Introduction: Endometriosis is an oestrogen-dependent inflammatory disorder characterised by growth of ectopic endometrium (lesions), chronic pelvic pain and infertility. In endometriotic lesions, nerve fibres and macrophages exist in close proximity.

Hypothesis: Oestrogen regulates the neuro-modulatory effects of macrophages in endometriosis.

Materials and Methods: Ectopic endometrium (lesions) and peritoneal biopsies were collected from women with endometriosis. Human peripheral blood derived monocytes (PBDMs) were differentiated into M1 or M2 phenotypes using macrophage-stimulating factors (GM-CSF, M-CSF) and together with rat dorsal root ganglia neurons (DRGs) used for migration/outgrowth assays. Cells were treated for 24h with vehicle, E2, DPN (ERß agonist) or PPT (ER? agonist) +/- an ER antagonist. mRNAs were determined by qRTPCR, proteins detected by immunohistochemistry and Western blotting.

Results: Oestrogen receptors alpha and beta (ER?/ ERß) were both expressed in peritoneal and endometriosis-associated macrophages, in M1 and M2 macrophages differentiated in vitro as well as rat DRGs. Incubation of DRGs with E2, DPN or PPT increased expression of GM-CSF, M-CSF and chemokines (CCL2, CCL3); receptors for these factors (CSFR1, CSFR2, CCR2, CCR3) were up-regulated in E2-treated macrophages. Conditioned media (CM) from E2-treated M2 macrophages significantly enhanced neurite outgrowth from DRGs. Expression of neurotrophic factors (BDNF and NT-3) was up-regulated by E2 in M2 but not M1 macrophages; expression of their receptors (TRKB and TRKC) was increased in E2-treated DRGs.

Conclusion: These studies highlight a role for the E2-dominated microenvironment in lesions in promoting expression of key factors likely to orchestrate the neuro-modulatory effects of M2 macrophages in endometriosis. This interplay may be modified by ER subtype-selective antagonists.