ORIGINAL SCIENTIFIC ARTICLE

NUMBER AND DISTRIBUTION OF MAST CELLS IN REPRODUCTIVE SYSTEMS OF GRAVID AND NON-GRAVID FEMALE MICE

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ABSTRACT

Mast cells are mainly distributed in tissues exposed to the external environment, but they are also found in ovaries, oviducts and uterus. We determined the difference in the number and distribution of Alcian Blue (+) and Safranine O (+) mast cells in reproductive systems of gravid and non-gravid female mice by histological examination. We showed that the number of mast cells is significantly higher in the reproductive system of gravid mice than in the reproductive system of non-gravid mice. Mast cells are unevenly distributed in ovaries, oviducts and uterus in both gravid and non-gravid mice. A large number of mast cells reside close to blood vessels throughout the entire reproductive system.

Keywords: *mast cells, gestation, ovary, oviduct, uterus.*

INTRODUCTION

Mast cells, the so-called unicellular glands, are mainly distributed in tissues exposed to the external environment, such as skin and airways (1). Each mast cell contains about 500,000 secretory granules that contain a large number of biologically active molecules (2). Mast cells are activated by allergens, anaphylatoxins (C3a, C5a), hormones, physical stimuli (pressure and temperature change), cytokines and neuropeptides (2).

Mast cell stimulation leads to the release of vasoactive and proinflammatory mediators (2). Some mediators are produced before stimulation and activation of mast cells and are kept in cytoplasmic granules: histamine, serotonin, heparin, tryptase, chymase, TNFα. Other mediators are synthesized *de novo* only when mast cells are stimulated and activated: leukotrienes, cytokines, and chemokines (1). Mast cells are able to selectively release the contents of individual granules or mediators without degranulation (like in the case of serotonin). That enables them to participate in many processes, without starting allergic or inflammatory reactions (2).

The difference in mast cells granules content is connected with their maturation: through the maturation of mast cells with tryptase granules only (MC_T), mast cells with both tryptase and chymase granules (MC_{TC}) are produced (3). Local factors cause mast cells to change their phenotype (4).

Uterine mast cells differ substantially from mast cells in other tissues (5). They hold 3-5% of the total endometrial cell number (6). Number, maturation and degranulation of mast cells are controlled by female sex hormones (1). The hormone modulation prepares the uterus for possible implantation (7).

The number of mast cells increases during the fertile period of the estrous cycle in mice and reaches its maximum during estrus when the female is sexually receptive, and when the endometrium is prepared for nidation. If fertilization does not occur, the number of mast cells decreases rapidly (8).

The number of mast cells in the uterus is relatively constant during the menstrual cycle. Mast cells are dispersed and moderately present in the uterus (9). They are placed in close proximity to fibroblasts and collagen fibers during the menstrual cycle, which may indicate that they have an important role in uterine tissue reconstitution (10). During the late secretory phase, extracellular tryptase expression increases, probably because of the intensification of mast cell activation during this period. Tryptase and other mast cells mediators (such as histamine, cytokines and growth factors) induce tissue edema and have a role in extracellular matrix degradation via proteolytic enzymes and metalloproteinases activation. Mast cell and metalloproteinases activity persist during the menstrual phase of the cycle. Metalloproteinases make the endometrial lining easier. However, most of the lining happens before menstrual bleeding - during the menstrual phase, when mechanisms of endometrial repair are already established (9).

After menopause, the number of mast cells declines in all parts of the uterus (10).

The application of luteinizing hormone (LH), follicle-stimulating hormone (FSH) or estradiol in mice increases mast cell degranulation in the ovaries (11). In the ovaries of rats, significantly larger number of mast cells are seen at estrus and diestrus. There is a possible involvement of mast cells products in vascularization of *corpora lutea* (12). Ovarian mast cells change their histamine content during the rat estrus cycle (11).

AIM OF THE STUDY

The aim of this study was to determine the difference in the number and distribution of Alcian Blue (+) and Safranine O (+) mast cells in the reproductive systems of gravid and non-gravid NMRI mice.

