Metabolomic Markers of Neurotransmitter-Related Metabolism in Women with Ovarian Endometriomas: The Role of the Kynurenine Pathway and Changes During Progestin Therapy

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BACKGROUND AND AIMS

Endometriosis, including ovarian endometriomas, is associated with chronic inflammation, pelvic pain, fatigue, and affective symptoms. Metabolites of the kynurenine cascade (tryptophan catabolism) are of particular interest as potential non-invasive biomarkers reflecting immune activation and neuro-metabolic shifts. This study aimed to characterise neurotransmitter-related metabolomic features (selected amino acids and kynurenine-pathway metabolites) in women with ovarian endometriomas compared with controls, to assess changes during progestin therapy, and to explore associations between metabolite dynamics and clinical symptom severity.[1]

MATERIALS AND METHODS

A case-control study was performed, including women with ovarian endometriomas (Group I-A; n=60) and women without endometriosis (controls: Group II-B; n=30). Plasma metabolite concentrations were assessed at baseline (time point 1) and after a course of hormonal therapy with progestins (time point 3). The metabolomic panel included kynurenic acid, xanthurenic acid, picolinic acid, quinolinic acid, glycine, glutamine, tryptophan, and tyrosine. Clinical outcomes were evaluated using PainDETECT (pain), the Multidimensional Fatigue Inventory (MFI-20; fatigue), the Hospital Anxiety and Depression Scale (HADS; anxiety/depression), and the Gastrointestinal Symptom Rating Scale (GSRS; gastrointestinal symptoms). Associations between changes in metabolites and changes in clinical scores were analysed using Spearman correlation.

RESULTS

At baseline, women with ovarian endometriomas showed significantly higher plasma kynurenic acid compared with controls (values are presented as median [IQR]; 1.82 [1.13– 2.31] versus 1.05 [0.84–1.80] µmol/L; p=0.001) and higher glycine (238.04 [221.59–270.14] versus 203.61 [99.75–250.43] µmol/L; p=0.008). Xanthurenic acid demonstrated a non-significant trend towards group differences (p=0.063), whereas picolinic acid, glutamine, tryptophan, tyrosine, and quinolinic acid did not differ significantly between groups at baseline.

Following progestin therapy (time point 3), partial normalisation of several metabolites was observed in Group I-A: kynurenic acid decreased to 1.46 (0.79–1.89) µmol/L (p<0.001), glycine decreased to 184.02 (105.32–292.60) µmol/L (p=0.004), picolinic acid decreased to 0.72 (0.49–1.42) µmol/L (p=0.004), and glutamine decreased to 499.31 (394.84–572.61) µmol/L (p=0.016). Xanthurenic acid increased to 0.54 (0.33–0.78) µmol/L (p=0.018).

Clinically, after 3 months of therapy, gastrointestinal symptoms improved significantly (GSRS: 36.5 [27–44] → 29 [20–38]; p<0.001). No significant changes were detected for pain (PainDETECT: 7 [6–10] → 7 [3–12]; p=0.80) or fatigue (MFI-20: 37.5 [30–57] → 39 [30–58]; p=0.77). A statistically significant increase in depressive symptoms was observed (HADS depression: 3.5 [1.8–6.0] → 5.0 [3–8.3]; p=0.017).

In correlation analysis, changes in picolinic acid were associated with changes in fatigue (Δpicolinic acid versus ΔMFI-20: ρ=+0.28; p=0.03). Borderline trends were observed for pain (ρ=+0.25; p=0.06) and depression (ρ=−0.24; p=0.06).

FUTURE RESEARCH AND LIMITATIONS

Prospective studies in larger, well-characterised cohorts with standardised progestin regimens are needed to validate these findings. Expanding the biomarker panel to include inflammatory cytokines and vitamin B6 status may clarify mechanistic links between immune activation, kynurenine-pathway shifts, and neuropsychological symptom dynamics.

CONCLUSION

Women with ovarian endometriomas demonstrate metabolomic evidence of kynurenine-pathway activation (elevated kynurenic acid) and altered amino acid profile (elevated glycine) at baseline. Progestin therapy is associated with partial normalisation of several metabolites; however, short-term clinical benefit appears most pronounced for gastrointestinal symptoms, while pain and fatigue may remain unchanged. Notably, depressive symptoms may increase during therapy, highlighting the importance of monitoring mental health outcomes. Picolinic acid may represent a candidate marker related to fatigue dynamics and warrants further investigation.

Reference

1. Dubrovina S. The personalized approach for MHT selection according to women's androgen status during menopausal transition. P.017. ISGE Congress, 4-6 March, 2026.