

WHICH TREATMENTS ARE EFFECTIVE FOR ENDOMETRIOSIS-RELATED
INFERTILITY? “I NEITHER KNOW NOR THINK THAT I KNOW” *

*In Plato’s Socrates, *Apology* 21d.

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Hodgson and co-workers conducted a systematic review and network meta-analysis (NMA) with the objective of comparing the effectiveness of available treatments for endometriosis-related infertility (1). Compared to placebo, GnRH agonists alone and laparoscopic surgery alone significantly increased the clinical pregnancy rate to a similar extent (OR 1.68, 95% CI 1.07-2.46; and 1.63, 95% CI 1.13-2.35, respectively). Although based on limited data, a hysterosalpingogram (HSG) with lipiodol, an oil-based contrast medium, and laparoscopic surgery plus postoperative pentoxifylline demonstrated an even larger effect. No significant difference versus placebo was observed in the likelihood of conception for any of the other 10 interventions included in the NMA.

Using the conventional pair-wise meta-analysis approach, only two interventions at a time can be compared, by selecting only those head-to-head trials comparing directly the two interventions. The NMA technique allows the comparison of multiple interventions at the same time by combining direct (head-to-head) and indirect evidence derived from randomized controlled trials (RCT). Indirect evidence refers to the estimate of the relative effects of different treatments that was not obtained through direct comparison but, instead, through comparison with one or more different but common comparators. Simplistically, an NMA could be viewed as a sort of inclusive trial in which participants could be allocated to any of the selected treatments. Basing on mixed (direct plus indirect) relative effect estimates, an NMA consents the hierarchical ranking of the interventions available for a given condition (2). A concise primer of NMA for clinicians is available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5247317/> (accessed on October 12, 2019).

The authors should be commended for the application of a sophisticated statistical technique in a field still full of uncertainties. However, if the quality of the selected studies is poor or the amount of available data is small, the results of NMA should be interpreted with caution and the resulting ranking may be misleading (2). Between-study qualitative and quantitative heterogeneity appears high. The definition of infertility was inconsistent, its duration variable or not stated. Other causes of infertility in addition to endometriosis were unfrequently excluded. The sample size of

several trials was very limited, and the evidence on some of the considered treatments scanty. Most trials were at risk of bias, and six were published in the eighties, thus were designed more than 30 years ago. Some studies had multiple aims and the effect on infertility was not always the primary objective. Different treatment periods were chosen for the same type of medication (e.g., from 2 to 6 months for GnRH agonists and 6 or 12 months for pentoxifylline). In most studies only conception rate, i.e., a surrogate marker for live birth rate, was indicated. The vast majority of the trials were conducted in a single center, thus limiting the generalizability of the overall results. Owing to missing information in 40% of the studies, the treatment effects in women with different endometriosis severity could not be explored. The authors acknowledge that *"the majority body of evidence in endometriosis had overall low to very low certainty due to imprecision and concerns on risk of bias"*, and findings regarding some interventions should be interpreted with caution. (1)

Up to now, GnRH agonists, similarly to all available hormonal treatments used to suppress ovarian function, have generally been considered of no benefit in enhancing the pregnancy rate in women with endometriosis-related infertility (3,4). The evidence changed when a single large study with 450 participants demonstrated a similar effect of a GnRH agonist alone, laparoscopic surgery alone or a combination of both interventions (1), with pregnancy rates ranging from 55% to 65%. However, conception is prevented during GnRH agonist treatment and this should be taken into account especially in women in their late reproductive years. Moreover, in which patients should GnRH agonists be indicated? Ovarian and deep endometriosis are reliably detected at ultrasonography, but a laparoscopy is necessary for the diagnosis of superficial peritoneal lesions that would be treated immediately. This would increase the odds of pregnancy exactly as GnRH agonists would do and, at that point, independently of their use. In fact, based on the results of Hodgson *et al.*, the effects of laparoscopy surgery and postoperative GnRH agonists are not synergistic (1).

