defined as harmful effects on sexual function and fertility of adult men and women, as well as effects on the development of offspring. Reproductive toxicity is a harmful effect on male and female sexual function and fertility, as well as toxic effects on the development of offspring. Definition adapted by the Working Group on Harmonization and Risk Assessment for Reproductive and Developmental Toxicity of PC8/OEC (17-21.10.1994), [1,8,9,10,11,12,13,14].

Reproductive toxicity includes two groups of effects.

• 1. Reproductive toxicity - changes in the male and female reproductive system and associated endocrine system, adverse effects on maturation, gamete production and transport, the reproductive cycle, sexual behavior, fertility, childbirth, premature reproductive aging, and changes in other body functions , determining the integrity of the reproductive system.

• 2. Developmental toxicity - effects from the time of conception to and after birth, resulting from harmful exposure to the parents before conception, or exposure to the developing organism prenatally, postnatally until puberty. The main manifestations of developmental toxicity are lethal effects, structural abnormalities, growth disturbances and functional impairment.

In order to assess the possible risk of damage to reproductive function, gynecologists must conduct preliminary and periodic medical examinations of women entering work and working in hazardous conditions. Under equal conditions, examinations of men by a urologist or andrologist are not provided.

To obtain a real picture of the working conditions in which employees work, a special assessment of working conditions is carried out. Based on the results obtained, the risk of developing pathologies in the reproductive function of workers and their offspring is determined, and measures are developed to prevent possible violations.

Thus, harmful occupational factors create high levels of risk for reproductive health. This is manifested by reproductive dysfunction in both men and women, which makes a certain contribution to the increase in the number of weakened and sick generations.

The mechanism of the damaging action of chemicals. There are relatively few poisons that have a specific effect on the gonads (or the direct apparatus for regulating their functions). Among them are ethyleneimine, chloroprene, manganese, vinyl chloride, allyl-allyloxy-carbonyloxyacrylate, phosphate-pol and-2-pyridylethyl methacrylate, tert-butyl peracetate, phenol. [1,21,22,23,24,25,26,27,28,32]. The adverse effects of toxicants (and their metabolites) on the male and female organs of the reproductive system can be due to both direct cytotoxic effects and indirect effects due to disruption of the mechanisms of physiological regulation of their functions.

The direct effect of chemicals lies in their structural similarity to endogenous hormones (endocrine disruptors). Estrogen-like effects are inherent in a large number of different chemical compounds, which include herbicides, fungicides, insecticides, nematicides, organophosphates, pyrethroids, heavy metals, polychlorinated biphenyls (PCBs), phthalates [1,15,16 ,17,18,19,20]. Interaction with endogenous hormones is possible through various mechanisms. First, xenobiotics affect the synthesis, secretion, transport, effects, metabolism and release of hormones. The second group of foreign compounds interferes with hormones at the receptor level. This group includes the phytoestrogens coumestrol, daidzein, genistein, drugs diethylstilbestrol, ethinyl estradiol, tamoxifen, as well as industrial products dichlorodiphenyl trichloromethylmethane (DDT), p-nonylphenol and bisphenol A. These substances interact with estrogen receptors and interfere with the

process binding of endogenous hormones. The third group of substances - DDT metabolite p, p'-EEE and vinclozolin metabolites - block androgen receptors.

Chemical substances that act through metabolic activation and transformation into toxic metabolites include polycyclic aromatic hydrocarbons, cyclophosphamide, and ethanol. This also includes substances that cause induction or inhibition of various enzymes. Thus, ovarian dysfunction was observed with changes in the activity of microsomal monooxygenases, epoxide hydrases and transferases, which are actively involved in the metabolism of certain chemicals in the ovaries.

