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Antibiotic therapy with metronidazole reduces endometriosis disease progression in mice: a potential role for gut microbiota.

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Abstract

STUDY QUESTION: Does altering gut microbiota with antibiotic treatment have any impact on endometriosis progression?

SUMMARY ANSWER: Antibiotic therapy reduces endometriosis progression in mice, possibly by reducing specific gut bacteria.

WHAT IS KNOWN ALREADY: Endometriosis, a chronic condition causing abdominal pain and infertility, afflicts up to 10% of women between the ages of 25 and 40, ~5 million women in the USA. Current treatment strategies, including hormone therapy and surgery, have significant side effects and do not prevent recurrences. We have little understanding of why some women develop endometriosis and others do not.

STUDY DESIGN, SIZE, DURATION: Mice were treated with broad-spectrum antibiotics or metronidazole, subjected to surgically-induced endometriosis and assayed after 21 days.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The volumes and weights of endometriotic lesions and histological signatures were analysed. Proliferation and inflammation in lesions were assessed by counting cells that were positive for the proliferation marker Ki-67 and the macrophage marker Iba1, respectively. Differences in faecal bacterial composition were assessed in mice with and without endometriosis, and faecal microbiota transfer studies were performed.

MAIN RESULTS AND THE ROLE OF CHANCE: In mice treated with broad-spectrum antibiotics (vancomycin, neomycin, metronidazole and ampicillin), endometriotic lesions were significantly smaller (~ 5-fold; $P < 0.01$) with fewer proliferating cells ($P < 0.001$) than

those in mice treated with vehicle. Additionally, inflammatory responses, as measured by the macrophage marker Iba1 in lesions and IL-1β, TNF-α, IL-6 and TGF-β1 in peritoneal fluid, were significantly reduced in mice treated with broad-spectrum antibiotics ($P < 0.05$). In mice treated with metronidazole only, but not in those treated with neomycin, ectopic lesions were significantly ($P < 0.001$) smaller in volume than those from vehicle-treated mice. Finally, oral gavage of faeces from mice with endometriosis restored the endometriotic lesion growth and inflammation ($P < 0.05$ and $P < 0.01$, respectively) in metronidazole-treated mice.

LARGE-SCALE DATA: N/A.

LIMITATIONS, REASONS FOR CAUTION: These findings are from a mouse model of surgically-induced endometriosis. Further studies are needed to determine the mechanism by which gut bacteria promote inflammation, identify bacterial genera or species that promote disease progression and assess the translatability of these findings to humans.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings suggest that gut bacteria promote endometriosis progression in mice. This finding if translated to humans, could aid in the development of improved diagnostic tools and personalised treatment strategies.

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KEYWORDS: endometriosis; gut bacteria; inflammation; metronidazole; microbiome

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