When considering the effect of laparoscopic surgery, a distinction should be made between statistical significance, which is objective, and clinical importance, which is subjective. Reporting

the benefit in terms of crude percentages and number-needed-to-treat (NNT) may facilitate women's comprehension and inform their decision. What does an OR 1.63 of conception mean for lay people? In practice, this estimate translates into an increase in the 12-month likelihood of live birth from slightly less than 20% to slightly over 30%. However, this approximate 10% difference has been demonstrated in RCTs conducted on women with minimal or mild endometriosis, that is, mostly superficial peritoneal implants. Because it is currently impossible to detect this type of lesions pre-operatively, endometriosis will be eventually diagnosed in only 30-50% of women undergoing laparoscopy for unexplained infertility (1). Thus, the benefit of surgery will be "diluted", as in most patients early-stage endometriosis will not be found. Some women might wonder whether it is worthwhile to undergo a laparoscopy when informed that about 20 procedures are needed to obtain one additional live birth compared with expectant management (3,4). Such information should be of interest also for health policy makers when assessing the cost-effectiveness of available interventions for endometriosis-associated infertility. Unfortunately, the results of the present NMA do not apply to women with more advanced endometriosis, also because trials which examined only women with infertility and ovarian endometriomas were excluded.

Despite some methodological limitations, in the hierarchical ranking based on treatment effectiveness, lipiodol-HSG and laparoscopic surgery plus pentoxifylline were associated with the strongest effect compared with no treatment (OR 7.56, 95% CI, 2.02-29.37; and OR 3.91, 95% CI 1.08-10.93, respectively).

A potential fertility-enhancing effect of lipiodol-HSG has been reported since a long time ago. However, the use of oil-based contrast media was progressively replaced by water-soluble contrast media for technical, safety, and economic reasons. Data on the effectiveness of lipiodol-HSG refers to women who had endometriosis but unaffected Fallopian tubes and ovaries in the context of otherwise unexplained infertility. In other words, lipiodol-HSG seems effective in women with minimal-mild superficial peritoneal endometriosis, thus, the same population considered in the available RCTs on the effect of laparoscopic surgery (3,4). However, the NNT of

lipiodol-HSG would be substantially lower than that of laparoscopic surgery. As the NNT of lipiodol-HSG is 3 in women with known peritoneal endometriosis, around 6 lipiodol-HSGs would be needed to achieve one additional pregnancy in infertile women without a previous diagnosis of minimal-mild lesions.

Conversely, the observed large benefit of laparoscopic surgery plus postoperative pentoxifylline is somewhat unexpected as, according to a Cochrane review including three RCTs (5), the clinical pregnancy rate did not increase in women with endometriosis using pentoxifylline compared with those taking placebo (OR 1.54, 95% CI 0.89 to 266).

Because the authors considered only natural pregnancies and excluded the assisted reproduction trials, ART is the great absentee of this NMA. Although ART interventions were included in the systematic review, comparison with other non-ART interventions was not possible. Such an assessment would have been important and, indeed, the authors foster the conduction of studies on the effectiveness of IVF and IUI compared with other treatments.

Hodgson *et al.* rightly recognize that methodological and biometric aspects affecting estimates of effectiveness of interventions for endometriosis-associated infertility are essential, but therapeutic decisions should be eventually personalized. Indeed, multiple factors may influence the final choice, including patient's age as well as preferences and priorities, severity of pain symptoms, and characteristics of different health care services and reimbursement systems. Ideally, the information on the potential benefits of available treatments should be provided separately for women with superficial peritoneal, ovarian, or deep infiltrating lesions, or for those who had already undergone surgical procedures or ART interventions. Especially among women who are not in favor of IVF, the presence of pelvic pain in addition to infertility may tip the balance toward surgery, as this would not only moderately increase the chances of pregnancy, but would also temporarily reduce pain symptoms severity, thus consenting an acceptable quality of life during periods of natural pregnancy seeking. On the other hand, IVF might be preferred when the risk of surgical harms is increased owing to severely distorted pelvic anatomy.

According to the ESHRE Endometriosis Guideline Development Group, “*during the literature searches and discussion of the availability and strength of the evidence, several topics were found for which there is insufficient evidence to answer the key questions*” (4). It does not seem that these gaps have been filled yet, as several years later Hodgson *et al.* conclude “*there is a lack of good quality research in the field of infertility and endometriosis, and targeted, well designed RCTs need to be undertaken to further clarify and provide clear direction on the optimal patient management.*” (1). In the meantime, informing infertile women with endometriosis regarding these uncertainties appears crucial when a medical decision has to be taken.

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