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P-323 Endometriomas are extremely heterogenous for steroidogenic activity, functional FSH receptor expression and FSH-responsive aromatase transcript variants

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Study question: Do all ovarian endometriomas uniformly express functional FSH receptors and the full cascade of steroidogenic enzymes?

Summary answer: No. They are extremely heterogenous for the expression of FSH receptors, in response to FSH and steroidogenic enzymes and estrogen production.

What is known already: Endometriotic stromal cells express aromatase and other steroidogenic enzymes required for de novo estradiol synthesis. Previous studies demonstrated the expression of FSH receptors in ovarian endometriomas and other types of endometriosis lesions mainly by immunohistochemistry and qRT-PCR methods. These methodologies, however,

cannot prove the functionality of these receptors. We therefore aimed to investigate 1) if all endometriomas uniformly express FSH receptors and full cascade of steroidogenic enzymes and, 2) if FSH treatment uniformly up-regulates the expression of aromatase transcript variants and stimulates estrogen production in the endometriomas expressing FSH receptors.

Study design, size, duration: A basic science study was conducted in surgical endometrioma samples of 18 patients (mean±SD 36.4±3.7) undergoing laparoscopic endometrioma surgery between January 2020 and December 2024.

Participants/materials, setting, methods: Expression of the steroidogenic enzymes, gonadotropin receptors, and sex steroids in endometrioma samples was investigated using qRT-PCR, quantitative immunoblotting, and immunohistochemistry methods in 18 patients. Five different aromatase (CYP19A1) transcript variants known to be FSH-responsive were used to test FSH response of the endometriomas. E2 and P4 productions were measured in the spent culture media. Primary luteinized mural granulosa cells and normal endometrium samples were used as positive controls for steroidogenesis, FSH, and estrogen receptors.

Main results and the role of chance: Quantitative RT-PCR and immunoblotting experiments revealed significant heterogeneity among the samples in terms of the expression of the steroidogenic enzymes (StAR, SCC, aromatase, 3beta-HSD, 17beta-HSD, 17a-OH) with StAR and aromatase being the most uniformly expressed enzymes. The expression of FSH-R and ER-beta were several folds higher in all samples compared to control granulosa cells. However, FSH treatment resulted in significant up-regulation of all five of the aromatase transcript variants only in 6 of 18 (33.3%) endometriomas. In the remaining eight samples FSH either did not up-regulate any of these variants (44.4%) or up-regulated only one or two of them (four samples). Baseline E2 production of the samples after 24 hours in culture without FSH stimulation significantly varied from 35 to 578pg/mL. These E2 levels did not correlate with the protein expression level of aromatase in immunoblotting and the level of its transcripts in qRT-PCR [(p=0.21, 95%(CI): -0.66 to 0.17)]. Interestingly, FSH treatment significantly increased E2 production (225.7 ±25 vs. 398±65, p=0.01) in only one sample in which only one aromatase transcript variant (variant-3:256bp) was found to be significantly up-regulated following FSH treatment. Noteworthy, 3beta-HSD expression was detected in some samples but P4 production was not observed in any of them.

Limitations, reasons for caution: These findings were obtained in patients who had unilateral ovarian endometriomas. Therefore, it is unclear if these findings are generalizable to other types of endometriosis lesions (DIE, endometriotic nodule, peritoneal implants). It is also unknown if the segmental piece used in the experiments truly represent the whole endometrioma.

Wider implications of the findings: Significant heterogeneity and discordance among the ovarian endometrioma samples for steroidogenic enzymes, FSH response, aromatase expression, and E2 production indicates that intrinsic pathogenetic mechanism regulating them are indeed much more complicated and molecular signatures of each individual patient may differ from each other, underscoring the necessity of personalized approaches.

Trial registration number: No