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Short title: Comments on the ESHRE recommendations about minimal endometriosis

Comments on the ESHRE recommendations for the treatment of minimal endometriosis in infertile women

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Abstract

According to ESHRE recommendations for women with stage I/II endometriosis, if a decision is made to proceed to laparoscopy then operative laparoscopy (excision or ablation of the endometriotic lesions) should be performed rather than only diagnostic laparoscopy, to increase ongoing pregnancy rates. Also, for infertile women with stage I/II endometriosis doctors may consider complete surgical removal of endometriosis to improve live birth rate prior to assisted reproductive treatment. This last recommendation is not well established. Does laparoscopic treatment of minimal endometriosis increase the fertility of women with minimal endometriosis? Should we perform surgery in all cases of minimal endometriosis to improve reproductive outcomes prior to assisted reproductive treatment? The aim of this article is to present evidence on these two questions and comment on the ESHRE recommendations. Evidence is quite robust that laparoscopic destruction of minimal to mild endometriosis and associated adhesions enhances fecundity. On the other hand, to date no clear benefit has been demonstrated of performing laparoscopy for minimal endometriosis in women undergoing IVF/intracytoplasmic sperm injection, therefore it is not recommended in these cases. Further studies are needed to assess the mechanisms of endometriosis-associated infertility and how it may be overcome in cases of minimal and mild endometriosis.

Keywords: endometriosis, IVF, laparoscopy

Introduction

The 'gold standard' method for the accurate diagnosis of minimal/mild endometriosis is laparoscopy combined with histological assessment, because positive histology establishes the diagnosis of endometriosis, although negative histology does not exclude the presence of it. A positive laparoscopy, in which endometriosis is identified, is less indicative of endometriosis when used without histology, while a negative diagnostic

laparoscopy seems to be highly accurate for excluding endometriosis and useful in helping decision-making (Wykes *et al*., 2004).

In order to improve the fertility of women with minimal endometriosis, we should try to give the best available treatment options based on the available evidence and of course the individual needs of each patient. Does laparoscopic treatment of minimal endometriosis increase the fertility of women with minimal endometriosis? Should we perform surgery in all cases of minimal endometriosis to improve our reproductive outcomes prior to assisted reproductive treatment? According to the ESHRE recommendations (Dunselman *et al*., 2014) in women with American Fertility Society (AFS)/American Society of Reproductive Medicine (ASRM) stage I/II endometriosis, if there is a decision to proceed to laparoscopy we should perform operative laparoscopy (excision or ablation of the endometriotic lesions) rather than only diagnostic, to increase ongoing pregnancy rates. Also, for infertile women with AFS/ASRM stage I/II endometriosis doctors may consider the complete surgical removal of endometriosis to improve live birth rates prior to assisted reproductive treatment. The guideline continues with the phrase that the benefit of this last recommendation is not well established (Dunselman *et al*., 2014).

The aim of this article is to present evidence on these two main questions and at the same time to comment on the ESHRE recommendations on the aforementioned questions.

Does laparoscopic treatment of minimal to mild endometriosis increase the fertility of women?

Paolo Vercellini (Vercellini *et al.*, 2009) performed a meta-analysis with the aim of evaluating the effect of destruction of peritoneal endometriosis on pregnancy rate in infertile women. Pooling the results of two trials the odds ratio (OR) was 1.65 (95% confidence interval [CI]: 1.06–2.58), which indicated a statistically significant difference of marginal clinical importance (the experimental event rate was 26% versus a control event rate of 18%). The absolute benefit increase of 8% (18–26%) to the main outcome of interest, late pregnancies (completed 20 weeks of gestation), was equivalent to a number-needed-to-treat (NNT) of 12. According to the comments of the authors, perhaps preoperative accurate identification of subjects with stage I/II disease is not feasible, and only one-third to one-half of the women undergoing laparoscopy for unexplained infertility actually have this entity, thus this estimate should at the end be doubled or tripled, and the number of laparoscopies that need to be performed will be almost 40 to achieve one more pregnancy.