In addition, chemicals have an effect (stimulating or inhibiting steroid secretion) and changing the rate of hormonal synthesis. Changes in hormonal balance were observed in rodents under the influence of polycyclic halogenated hydrocarbons, including DDT, polychlorinated and polybrominated biphenyls, and tricresol [1,29,30,31]. High chemical reactivity underlies the action of heavy metals lead, cadmium, mercury, boron, which cause disturbances in the reproductive function of animals.

Indirect action associated with disturbances of hormonal regulation. For example, polyhalogenated biphenyls disrupt the metabolism of sex hormones. When administered to newborn rats, these substances significantly alter liver function, significantly changing the level of sex hormones circulating in the blood. Subsequently, this leads to impaired fertility of animals.

Purpose of the study: Study of the effect of titanium dioxide nanoparticles when administered orally on the morphofunctional state of the liver of rats.

Research methods. In this work, using classical morphological approaches and specific markers: proliferation - Ki-67, apoptosis - protein p53 and macrophages - CD68, which make it possible to adequately identify not only the cells themselves, but also their functional state, we studied the liver of rats after oral administration (10 mg/kg animal body weight, 28 days) of a nanodispersed form of TiO (rutile form, 40–60 nm), obtained by diluting TiO powder in distilled water. Aggregation of nanoparticles was prevented by treating a suspension of nanodispersed TiO in an ultrasonic bath. Rats in the control group were orally administered distilled water in the same volume. Serial paraffin sections of the liver were stained with hematoxylin-eosin, picrofuchsin according to Van Gieson, and immunohistochemical staining was performed using antibodies to Ki-67, CD68, p53.

Results. Significant changes in liver tissue were revealed when exposed to TiO NPs. In the liver of experimental animals, a decrease in the proportion of the cortical

substance by 17.6% was established, and a significant decrease in the density of the cell population was noted due to a decrease in the number of hepatocytes. Immunohistochemical typing revealed that under conditions of exposure to TiO NPs, there is a decrease in the number of Ki-67-positive cells in the cortex of the thymus lobule, which indicates inhibition of proliferation processes under these conditions. Under the influence of TiO NPs, an increase of 5.18 times in the number of cells entering apoptosis in the cortex of the liver lobule of the experimental group was found, as evidenced by the results of an immunohistochemical study of the expression of the apoptosis marker p53 protein. Perhaps, as a compensatory mechanism, there is a pronounced increase in the number of macrophages, as indicated by an increase in the average number of CD68-immunopositive cells in the liver cortex of the experimental group by 2.61 times, and in the medulla by 1.35 times.

Morphological changes in the liver under the influence of TiO NPs may be associated, among other things, with damage to the DNA of lymphocytes, which is manifested in a decrease in their proliferative activity and increased apoptosis. This was confirmed by the results of the study. Our data are consistent with the data of studies conducted in recent years on the toxic effect of TiO NPs on other models, indicating the immunosuppressive effect of the latter. Thus, when studying the effect of intraperitoneal injection of TiO NPs into mice for four weeks on immune cells and the growth of melanoma cells (B16/F10), Moon E.Y., et al. (2018) found inhibition of proliferation of B- and T-lymphocytes, increased apoptosis of various types of cells, activation of macrophages, as well as a significant increase in tumor size [1]. In another study, intragastric administration of TiO NPs significantly reduced the proliferation of CD4+ and CD8+ T cells, as well as their ratio in the liver of mice, which ultimately led to suppression of the immune response [2].

Conclusion: The detected morphofunctional changes in the liver after oral administration of TiO nanoparticles indicate their immunosuppressive effect.

Literature

1. Karimipour M., Zirak Javanmard M., Ahmadi A., Jafari A. Oral administration of titanium dioxide nanoparticle through ovarian tissue alterations impairs mice embryonic development. J. Reprod. Biomed (Yazd). 2018; 16 (6): 3 97–404. DOI: 10.29252/ijrm.16.6.397.

