**Abstract**

**Background:** Endometriosis is a chronic inflammatory condition that occurs during the reproductive years. It is characterised by endometrium-like tissue developing outside the uterine cavity. This endometriotic tissue development is dependent on oestrogen produced primarily by the ovaries and partially by the endometriotic tissue itself, therefore traditional management has focused on ovarian suppression. In this review we considered the role of modulation of the immune system as an alternative approach. This is an update of a Cochrane Review previously published in 2012.

**Objectives:** To determine the effectiveness and safety of pentoxifylline in the management of endometriosis. SEARCH METHODS: We searched the Cochrane Gynaecology and Fertility (CGF) Group Trials Register, CENTRAL, MEDLINE, Embase, PsycINFO, and AMED on 16 December 2020, together with reference checking and contact with study authors and experts in the field to identify additional studies.

**Selection criteria:** We included randomised controlled trials (RCTs) comparing pentoxifylline with placebo or no treatment, other medical treatment, or surgery in women with endometriosis. The primary outcomes were live birth rate and overall pain (as measured by a visual analogue scale (VAS) of pain, other validated scales, or dichotomous outcomes) per woman randomised. Secondary outcomes included clinical pregnancy rate, miscarriage rate, rate of recurrence, and adverse events resulting from the pentoxifylline intervention.

**Data collection and analysis:** Two review authors independently assessed studies against the inclusion criteria, extracted data, and assessed risk of bias, consulting a third review author where required. We contacted study authors as needed. We analysed dichotomous outcomes using Mantel-Haenszel risk ratios (RRs), 95% confidence intervals (CIs), and a fixed-effect model. For small numbers of events, we used a Peto odds ratio (OR) with 95% CI instead. We analysed continuous outcomes using the mean difference (MD) between groups presented with 95% CIs. We used the I2 statistic to evaluate heterogeneity amongst studies. We employed the GRADE approach to assess the quality of the evidence.

**Main results:** We included five parallel-design RCTs involving a total of 415 women. We included one additional RCT in this update. Three studies did not specify details relating to allocation concealment, and two studies were not blinded. There were also considerable loss to follow-up, with four studies not conducting intention-to-treat analysis. We judged the quality of the evidence as very low. Pentoxifylline versus placebo No trials reported on our primary outcomes of live birth rate and overall pain. We are uncertain as to whether pentoxifylline treatment affects clinical pregnancy rate when compared to placebo (RR 1.38, 95% CI 0.91 to 2.10; 3 RCTs, n = 285; I2 = 0%; very low-quality evidence). The evidence suggests that if the clinical pregnancy rate with placebo is estimated to be 20%, then the rate with pentoxifylline is estimated as between 18% and 43%. We are also uncertain as to whether pentoxifylline affects the recurrence rate of endometriosis (RR 0.84, 95% CI 0.30 to 2.36; 1 RCT, n = 121; very low-quality evidence) or miscarriage rate (Peto OR 1.99, 95% CI 0.20 to 19.37; 2 RCTs, n = 164; I2 = 0%; very low-quality evidence). No trials reported on the effect of pentoxifylline on improvement of endometriosis-related symptoms other than pain or adverse events. Pentoxifylline versus no treatment No trials reported on live birth rate. We are uncertain as to whether pentoxifylline treatment affects overall pain when compared to no treatment at one month (MD -0.36, 95% CI -2.12 to 1.40; 1 RCT, n = 34; very low-quality evidence), two months (MD -1.25, 95% CI -2.67 to 0.17; 1 RCT, n = 34; very low-quality evidence), or three months (MD -1.60, 95% CI -3.32 to 0.12; 1 RCT, n = 34; very low-quality evidence). No trials reported on adverse events caused by pentoxifylline or any of our other secondary outcomes. Pentoxifylline versus other medical therapies One study (n = 83) compared pentoxifylline to the combined oral contraceptive pill after laparoscopic surgery to treat endometriosis, but could not be included in the meta-analysis as it was unclear if the data were presented as +/- standard deviation and what the duration of treatment was. No trials reported on adverse events caused by pentoxifylline or any of our other secondary outcomes. Pentoxifylline versus conservative surgical treatment No study reported on this comparison.

**Authors' conclusions:** No studies reported on our primary outcome of live birth rate. Due to the very limited evidence, we are uncertain of the effects of pentoxifylline on clinical pregnancy rate, miscarriage rate, or overall pain. There is currently insufficient evidence to support the use of pentoxifylline in the management of women with endometriosis with respect to subfertility and pain relief outcomes.