In women with minimal to mild endometriosis, the evidence, initially shown in the EndoCan study (Marcoux *et al.*, 1997) and summarized in a Cochrane review, showed that operative laparoscopy was more effective than diagnostic laparoscopy in improving ongoing pregnancy rate (Duffy *et al*., 2014). Four RCTs compared laparoscopic ablation or excision versus diagnostic laparoscopy only. Two RCTs compared laparoscopic excision versus diagnostic laparoscopy only. Two RCTs compared laparoscopic

excision versus ablation and, although both of these techniques were similarly effective in relieving pain, there is insufficient evidence in favour of one over the other with regard to subfertility associated with endometriosis. Compared with diagnostic laparoscopy, laparoscopic surgery was also associated with an increased live birth or ongoing pregnancy rate (OR 1.94, 95% CI: 1.20 to 3.16, P = 0.007, two RCTs, 382 participants, I^2 = 0%, moderate quality evidence, 382 participants) and increased clinical pregnancy rate (OR 1.89, 95% CI: 1.25 to 2.86, P = 0.003, three RCTs, 528 participants, I^2 = 0%, moderate quality evidence). Laparoscopic surgery and diagnostic laparotomy had a similar effect on the rate of miscarriage per pregnancy (OR 0.94, 95% CI: 0.35 to 2.54, two studies, 112 women, moderate quality evidence). Three RCTs showed that laparoscopic ablation or excision was associated with an increased clinical pregnancy rate compared with diagnostic laparoscopy only (OR 1.89, 95% CI: 1.25 to 2.86, P = 0.003, 528 participants, I^2 = 0%).

Comment

Based on the premise that minimal and mild endometriosis are associated with decreased fertility, evidence is quite robust that laparoscopic treatment and eradication of these lesions may improve fertility. The surgical destruction of minimal to mild endometriosis and associated adhesions was indeed shown to enhance fecundity compared with diagnostic laparoscopy alone.

Should we perform surgery prior to assisted reproductive treatment to improve our reproductive outcomes in cases of minimal endometriosis?

The results of surgical treatment are highly dependent upon age, ovarian reserve, duration of infertility and of course other associated infertility factors (sperm, anovulation). The Guideline Development Group (GDG) recommends the use of assisted reproductive treatment for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed (Dunselman *et al.*, 2014). For infertile women with AFS/ASRM stage I/II endometriosis clinicians may consider the complete surgical removal of endometriosis to improve live birth rate, but the benefit of this last recommendation is not well established (Dunselman *et al*., 2014).

This last recommendation is based on one retrospective cohort study which compared reproductive outcomes in a group of women (n = 399) with minimal to mild endometriosis in whom all visible endometriosis was completely removed by laparoscopy prior to IVF, to women undergoing only diagnostic laparoscopy (n = 262). The authors found significantly higher implantation rates (30.9% versus 23.9%, P = 0.02), pregnancy rates (40.1% versus 29.4%, P = 0.004) and live birth rates per oocyte retrieval (27.7% versus 20.6%, P = 0.04) in favour of the treated group (Opoien *et al.*, 2011). According to this study surgical treatment prior to assisted reproductive treatment also gave shorter time to first pregnancy and a higher cumulative pregnancy rate (P < 0.01).

But the same author just a year later (Opoien *et al*., 2012) published another retrospective cohort study on infertile women (*n* = 2245) with various stages of endometriosis. Specifically, pregnancy [87% (95% CI: 81–92%)] and ongoing pregnancy/birth rates [73% (95% CI: 58–75%)] were comparable for the ASRM I/II group and for the tubal factor group: 84% (95% CI: 79–88%)and 66% (95% CI: 58–75%), respectively. The conclusion was that infertile women with various stages of endometriosis have the same success rates with IVF and intracytoplasmic sperm injection as patients with tubal factor.

In 2013 Harb published a meta-analysis with 27 observational studies (*n* = 8984 women) on the effect of endometriosis on IVF outcome (Harb *et al*., 2013). Pooling of results from seven studies that reported fertilization rate as an outcome for stage I/II endometriosis found a 7% reduction in fertilization rate (relative risk [RR] = 0.93, 95% CI: 0.87–0.99, *P* = 0.03). As for implantation, eight studies reported no difference in implantation rate compared with controls (RR = 0.83, 95% CI: 0.68–1.01). Fourteen studies that reported clinical pregnancy as an outcome for stage I/II endometriosis did not show any difference at all in clinical pregnancies (RR = 0.94, 95% CI: 0.83–1.07). As for live births, results from six studies did not show a difference in live birth rates compared with controls (RR = 0.92, 95% CI: 0.83–1.02). The analysis by Harb did not evaluate live birth rates and is weakened by the heterogeneity of comparison groups, which were defined as 'women without endometriosis'. A more recent meta-analysis by Hamdan *et al*. (2015) concluded after subgroup analysis that, in women with less severe disease, all of the outcomes of IVF were comparable with women with no endometriosis. Thus, live birth rates in eight studies (4157 patients) had OR 0.96, 95% CI 0.82–1.12, clinical pregnancy rate in 15 studies (9692 patients) had OR 0.84, 95% CI 0.69–1.03, and mean number of oocytes retrieved per cycle in 11 studies (mean difference –0.58, 95% CI: 21.16 to 0.01).