2. Winkler H.C., Notter T.,Meyer U.,Naegeli H. Critical review of the safety assessment of titanium dioxide additives in food. J. Nanobiotechnology. 2018; 16: 51 DOI: 10.1186/s12951-018-0376-8.
3. Weir A., Westerhoff P., Fabricius L., Hristovski K., von Goetz N. Titanium dioxide nanoparticles in food and personal care products. Environ. Sci. Technol. 2012; 46: 2242–2250. DOI: 10.1021/es204168d.
4.Kovaleva N.Yu., Raevskaya E.G., Roshchin A.V. Aspects of nanomaterial safety: nanosafety, nanotoxicology, nanoinformatics. Khimicheskaya bezopasnost'. 2017; 1 (2): 44–87. (In Russ.)]DOI: 10.25514/CHS.2017.2.10982.
5. Khamdamov I.B. Clinical evaluation of the effectiveness of the traditional approach to the treatment of hernias of the anterior abdominal wall in women of fertile age // Doctor's Bulletin. –Samarkand 2022. No. 2.2 (104).-P.65-70.
6. Khamdamov I.B., Mirkhodzhaev I.A. Khakimov M.Sh. Khamdamov B.Z. Evolution of the use of polymer implants for hernioplasty // Tibbiyotda Yangi kun. – Tashkent; 2021,- No. 2 (34) P.-107-111.
7.Khamdamov I.B., Khamdamov A.B. Differentiated approach to the choice of hernioplasty method in women of fertile age (Clinical and experimental study) // Tibbiyotda Yangi kun. – Bukhoro, 2021.-No. 6 (38/1).-P. 112-114.
8. Khakimov M.Sh., Urmanova N.M., Khudoiberdiev S.S., Khamdamov I.B. Possibilities of allohernioplasty in women of fertile age // Nazariy va clinic tibbiyot journals. Tashkent.-2022.-No.3.P.89-93.
9. Khamdamov I.B., Khamdamov A.B. Fertil yoshdagi ayollarda endovideo surgeon hernioplasty // Tibbiyotda yangi kun. Bukhoro, 2021.-№6 (38/1) -S. 25-27.
10. Khamdamov I.B. Experimental determination of the extensibility of the anterior abdominal wall tissues at different times of pregnancy using various approaches to hernioplasty // Academicia: An International Multidisciplinary Research Journal Vol. 12, Issue 04, April 2022 SJIF 2022 = 8.252 R.193-201 (Scopus).
11. Khamdamov I.B. Improving tactical approaches in the treatment of hernias of the anterior abdominal wall in women of fertile age // Tibbiyotda Yangi kun. Bukhoro, 2022.-№10(48)- pp. 338-342.
12. Khamdamov I.B. Morphofunctional features of the abdominal press in women of reproductive age // Tibbiyotda Yangi kun. Bukhoro, 2022.-№3(41)- pp. 223-227.
13. Khamdamova M.T. Ultrasound features of three-dimensional echography in assessing the condition of the endometrium and uterine cavity in women of the first

