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Do bioactive lipids play a role in leuprolide acetate treatment of endometriosis?

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Introduction: Endometriosis, the presence of endometrial-like cells (glands and stroma) outside the uterus, is the leading cause of chronic pelvic pain and infertility in women (1). Therapy with leuprolide acetate (Prostap SR™), a potent analogue of gonadotropin-releasing hormone, is widely used to relieve pain symptoms by inducing a hypo-oestrogenic state. However, endometriosis returns at drug discontinuation. The aim of this study was to examine the effect of leuprolide acetate on omega-6 and omega-3 derived lipid mediators and elucidate its role in suppressing endometrial tissue growth.

Method: Eutopic endometrium from women not diagnosed with endometriosis (controls; n=18) and from women diagnosed with endometriosis either treated with (n=8) or without leuprolide acetate (n=11) were obtained at St Mary's Hospital, Manchester. Dosage regimen was monthly injections of leuprolide acetate (3.75mg) for up to 6 months before surgery and studies were carried out in accordance with the Local Regional Ethics Committees. Tissue histology was observed by H&E staining. Samples were analysed using liquid chromatography coupled to tandem mass spectrometry with electrospray ionisation (UPLC/ESI-MS/MS) using an array of 79 lipid mediators (2). Significance was determined using the Kruskal-Wallis test with Tukey's *post-hoc* adjustment.

Results: Treatment with leuprolide acetate caused partial decidualisation of endometrial stromal cells and atrophy of glands. Lipidomic analysis showed lower prostaglandin (PG)E_2 ($p<0.05$) and $PGF_{2\alpha}$ ($p<0.05$) and higher 9,10-epoxyoctadecenoic acid (EpOME; $p<0.05$) products in the untreated endometriosis group compared with controls. Apart from a 1.8-fold increase in 5,6-epoxyeicosatrienoic acid (EET) ($p<0.05$), leuprolide acetate appeared to restore endometrial lipid profiles to a similar concentration as controls.

Conclusions: Our findings indicate that a reduction in cyclooxygenase-derived lipids contributes to the pathophysiology of endometriosis. Whilst paradoxical to other reports (3,4), dysregulation of EpOME and other cytochrome P450 products are hallmarks of oxidative stress, implicated in pain-related symptoms of the disease (5,6). Interestingly, not only did leuprolide acetate treatment cause endometrial atrophy, it resolved the lipid profile and enhanced activity of anti-inflammatory EETs. This provides new insights into the endometrial lipidome and the therapeutic value of leuprolide acetate in endometriosis.

References:

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