

References

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Reply: LNG-IUDs in treating dysmenorrhea

Sir,

We appreciate Dr Wildemeersch's interest in our review and comments about the potential effectiveness of hormonal intrauterine technology in treating primary and secondary dysmenorrhea. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common treatment for dysmenorrhea and are given more extensive coverage in our review (Iacovides *et al.*, 2015).

We would like to take this opportunity to extend Dr Wildemeersch's discussion about the use of intrauterine devices (IUDs) as a treatment strategy for dysmenorrhea. The levonorgestrel-releasing IUD (LNG-IUD) is an effective contraceptive option in women and usage rates are increasing, although usage is still relatively low in women under the age of 20 years (Ott *et al.*, 2014); the age-group in which primary dysmenorrhea is common. More recently, smaller framed (28 × 30 mm) LNG-IUDs (LNG 13.5 mg) have become available (<http://www.medicines.org.uk/emc/medicine/28672/SPC/Jaydess+13.5+mg+intrauterine+delivery+system>. Accessed on 5/10/2015), thereby creating the opportunity for increased use of intrauterine technology in nulliparous women and adolescents. Insertion of a smaller IUD may be easier for these groups of women, who have smaller uterine dimensions compared with parous women. The frameless LNG-IUDs are promising for similar reasons, as highlighted by Dr Wildemeersch. However, it should be noted that recent published data showed that most insertions of a standard-size framed IUD (LNG 52 mg, size 32 × 32 mm) were uneventful in nulliparous adult women with small uterine measures (Kaislasuo *et al.*, 2014) and a smaller uterine cavity size predicted less bleeding and pain during use compared with adult women with larger uterine cavity measurements (Kaislasuo *et al.*, 2015).

The LNG-IUD has well-established non-contraceptive benefits, including reduction of severe dysmenorrhea and/or heavy menstrual bleeding associated with endometriosis, adenomyosis, and chronic pelvic pain (Bahamondes *et al.*, 2007). The reduction in menstrual pain is thought to be due to the effects of LNG on the endometrium leading to oligomenorrhea and amenorrhea, as well as inhibition of inflammatory mediators present in the peritoneum (Bahamondes *et al.*, 2007). However, the pain-reducing benefit of the LNG-IUD may not be immediately evident, and is influenced by dysmenorrheic pain severity at baseline: women with dysmenorrhea are more likely to experience greater pain when inserting (Kaislasuo *et al.*, 2014) and when using a LNG-IUD during the first 3 months of use (Kaislasuo

et al., 2015). Given the evidence that women with dysmenorrhea are hypersensitive to experimental pain (Iacovides *et al.*, 2015), they may also be hypersensitive to the pain of IUD insertion and the initial uterine irritation. Lack of immediate relief of menstrual pain in some women may also explain why pre-existing dysmenorrhea predicts removal of an IUD 1 year later (Maguire *et al.*, 2015). Self-reported bleeding and cramping are associated with lower user satisfaction with the LNG-IUD, however, the majority of women (>90%) are satisfied with their device at 6 months (Diedrich *et al.*, 2015). Further study is needed to follow up on associations between dysmenorrhea and IUD use so that women can be adequately counseled on what to expect. As with any treatment, side effects need to be considered; LNG-IUD use in women is associated with increased risk of acne, headache, migraine and mental side effects (<http://www.medicines.org.uk/emc/medicine/28672/SPC/Jaydess+13.5+mg+intrauterine+delivery+system>. Accessed on 5/10/2015).

For women who are seeking contraception in addition to menstrual pain relief, intrauterine devices as well as oral contraceptives, are good options. Short-term use (i.e. only during painful menstruation) of NSAIDs should not be excluded as an effective means of pain relief, particularly for nulliparous women not seeking contraception, and particularly since gastrointestinal side effects associated with NSAID use are of less concern with acute, rather than chronic, use (Iacovides *et al.*, 2015).

As commented by Dr Wildemeersch, current research on the effectiveness of intrauterine technology in alleviating dysmenorrhea is promising although we await collection of further data to confirm the efficacy of the new smaller framed and frameless LNG-IUDs in the long-term alleviation of dysmenorrhea in different populations, including adolescents, considering primary versus secondary dysmenorrhea. Finally, looking ahead to potential alternative treatments that are currently under development, we note the recent publication showing, for the first time, efficacy of PDC31 (prostaglandin F2α receptor inhibitor) in decreasing uterine activity and alleviating pain in primary dysmenorrhea (Böttcher *et al.*, 2014). Having more options available to women for treating dysmenorrhea is optimal and will improve management of this very common gynecological disorder.