period of middle age using intrauterine contraceptives // Biology va tibbyot muammolari. - Samarkand, 2020. - No. 2 (118). - P.127-131.
14. Khamdamova M. T. Ultrasound assessment of changes in the endometrium of the uterus in women of the first and second period of middle age when using intrauterine and oral contraceptives // Биомедицина ва амалиёт журнали. – Ташкент, 2020. - №2. - 8 часть. - С.79-85.
15.Khamdamova M. T. Anthropometric characteristics of the physical status of women in the first and second period of middle age // A new day in medicine. Tashkent, 2020. - № 1 (29). - С.98-100.
16. Khamdamova M.T. Age-related and individual variability of the shape and size of the uterus according to morphological and ultrasound studies // News of dermatovenereology and reproductive health. - Tashkent, 2020. - No. 1-2 (88-80). - P.49-52.
17.Khamdamova M. T. Anthropometric characteristics of the physical status of women in the first and second period of middle age // Тиббиётда янги кун. Ташкент, 2020. - № 1 (29). - С.98-100.
18. Khamdamova M.T. Age-related and individual variability of the shape and size of the uterus according to morphological and ultrasound studies // News of dermatovenereology and reproductive health. - Tashkent, 2020. - No. 1-2 (88-80). - P.49-52.
19. Khamdamova M.T. Ultrasound features of three-dimensional echography in assessing the condition of the endometrium and uterine cavity in women of the first period of middle age using intrauterine contraceptives // Biology va tibbyot muammolari. - Samarkand, 2020. - No. 2 (118). - P.127-131.20.Khamdamova M. T. Ultrasound assessment of changes in the endometrium of the uterus in women of the first and second period of middle age when using intrauterine and oral contraceptives // Biomedicine va amaliyot journals. – Tashkent, 2020. - No. 2. - Part 8.- C.79-85.
21. Khamdamova M.T. Features of ultrasound parameters of the uterus in women of the first and second period of middle age using injection contraceptives // Tibbiyotda yangi kun. - Tashkent, 2020. - No. 2/1 (29/1). - pp.154-156.
22. Khamdamova M.T. Features of ultrasound images of the uterus and ovaries in women of the second period of middle age using combined oral contraceptives // Tibbiyotda yangi kun. - Tashkent, 2020. - No. 2 (30). - pp. 258-261.
23. Khamdamova M.T. Individual variability of the uterus and ovaries in women who use and do not use various types of contraceptives // Tibbiyotda yangi kun. -

Tashkent, 2020. - No. 3 (31). - pp. 519-526.24.Khamdamova M. T. Echographic features variability in the size and shape of the uterus and ovaries in women of the second period of adulthood using various contraceptives // Asian Journal of Multidimensional Research - 2020. – N9 (5). - P.259-263.

25.Khamdamova M. T. Somatometric characteristics of women of the first and second period of adulthood using different contraceptives with different body types // The american journal of medical sciences and pharmaceutical research - 2020. – N8 (2). - P.69-76.

26. Хамдамова М.Т., Жалолдинова М.М.,Хамдамов И.Б. Состояние оксида азота в сыворотке крови у больных кожным лейшманиозом // Тиббиётда янги кун. - Бухоро, 2023. - № 5 (55). - С. 638-643.

27. Хамдамова М.Т., Жалолдинова М.М.,Хамдамов И.Б. Значение церулоплазмина и меди в сыворотки крови у женщин носящих медьсодержащих внутриматочной спирали // Тиббиётда янги кун. - Бухоро, 2023. - № 6 (56). - С. 2-7.

28. Khamdamova M. T. Bleeding when wearing intrauterine contraceptives and their relationship with the nitric oxide system // American journal of pediatric medicine and health sciences Volume 01, Issue 07, 2023 ISSN (E): 2993-2149. P.58-62

29. Khamdamova M. T. The state of local immunity in background diseases of the cervix // Eurasian journal of medical and natural sciences Innovative Academy Research Support Center.Volume 3 Issue 1, January 2023 ISSN 2181-287X P.171-175.

30. Хамдамова М.Т., Хасанова М.Т. Различные механизмы патогенез гиперплазии эндометрия у женщин постменопаузального периода (обзор литературы) // Тиббиётда янги кун. - Бухоро, 2023. - № 8 (58). - С. 103-107.

31. Khamdamova M. T., Khasanova Makhfuza Toyqulovna, Umidova Nigora Nabievna The role of genetic determinants in the occurrence of hyperplastic processes of the reproductive system of women's menopausal age // Journal of Advanced Zoology ISSN: 0253-7214 Volume 44 Issue Special Issue-2 Year 2023 Page 3724:3730

32. Wang X., Reece S.P., Brown J.M. Immunotoxicological impact of engineered nanomaterial exposure: mechanisms of immune cell modulation. Toxicol. Mech. Methods. 2013; 23 (3): 168–177. DOI: 10.3109/15376516.2012.757686.