MATERIALS AND METHODS

Experimental animals

The experimental group consisted of five adult NMRI mice: one male, and four non-gravid females. The control group consisted of four adult non-gravid female NMRI mice. Mice were bred at Pasteur Institute, Novi Sad, Serbia. Mice were housed under standard vivarium conditions: exposed to a 12:12-hour light:dark cycle, the ambient temperature of 25±2ºC, with food and water provided ad libitum.

The experiment was approved by the Ethical Committee of Pasteur Institute, Novi Sad, Serbia.

Experiment

Four female mice from the experimental group were marked with a saturated picric acid water solution for proper identification and then placed in a cage with the male mouse. Every morning, vaginal flushes were performed, by pumping technique with distilled water. The flushes were used for smear preparation, fixed with methanol, and then stained with Eriochrome cyanine R-Eosin Y method by Stefanović and coauthors (13). The day when the smear was sperm positive was considered as the zero-day of the experiment. 10 days later, female mice were sacrificed by cervical dislocation. Ovaries, oviducts and uteri were dissected out, examined macroscopically, and fixed in 10% formalin. After gradient ethanol dehydration and xylene clearing, the organs were molded into paraffin, and 7µm slices were cut using Leica RT350 rotary microtome. The slices were deparaffinized by heating to 60ºC and then stained with Alcian Blue and Safranine O. Alcian Blue-Safranin O staining was conducted according to the protocol of Tas and coauthors (14).

The experiment was conducted in the laboratory of Pasteur Institute, Novi Sad, Serbia.

Analysis

Histological examination was performed using Leica DM 2500 light microscope with a camera connected to a computer and it included morphological analysis and description using free software ImageJ. In every group, mast cell presence was analyzed in 15 high-power fields (HPF) at a magnification ^{x} 400.

Results from the experimental and control group were compared using two-tailed Student t-test; a significant difference was considered at $p<0.05$.

Chemicals

- DPX mountant for histology- Fluka, Sigma-Aldrich Chemie GmbH, Germany
- Picric acid ($(O_2N)_3C_6H_2OH$)- Fluka, Sigma-Aldrich Chemie GmbH, Germany
- Formalin (37% formaldehyde solution) - Centrohem, Stara Pazova, Serbia.
- 70%, 80%, 90%, 96%, and absolute ethanol- Centrohem, Stara Pazova, Serbia
- Xylene, HCl, FeCl3·6H20 - Centrohem, Stara Pazova, Serbia
- Alcian Blue 8GX (Sigma-Aldrich Chemie GmbH, Germany, 861006), as 0.5%(w/v) stain powder solution, and 3% (v/v) acetic acid solution, pH=2.4
- Safranine O (Sigma-Aldrich Chemie GmbH; Germany; 50240), as 0.3%(w/v) solution with dissolvent 0.125M HCl, pH=0.9
- Eosin Y (Fluka Sigma-Aldrich Chemie GmbH, Germany; HT110116), as 0.5%(w/v) ethanol solution.

Eriochrome cyanine R working solution was prepared as follows: 450 ml distilled water was acidified by HCl to pH 1.5, 1 g of Eriochrome cyanine R powder (Magnacol Ltd.; Wales, Great Britain) and 1.12 g FeCl3·6H20 were added to the solution, followed by mixing and filtering. Water was added to a final volume of 500 ml. The pH of the final solution was adjusted to 1.5.

Distilled water was prepared in Pasteur Institute, Novi Sad, Serbia, cooled to 25ºC and buffered by ion exchange resin.

RESULTS

During histological preparations, Alcian Blue (+) mast cells and Safranine O (+) mast cells were detected in both experimental and control group. They preserved their structure and were unevenly distributed in the tissue - individually or in small groups. Their shape ranged from spherical to oval and slightly spindle. Intracellular metachromatic granules were detected in mast cells, but their nuclei were poorly marked. In some places, mast cell degranulation was observed (Figures 1 and 2).

In both experimental and control group, mast cells were found in the ovaries - in interstitial stroma and medulla, and in follicles and cortex. In oviducts of the experimental females, Alcian Blue (+) mast cells were observed. However, Safranine O (+) mast cells were absent or detected in a small number. In uteri, mast cells were distributed around uterine glands, in basal and deeper layers of endometrial stroma, and also in the myometrium, where they were predominantly detected in close proximity to smooth muscle cells in both experimental and control group. A large number of mast cells were found around blood vessels throughout the entire reproductive tract (Figure 3).