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Metformin for women with hyperandrogenic anovulation

Sir,

I read with great interest a systematic review comparing metformin and lifestyle modification in women with hyperandrogenic anovulation (Naderpoor *et al.*, 2015) where the authors concluded that metformin + lifestyle modification is able to reduce body mass index (BMI). However, reading the forest plots, I noticed that >90% of the weight of the pooled estimated comes from only one study (Karimzadeh and Javedani, 2010). When reading this study, which is at high risk of bias (no details regarding randomization or allocation concealment are

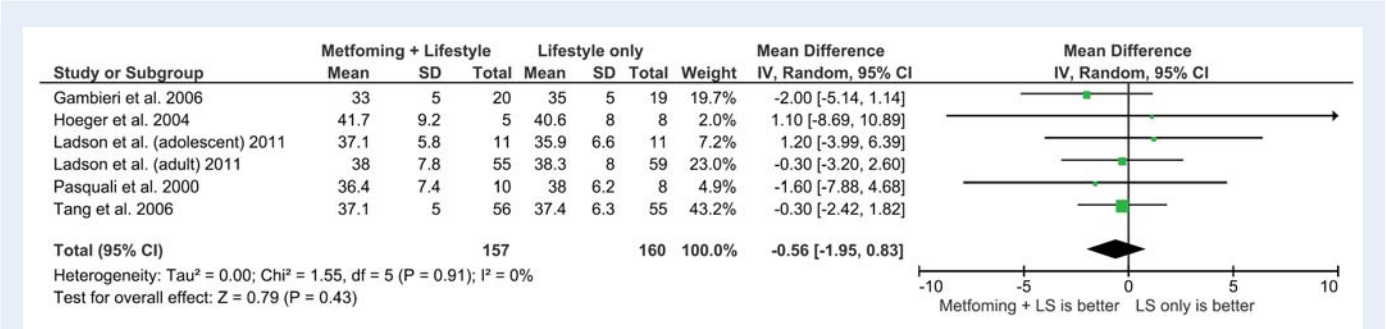


Figure 1 Forest plot comparing the body mass index after metformin + lifestyle versus lifestyle modifications only in women with hyperandrogenic anovulation, without including the study by Karimzadeh and Javedani (2010) (total = 6 studies, 317 women).

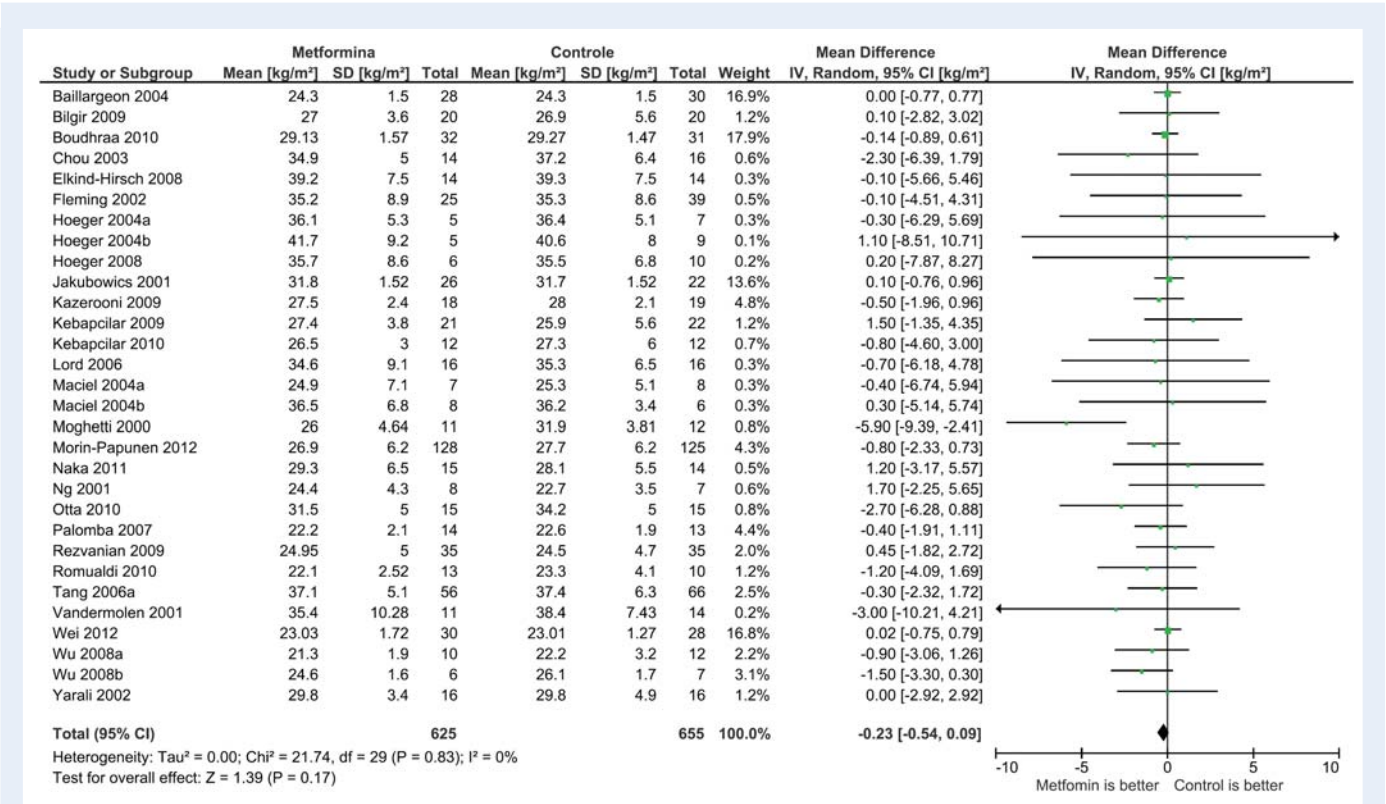


Figure 2 Forest plot comparing metformin versus placebo or no intervention in women with hyperandrogenic anovulation (total = 30 studies, 1280 women).