According to the outcome of the population-based retrospective cohort study from the Society for Assisted Reproductive Technology Clinic in 39,356 initiated cycles of patients with endometriosis, all women with isolated endometriosis had similar or higher live birth rates compared with those of unexplained infertility (RR = 1.04), tubal factor (RR = 1.04) or all other diagnoses (RR = 1.1). In this study women with endometriosis and concomitant diagnoses had lower implantation rates and live birth rates compared with all other diagnostic groups. Perhaps this can be explained by the fact that women with isolated endometriosis represent a subgroup of women with mild disease. Thus, they may have a more favourable response to IVF (Senapati *et al*., 2016).

Comment

In principle, IVF pre-empts most of the deleterious effects of endometriosis as it removes the oocyte–sperm interaction from the peritoneal cavity and is not dependent on Fallopian tube function. However, controversy exists as to whether surgical treatment of endometriosis stage I and II prior to IVF improves the chance of success.

The surgical destruction of minimal to mild endometriosis and associated adhesions was indeed shown to enhance spontaneous fertility and fecundity. On the other hand, the outcome of IVF/ICSI seems to be unaffected by the presence or not of minimal endometriosis and therefore laparoscopy should not be performed in all asymptomatic women prior to assisted reproductive treatment with the aim of diagnosing minimal/mild endometriosis and proceeding to subsequent treatment. Thus, surgical treatment prior to assisted reproductive treatment in order to improve fertility cannot be safely recommended for all patients, while the inherent risks of laparoscopic intervention and anaesthesia should be taken into consideration.

Discussion

IVF is supposed to bypass anatomic distortion, any type of compromise in tubal function, and mainly the peritoneal environment aberrations which are associated with endometriosis. On the other hand, the logic behind surgical resection/destruction of peritoneal disease would be to minimize any deleterious effects that peritoneal implants might have on oocyte quality, or implantation. Unfortunately, the evidence to support the fact that any of these phenomena actually occur is lacking. The surgical resection of minimal disease as a routine procedure before IVF treatment has not been consistently shown to improve outcomes, with the possible exception of resection of deeply invasive disease (Surrey, 2015).

Perhaps one of the reasons for this discrepancy might be the available AFS and r-AFS endometriosis classification system. It has indeed been helpful for documenting but does not seem to have adequate power in discriminating between clinical conditions with different long-term outcomes, and as a consequence is not clinically useful for predicting a reliable prognosis for infertility. Perhaps the EFI (Endometriosis Fertility Index) might be a more helpful tool as it seems to be able to predict pregnancy rates in infertility patients. It is thought to be useful only for infertility patients who have had surgical staging of their disease and it is a prerequisite that the male and female gametes are sufficiently functional to enable attempts at non-IVF conception (Adamson and Pasta, 2010). The EFI might be used in order to decide what type of treatment patients should undergo, for how long and when the assisted reproductive treatment following endometriosis surgery should be considered. Further research is certainly needed on this subject.

It is beyond doubt that assisted reproductive treatment should not be seen as a technique competing with surgical treatment of endometriosis-associated infertility but as a complementary therapeutic strategy. In a disease as diverse as endometriosis, treating individual components of the disease may have a different impact on each patient (Hamdan *et al*., 2015). If treating fertility is the main issue then perhaps surgery should be preferred for young women with good ovarian reserve and no other infertility factors. On the other hand, first-line treatment should be assisted reproductive treatment in the presence of additional infertility factors, in cases of reduced ovarian reserve and when history of previous (multiple) surgery is an issue.

In the majority of cases, couples diagnosed with endometriosis will have at least one other infertility diagnosis when they present for IVF. Undoubtedly, this fact contributes to the clinical challenge of assessing the real impact of a sole diagnosis on IVF outcomes for minimal endometriosis cases. After all, in all these studies there is always the possibility of bias due to diagnostic misclassification of cases with unexplained infertility who may have undiagnosed minimal endometriosis. It is unknown whether correct diagnostic classification would result in different statistical results for cases of minimal endometriosis and the live birth rates after IVF.

IVF is undeniably the most effective treatment for women with endometriosis-associated infertility in general. Yet for cases of minimal stages of this complex disease, counselling patients with respect to expected IVF outcomes is not always straightforward (Hamdan *et al*., 2015). Further studies are needed to assess the mechanisms of endometriosis-associated infertility and how it may be overcome in cases of minimal and mild endometriosis (Bulun, 2009).

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