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P-372 The role of the immune system in the physiopathology of infertility in case of adenomyosis: a mouse model study

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Study question: Are there any fertility disorders and related local and/or systemic immune changes during the early implantation period in a mouse model of adenomyosis?

Summary answer: An increase in fertility disorders was observed in adenomyosis mice and coincide with local and systemic immune changes observed during the period of implantation.

What is known already: Adenomyosis is as a common pathology that could be responsible for fertility alteration. Immune changes in uterus are implicated in adenomyosis physiopathology. One hypothesis is that the physiological immune environment necessary for a successful implantation can be altered in adenomyosis, leading to fertility disorders.

Study design, size, duration: Randomly selected CD-1 female neonatal pups were orally dosed with oral administration of tamoxifen in order to induce adenomyosis (TAM group), while other received solvent only (control group). At 3 months, CD-1 mice (F1) of both group were put into mating. 36 pregnant mice were included in the TAM group and 30 in the control group. Ultrasounds were performed during pregnancy at E(E=embryonic day)7.5 and E12.5 to evaluate fertility outcomes in mice of the TAM and control group. Mice were sacrificed at E18.5 and histological, morphometric and functional analysis were performed on the placentas. In order to identify local and/or systemic immune changes in the uterus, mice of both group were sacrificed at E4.5 of pregnancy, during the implantation period. Uterine horns and spleen were collected for flow cytometry and RT-qPCR analyzes.

Main results and the role of chance: We observed a significantly lower number of implantation sites and a significantly higher number of resorption (3.88±2.36 versus 1.00±0.82(p < 0.001)) in TAM compared to control group. Analysis of placentas showed a significantly higher junctional/labyrinthic area ratio (0.60±0.09 versus 0.30±0.05(p = 0.0052)) and a significantly lower expression of Vascular Endothelial Growth-Factor(GF), Platelet endothelial cell adhesion molecule, Insulin-like GF2 and Placental GF in the TAM group compared to the control group, indicating an altered placental vascularization compared to controls. To characterize the immune change during the early implantation period, we analyzed some immune cells populations in the uteri and the spleen: In the TAM group, the number of macrophages(F4/80), Natural Killers(NK) cells(NKP46+/NKG2D+) and dendritic cells (DC)(CD11b+) were significantly decreased compared to control uteri. However, the number of M1 macrophages(Ly6c+high) and their activation were significantly increased. DC activation was also increased in TAM group. In the spleen, a significant increase in the activation macrophages and DC was observed in adenomyosis group compared to control. In the uterus, the number of LT4(CD4+) cells and number of LTreg cells(CD25+/FOXP3+) were significantly increased in the TAM group compared to control group. In the spleen, a significant increase in LT4 cells count was observed in TAM compared to control group.

Limitations, reasons for caution: This study is limited by the use of an animal model and the lack of intervention.

Wider implications of the findings: This study provides evidence that adenomyotic lesions in mice induced fertility disorders and immune modifications at a local and at a systemic level during the early implantation period.