A highly significant difference between the mean number of mast cells in the experimental and the control group ($p<0.001$) has been found, with a significantly higher number of mast cells in the reproductive systems of the experimental group (Table 1, Figures 4 and 5).

Figure 1. a: Perivascular Safranine O (+) mast cell are marked with pointed arrow in uterus of control group. b: Alcian Blue (+) mast cells are marked with arrows, degranulated mast cells are marked with 5-point stars in uterus of experimental group (Alcian Blue-Safranine O staining, x400)

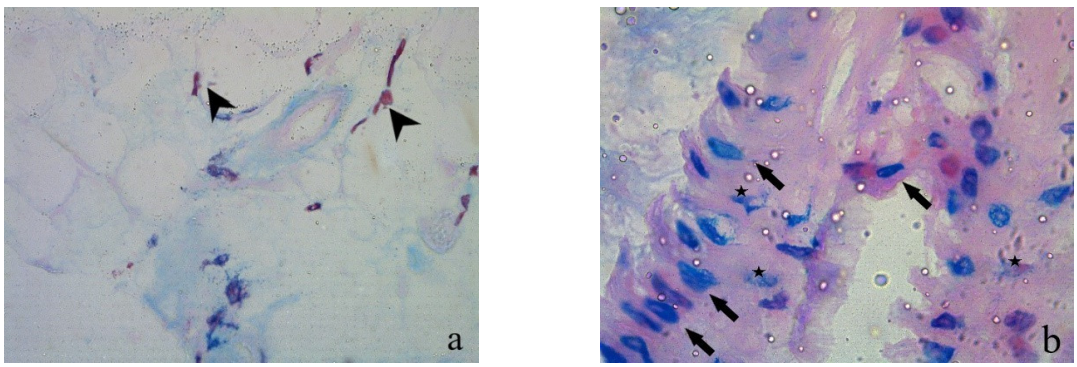


Figure 2. a: Safranine O (+) mast cell are marked with pointed arrow in uterus of control group. b: Alcian Blue (+) mast cells are marked with arrows, Safranine O (+) mast cell are marked with pointed arrow, degranulated mast cells are marked with 5-point stars in uterus of experimental group (Alcian Blue-Safranine O staining, x 400)

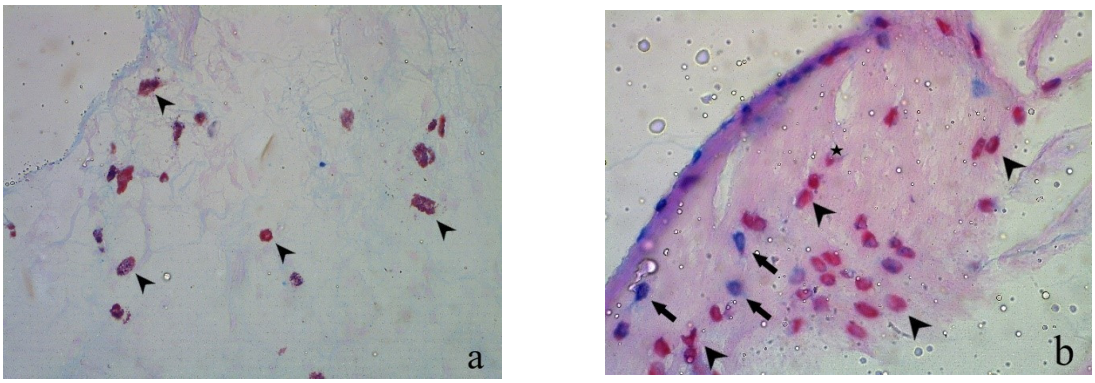


Figure 3. a,b: Distribution and density of the mast cells in the uterus tissue of the control group. Presence of mast cells is noticed in extremely small number, where the highest percentage is taken by Safranine O (+) mast cells; note Safranine O (+) cells surrounding blood vessels marked with X. c,d: Distribution and density of mast cells in the experimental group in the uterine tissue. Note the presence of a large number of Alcian Blue (+) and Safranine O (+) mast cells, unevenly distributed, presented individually or in groups; note majority of Alcian (+) cells surrounding blood vessels marked with X (Alcian Blue-Safranine O staining, x 200)

