Background: During the secretory phase of the menstrual cycle the functional layer of the endometrium undergoes dynamic remodelling characterised by decidualization of endometrial stromal cells (ESC), vascular remodelling and increases in the number of uterine natural killer (uNK) cells. uNK cells express estrogen receptor (ER)β but a role for estradiol (E2) in regulation of uNK cell function has not been described. We have discovered that biosynthesis of E2 parallels decidualization of human ESC. We used isolated uNK cells to investigate the impact of E2 on uNK-mediated endometrial angiogenesis in order to explore the role of E2 in cell-cell interactions within the endometrial microenvironment.

Methods: First trimester decidual samples (n=28) were obtained from women undergoing surgical termination of pregnancy. uNK cells were isolated from decidua and treated with E2 alone or in combination with the antiestrogen ICI 182,780. The impact of uNK conditioned media (CM) on human endometrial endothelial cell (HEEC) network formation was assessed. Expression of angiogenic factors by E2-treated uNK cells was investigated using a cytokine array, qRTPCR and ELISA.

Results: E2-dependent secretion of pro-angiogenic factors by uNK cells significantly increased HEEC network formation (p<0.001). Array analysis of CM revealed CCL2 as the most abundant cytokine in uNK-E2 CM. Array data were validated by confirming E2 treatment increased expression of mRNA encoded by CCL2 (p<0.05) and secretion of CCL2 protein by uNK cells (p<0.001).

Conclusion: Secretion of CCL2 from uNK cells is ER-dependent and CCL2 facilitates uNK-mediated endometrial angiogenesis. These data highlight the role played by local biosynthesis of E2 in mediating cross-talk between uNK and the endometrial vasculature.