

## Ovarian stimulation and endometriosis progression or recurrence: a systematic review

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## **Abstract**

Available evidence on the impact of ovarian stimulation on endometriosis progression or recurrence was systematically reviewed. Data from ovarian stimulation alone or associated to intrauterine insemination (IUI) or in vitro fertilization (IVF) were included. Sixteen studies were selected. Initial case reports (total, 11 patients cases) documented some frightful clinical complications. However, subsequent observational studies did not support this alarmism. Overall, five main conclusions can be drawn: 1) IVF does not worsen endometriosis-related pain symptoms (moderate quality evidence); 2) IVF does not increase the risk of ~~lesion~~ endometriosis recurrence (moderate quality evidence); 3) the impact of IVF on ovarian endometriomas is mild, if any (low quality evidence); 4) intrauterine insemination may increase the risk of endometriosis recurrence (low quality evidence); 5) deep invasive endometriosis might progress with ovarian stimulation (very low quality evidence). In conclusion, available evidence is generally reassuring (at least for IVF) and does not justify aggressive clinical approaches such as prophylactic surgery before ART to prevent endometriosis progression or recurrence. Further evidence is however required for definitive conclusions. In particular, the potential effects on deep invasive endometriosis and the possible synergic effect of stimulation and pregnancy are two arguments that need to be better explored.

**Key words:** endometriosis / ovarian stimulation / intrauterine insemination / IVF / recurrence

## INTRODUCTION

Endometriosis is a sex hormone-dependent chronic condition that is frequently associated with infertility. The prevalence of the disease in the general population has been estimated to be about 1-2% (Morassuto *et al.*, 2016; Eisenberg *et al.*, 2018) but raises up to 6% to 9% in infertile women requiring assisted reproductive technologies (ARTs) (CDC, 2014; Smith *et al.*, 2015). Reasons to explain the association between endometriosis and infertility have not been fully clarified, but adhesions and the inflammatory pelvic milieu may play a crucial role (Somigliana *et al.*, 2017).

In recent years, ARTs have become the first-line therapeutic approach to endometriosis-associated infertility (Practice Committee ASRM, 2012; Dunselman *et al.*, 2014). However, ARTs are not devoid of peculiar drawbacks and harms in this particular population (Somigliana *et al.*, 2015a; Somigliana *et al.*, 2015b). Of utmost relevance here is the possibility of disease progression or recurrence during or following treatment. Two main reasons support this concern. Firstly, peripheral oestrogens that play a fundamental role in endometriosis progression (Vercellini *et al.*, 2014) considerably raise during ovarian stimulation, reaching levels that are up to ten-folds higher than those observed in a physiological natural cycle (Macklon *et al.*, 2006). Secondly, multiple ovulations that typically occur during ovarian stimulation could boost the specific risk of endometriomas formation. There is indeed growing evidence that endometriomas may originate from ovulatory events (Vercellini *et al.*, 2010; Viganò *et al.*, 2013).

Overall, the possible impact of ovarian stimulation on endometriosis progression or recurrence is clinically relevant for both patients and physicians but has received scant consideration in the literature, mainly because collecting evidence is methodologically complex. However, some more evidence has emerged during the last decade and we deemed that a systematic review of the literature on this issue was timely and important.

## METHODS

This review was restricted to published research articles that reported on the impact of ovarian stimulation on endometriosis in infertile women with the disease. The main outcomes were progression (worsening of pain symptoms or growth of endometriotic lesions) or recurrence (onset of new pain symptoms, new lesions, need to be operated or to initiate medical therapy).

Literature overview was conducted according to the PRISMA guidelines for systematic reviews (Moher *et al.*, 2009). As published de-identified data were used, this study was exempt from institutional review board approval. Data from ovarian stimulation alone, intrauterine insemination (IUI) or in vitro fertilization (IVF) could all be included. Conversely, studies exclusively reporting on pregnant cases were excluded because discriminating between the detrimental effects of ovarian hyper stimulation and pregnancy was not possible. The primary search was conducted with Medline, including the time period from January 1990 to January 2018 and using the following search strings: (endometriosis OR endometrioma OR endometriotic) AND (in vitro fertilization OR IVF OR ICSI OR intracytoplasmic sperm injection OR intrauterine insemination OR IUI OR ovarian hyperstimulation OR ovarian stimulation OR ART OR assisted reproduction technique) AND (progression OR recurrence OR complication OR safety). The research was re-checked with EMBASE using the PICO system and entering the above-mentioned group of strings for Population, Intervention and Outcome, respectively while using the terms expectant management, placebo or no treatment for the Comparison category. Published cohort, case-control studies and case reports were eligible for inclusion. Studies reporting on complications related to the oocytes retrieval procedure itself were excluded. When study periods of studies performed in the same Institution overlapped, the smaller one was discarded. Publications not written in English were excluded. All pertinent articles were retrieved, and the relative reference lists checked to identify further publications. Moreover, the main review articles on endometriosis published over the last 10 years were consulted and their reference lists searched for potential additional studies. No attempt

was made to contact authors for incomplete information and to identify unpublished studies or abstracts submitted to national or international conferences. All these researches were conducted independently by two of the authors (ES and AB) and discordances were solved by discussion including also the other authors if needed. The main measure used was the rate of recurrence. A binomial distribution model was used to calculate the 95% Confidence Interval (CI) of proportions.

