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Mini-commentary on BJOG-19-1705.R2: Post-operative hormonal treatment for prevention of endometrioma recurrence after ovarian cystectomy: A systematic review and network meta-analysis

**Postoperative medical therapies for the prevention of endometrioma recurrence – do we now have the final answer?**

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Endometriosis is often described as a chronic condition. Surgical or medical treatment approaches do not always cure it, and recurrence of the disease or its symptoms is common.

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Medical treatment is usually used to achieve symptomatic control whilst surgery aims to eliminate the visible lesions. However, recurrence is frequently seen even after very radical surgery.

Endometriomas are frequently used for diagnosis and as a marker of recurrence due their easy recognition on imaging. In this issue of BJOG, Wattanayingcharoenchai et al (BJOG 2020 xxxx) present their systematic review and network metaanalysis (NMA) on the efficacy of postoperative medical therapies in reducing endometrioma recurrence with some mixed messages. They conclude that evidence from randomised controlled trials (RCTs) do not support the use of postoperative hormonal therapies, whereas data from cohort studies indicate a significant protective effect of levonorgestrel intrauterine system (LNG-IUS) followed by dienogest, gonadotrophin releasing hormone agonists (GnRHa) + LNG-IUS, continuous and cyclical oral contraceptives (OC). The most effective postoperative therapy (although non-significant) was GnRHa+LNG-IUS, followed by continuous OC and GnRHa based on RCTs.

Direct meta-analysis of RCTs in the Wattanayingcharoenchai et al. article indicate an approximately 40-50% reduction with OCs but this remained statistically non-significant. This finding is in contrast to an earlier meta-analysis (Vercellini et al. Acta Obstet Gynecol Scand. 2013;92:8-16) which concluded that the postoperative OC use dramatically reduced the risk of endometrioma recurrence and international guidelines that recommend use of hormonal contraceptives for the secondary prevention of endometrioma (Dunselman et al. Hum Reprod. 2014;29:400-12). So what are we to believe and what should we advise women affected by endometriosis to do?

There is a wide variation in the design of studies on which metaanalyses and the current NMA are based on in terms of inclusion criteria, duration of treatment and definition of recurrence. Some studies allocate the participants on the basis of their disease stage without taking the preoperative cyst size and bilaterality into account. The definition of a 'recurrent cyst' varies from 'no definition' to endometrioma of > 1 cm or >3 cm. These introduce significant heterogeneity which potentially compromise the validity of any meta-analysis. Furthermore, there is also a conceptual difference between using medical treatment (e.g. GnRHa) for 3-6

months postoperatively and continuing with therapy (e.g. hormonal contraceptives) in the long term and assessing the recurrence rates at 1-5 years. In fact the ESHRE guideline (Dunselman et al.) proposed distinguishing postoperative adjunctive treatment of < 6 months that aims to improve the outcome of surgery and longer treatments with the intention to reduce recurrences (secondary prevention). The former may have a significant side effect profile whereas the latter has a good safety record.

It is very plausible that suppression of ovulation and reducing/eliminating menstrual flow in the long term would reduce recurrences. The current literature is too heterogeneous and fragmented to confirm or refute this. Properly designed large scale studies with the required power are still required. The Pre-Empt trial which is currently ongoing in United Kingdom may give some of the answers.

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