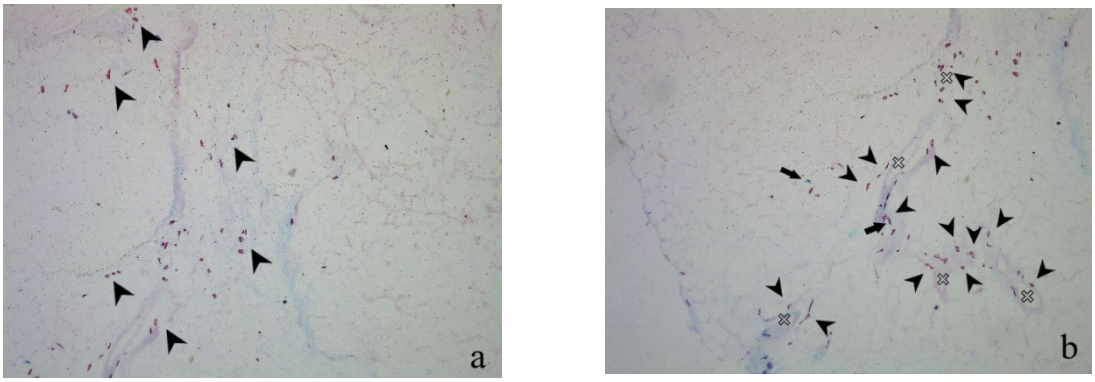


Figure 4. Comparison of Alcian blue (+) mast cells mean number in the control and the experimental group per HPF. Significantly higher number of Alcian blue (+) mast cells was found in each analyzed reproductive organ of gravid mice

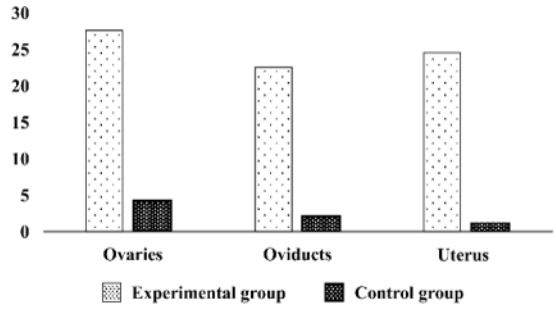


Figure 5. Comparison of Safranine O (+) mast cells mean number in control and experimental group per HPF. Significantly higher number of Safranine O (+) mast cells was found in each analyzed reproductive organ of gravid mice.

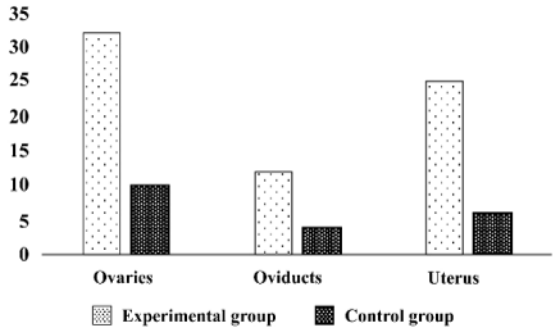


Table 1. Mast cell count (stated as mean±SD) in 15 high-power fields (x400). Each preparation included ovaries, oviducts, and uterus.

	Experimental group	Control group
Alcian Blue (+)	26.40±6.47	2.20±2.46
Safranine O (+)	18.33±6.16	6.00±5.41

DISCUSSION

In this study, we determined the difference in the number and distribution of Alcian Blue (+) and Safranine O (+) mast cells in the reproductive systems of non-gravid and gravid NMRI mice. Alcian Blue (+) mast cells and Safranine O (+) mast cells were detected in both non-gravid and gravid NMRI mice, but a substantially larger number of mast cells was present throughout the reproductive systems of gravid mice. In comparison with non-gravid mice, a larger number of mast cells was also found in each analyzed organ of gravid mice - ovary, oviduct and uterus. The observed presence of mast cells indicates their probable role in the homeostasis of a non-gravid reproductive system. Larger number of mast cells in the reproductive systems of gravid mice could mean that mast cells have an important physiological role in the reproductive system during gestation. Their abundance could also be explained by changing levels of female sex hormones during pregnancy, which affect the number, maturation and degranulation of mast cells. Mast cells are fruitful sources of biologically active molecules, which could mediate, determine, or enable processes in the reproductive tract during pregnancy. The magnitude of increase of mast cells' number in ovaries, oviducts and uteri might reflect their importance in those organs during pregnancy. We found a large number of mast cells around blood vessels in the reproductive systems of gravid mice. Mast cells might contribute to angiogenesis in the reproductive system during pregnancy and that could be a reason for their proximity to blood vessels. We observed mast cell degranulation in uteri of gravid mice, which showed that some of the mast cells had been activated.

Woidacki and coauthors previously showed that uterine mast cell number increases in mice if gestation takes place and stays high (higher than in estrus) during pregnancy. In abortus-prone gravid mice, the number of mast cells in the gravid uterus is similar to the number of mast cells in metestrus (and is far smaller than in normal pregnancies). The same study showed that during the middle of pregnancy, mast cells are numerous on the maternal side of the feto-maternal barrier and are usually close to blood vessels. Detailed characterization of mast cells in uterus showed that it is a heterogenic population consisting of connective tissue mast cells and mucosal mast cells, and also mast cells in different phases of differentiation and transdifferentiation. Mast cells in the uterus are mast cells protease 8 (Mcpt8) and CD117 positive, and 5-20% of mast cells in the uterus are also mast cells protease 5 (Mcpt5) positive (8). Padilla and coauthors found that mast cells are more numerous in myometrium than in endometrium in pregnant mice uteri (15).

Batth and coauthors showed that in the ovaries of rats, the number of mast cells was high during gestation, with a positive correlation between mast cell count and embryo number. After parturition, the mast cell count declined significantly (12). During late gestation, mast cells activation led to angiogenesis in the cervix of the rat. Mast cells degranulation modulated cervix contractility in guinea pigs (2).

Jeziorska and coauthors conducted a study on 107 women during normal menstrual cycle. There was a similar number of mast cells in the functional and basal endometrial layers and in the myometrium (16). In the study of De Leo and coauthors in tissue samples of 20 women, mast cells with both tryptase and chymase expression were identified in all three layers of the non-gravid uterus. In the same study, in the basal endometrium and myometrium, rare mast cells with chymase expression only (without tryptase expression), MC_C, were found (17). Mori and coauthors in a study on 24 non-pregnant women with different gynecological disorders observed that mast cells were located mainly in the inner half of the myometrium and the majority of them were MC_T (18). According to Gomez-Lopez and coauthors in humans, mast cells count is higher in gravid than in non-gravid uteri (19). Ivanišević and coauthors showed that the number of tryptase-positive mast cells in the myometrium of the non-gravid human uterus was significantly higher than in the myometrium of the gravid uterus (20). Garfield and coauthors showed that the number of mast cells in the myometrium was higher during human pregnancy, with more MC_T than MC_{TC} (21).

During degranulation, mast cells release various mediators that are very important for embryo implantation (such as histamine, proteases, metalloproteinases, and proangiogenic factors) (1). Angiogenesis and tissue remodeling are necessary for successful implantation. Many mediators involved in those processes are synthesized in mast cells (8). Histamine causes muscle contraction, exocrine glands cause secretion and vasodilatation (2). Histamine created in the uterus is a key regulator of implantation due to its ability to influence vascular permeability and induce decidualization. Before the implantation, human embryos provoke histamine release by histamine-releasing factor secretion (7). Mast cells and their products regulate trophoblast invasion and growth (3).

Mast cells in uteri positively affect placentation, spiral artery remodeling, size of the placenta and fetal growth. Spiral artery remodeling is necessary for oxygen and nutrients delivery to the fetus. Inadequate spiral artery remodeling is

associated with preeclampsia, slower fetal growth, miscarriages and preterm deliveries (22).

Mast cells affect the myometrium by proliferation and smooth muscle cell regulation (3). They play a central role in the initiation and progression of uterine contractions. Their activation increases contractility of the myometrium (2). Pregnant women with systemic mastocytosis or asthma often give birth before the term (8). In strong allergic reactions, there is a sufficient degree of mast cells activation to induce preterm labor. If antihistamines and steroid drugs are given, uterine contractions stop. During anaphylaxis, strong contractions of the uterus occur as a result of mast cells degranulation (3).

An especially large number of mast cells in the uterus is placed in close proximity to nerves, blood or lymph vessels (23). Stress significantly increases the number of mast cells in pregnant mice uteri (for about 55.6-76.9%) (24).

According to some authors, estrogens and progesterone are able to attract mast cells in the uterus *in vitro* and *in vivo* (4), individually and in combination, by modulation of receptor expression for chemokines on their surface (7). If ovaries are removed from mice, estradiol and progesterone are almost absent, and those mice have a lower number of mast cells compared to control (mice that do have ovaries). When mice without ovaries receive estradiol replacement or combination of estradiol and progesterone, the number of mast cells reaches control level. Application of these hormones also increases expression of mast cells proteases in the uterus and increases the degranulation degree (1).

Human mast cells express estrogen receptors and their activation increases mast cells stimulation and degranulation. Human mast cells express receptors for progesterone and testosterone, but activation of these receptors has an inhibitory effect (2). Progesterone prevents mast cells migration in response to chemokines, e.g. downregulates the expression of superficial chemokines receptors. Progesterone inhibits secretion of histamine from mast cells. It is possible that mast cells during pregnancy are inhibited by high levels of progesterone, and that transit of mast cells from circulation to uterus is limited. As the term of delivery approaches, functional sensitivity on estrogens is higher than on progesterone, and that is the reason why estrogens' effect on mast cells dominate (3). Estradiol and progesterone dose-dependently increase degranulation level in immature mast cells *in vitro*. The combination of these two hormones significantly increases degranulation compared to situations when each hormone is applied individually (7).

Corticotropin-releasing hormone (CRH) might be involved in endometrial mast cell activation (3).

Mast cells create and release galectin-1. It mediates fetal growth and aids in placentation, angiogenesis, syncytium synthesis, and trophoblast growth (8).

Myometrial stretching during fetal growth causes release of stem cell factor (SCF) and other chemokines, which attract mast cells progenitors and mature mast cells from the blood. Possibly, the release of mast cells mediators causes migration of other immune cells to the uterus (3). A high level of tryptase is associated with spontaneous abortions, probably as a result of inflammation induction. A high level of chymase is associated with severe preeclampsia. In the case of preeclampsia, the placenta contains high concentrations of histamine and a high number of mast cells (3). Decreasing the number of mast cells during pregnancy could prevent the creation of a critical quantity of proinflammatory mediators which induce preterm delivery. Since human myometrium sensitivity to mast cells mediators increases towards the end of pregnancy, the myometrium might be stimulated even if mast cells density is low (20).

Mast cells tryptase is a potent angiogenic factor (25). Chymase contributes to matrix degradation, tissue remodeling and angiogenesis (2). Chymase is also a potent proinflammatory mediator (26). Mast cells are involved in angiogenesis. Their accumulation is found in many conditions such as tumor growth, rheumatoid arthritis, ovulation, wounds healing and tissue renewal. Mast cells metalloproteinases degrade connective tissue to make space for neovascularization onset (10). *In vivo* exposition to mast cells stabilizers, which inhibit their degranulation, decreases uterine endothelial cells proliferation and vascular endothelial growth factor A (VEGF-A) secretion (8).

A limitation of this study was sample size. All our conclusions were based on one experiment with 9 mice. However, the difference observed between the number of mast cells in reproductive systems of gravid and non-gravid female mice was so significant that the sample size should not affect the study's findings. In addition, our results are in line with other published studies of mast cells' number and distribution in reproductive systems during pregnancy. The small sample size in our study opens a possibility for larger studies to validate our findings. Likewise, more research about the role of mast cells in the gravid and non-gravid uterus is needed, including examination of the molecular mechanisms of their activity. The definitive role of mast cells during successful and pathological pregnancy remains to be determined.

CONCLUSION

The number of mast cells is significantly higher in the reproductive systems of gravid mice than in the reproductive systems of non-gravid mice. Mast cells are unevenly distributed in ovaries, oviducts and uteri in both gravid and non-gravid mice. A large number of mast cells reside close to blood vessels throughout the entire reproductive system.

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