Quality of the case-control or cohort studies was evaluated using the Newcastle Ottawa Scale (NOS). This scale gives up to 9 stars to each study and classify them as low quality (0–4 stars), moderate quality (5-6 stars) and high quality (7-9 stars) (Wells *et al.*, 2018). The overall quality of the evidence was rated based on the Grading of Recommendation Assessment, Development and Evaluation (GRADE) guidelines into four possible categories, i.e. high, moderate, low and very low quality (Balshem *et al.*, 2011).

Data were primary presented according to the study design used (case reports and observational studies). Thereafter, they were analyzed taking into consideration separately the ARTs technique used (ovarian stimulation alone, IUI and IVF) and the form of the disease (ovarian endometriomas, deep peritoneal lesions and pain symptoms).

Even if the possibility of combining results into a meta-analysis was initially planned, this analysis was ultimately not performed because of the considerable variability in duration of follow-up, study designs and definitions of outcome.

## **RESULTS**

The flow-chart of the selection process is shown in Figure 1. Overall, sixteen papers were included.

### *Case reports*

The first evidence on the possible detrimental effects of ovarian stimulation on endometriosis progression was published in the form of a case report. Specifically, in 1995, Renier *et al.* documented a case of a woman with a history of surgery for endometriosis who was diagnosed with left hydronephrosis and complete ureteral stenosis 26 days after the oocytes retrieval. She recovered after distal resection of the ureter and bladder re-implantation. The histological examination revealed extensive transmural and intramural invasion of the ureter by endometriotic tissue (Renier *et al.*, 1995). The good response to ovarian stimulation (12 oocytes retrieved) and the close time-related occurrence of the event supported a possible causal relation.

Three subsequent case reports or small case series described 10 additional IVF-related cases. Anaf *et al.* described four women who required segmental bowel resection after IVF, owing to sigmoid endometriosis causing severe stenosis of the lumen (Anaf *et al.*, 2000). All women had a surgical diagnosis of endometriosis prior to IVF and all had a good response to ovarian stimulation (serum oestradiol at the time of ovulation trigger varied between 2,230 and 2,635 pg/ml). The time period between the stimulation and the occurrence of the symptoms was not clearly reported, but in at least one case this occurred during the stimulation. To note, all these cases were diagnosed with deep invasive forms of endometriosis. Jun and Lathi (2007) reported on five women who experienced onset or worsening of pelvic pain symptoms during ovarian stimulation for IVF. Two had to discontinue the stimulation because of pain. Endometriosis was surgically confirmed after the cycle in all cases, with ASRM classification varying between Stage I and IV. Details on the magnitude of the responsiveness to ovarian stimulation and on the specific forms of endometriosis detected at surgery were not reported. Finally, Halvorson *et al.* (2012) described a case of symptomatic thoracic endometriosis diagnosed immediately after IVF. The woman developed symptoms suggestive for Ovarian Hyper-Stimulation Syndrome (OHSS) three days after the retrieval of 30 oocytes. She had significant free fluid in the pouch of Douglas and severe bilateral hydrothorax that

necessitated bilateral thoracenteses. She then recovered but, after the pregnancy obtained with the frozen embryos, she was diagnosed with congenital diaphragmatic agenesis and underwent surgical repair that revealed the local presence of endometriosis. On these bases, the authors reinterpreted the events occurred at the time of IVF and opted for a final diagnosis of thoracic endometriosis syndrome rather than OHSS (Halvorson *et al.*, 2012).

We failed to identify case reports on endometriosis progression after ovarian stimulation (with or without IUI) without IVF.

### ***Case series and cohort studies***

Following the alarm raised by case reports 12 more informative observational studies were published (Govaerts *et al.*, 1998; D'Hooghe *et al.*, 2006; Benaglia *et al.*, 2009; Coccia *et al.*, 2010; Benaglia *et al.*, 2010; Benaglia *et al.*, 2011; van der Houwen *et al.*, 2014a; van der Houwen *et al.*, 2014b; van der Houwen *et al.*, 2014c; Crochet *et al.*, 2016; Santulli *et al.*, 2016; Seyhan *et al.*, 2017). The main characteristics of these studies are shown in Table 1. Five were prospective while the remaining seven were retrospective. Six studies were case series of women with endometriosis undergoing ARTs (Govaerts *et al.*, 1998; Benaglia *et al.*, 2009; Benaglia *et al.*, 2011; van der Houwen *et al.*, 2014a; Santulli *et al.*, 2016; Seyhan *et al.*, 2017). The remaining six fulfilled the criteria to be considered cohort studies: three of them included a group of unexposed women with the disease who did not undergo ovarian stimulation (Coccia *et al.*, 2010; van der Houwen *et al.*, 2014b; Crochet *et al.*, 2016) while, in the remaining three, comparisons were made based on a gradient of exposure (D'Hooghe *et al.*, 2006; Benaglia *et al.*, 2010; van der Houwen *et al.*, 2014c). Of these six studies, two were of moderate quality and four of high quality.

Data on IVF prevailed but some evidence was also available for IUI (D'Hooghe *et al.*, 2006; Coccia *et al.*, 2010; van der Houwen *et al.*, 2014c; Crochet *et al.*, 2016). No studies reported on ovarian stimulation alone. The definition of recurrence and the duration of follow-up varied widely.

The crude recurrence rate was reported in ten studies (Govaerts *et al.*, 1998; D'Hooghe *et al.*, 2006; Benaglia *et al.*, 2009; Coccia *et al.*, 2010; Benaglia *et al.*, 2010; Benaglia *et al.*, 2011; van der Houwen *et al.*, 2014a; van der Houwen *et al.*, 2014b; van der Houwen *et al.*, 2014c; Santulli *et al.*, 2016). Results are summarized in Table 2. The rates varied from 0% to 37%. