TITLE: EFFECTS OF MENOPAUSE IN THE IMMUNE RESPONSE OF SEPSIS INDUCED BY *Staphylococcus aureus*

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ABSTRACT:

The paradigm of hormonal influence on the immune response establishes that estrogen increases this response, however, data in the literature are still controversial. This study aimed to evaluate, in a menopausal and sepsis animal model, the immune response induced by the most common gram-positive pathogen in cases of sepsis: *Staphylococcus aureus*. Female Balb/c mice aged six to eight weeks were ovariectomized (OVX) or sham-operated (Sham). After two weeks, the females were inoculated intraperitoneally with *S. aureus* ATCC 25923 or sterile saline (Control). Euthanasia occurred in seven times with a 24-hour interval. Ten females (n = 5 Sham/n = 5 OVX) were used at each time. Females of the control group were euthanized at 168 h. After euthanasia, blood samples were collected for leukocyte count and quantification of *S. aureus* by real-time PCR (qPCR). The uterus was removed and weighed to calculate the uterine index, the spleen was removed, weighed and homogenized for the measurement of the cytokines IL-6, IL-1β and TNF-α by ELISA. Blood serum was used to measure the serum estradiol concentration. Lungs were removed and fractionated to perform histopathological analysis and relative gene expression of IL-6, IL-1β and TNF-α by qPCR. Results show that there was systemic presence of *S. aureus* in both groups, however, there was no statistical difference in bacterial load between them. Nevertheless, ovariectomy caused splenomegaly, an increase in circulating lymphocytes, higher IL-1β levels in the spleen even in the absence of infection. In *S. aureus* sepsis, OVX females had a perpetuation of the initial reduction of lymphocytes, a monocyte and neutrophil late response and higher IL-6 and IL-1β levels compared to Shams, but, lower TNF-α levels. Moreover, OVX females showed neutropenia on the last day of infection compared to control group. Lung damage was observed and the neutrophil response in this organ occurred later in OVX compared to Shams. Also, in the lungs, OVX group had a higher relative expression of IL-1β and TNF-α genes in the first three and two days of infection, respectively, compared to Shams. We conclude that in this model the presence of female sex hormones acted as an immunoprotective in the cellular response of *S. aureus* sepsis.

Keywords: Sepsis. Staphylococcus aureus. Female sex hormones. Ovariectomy. Cytokines.
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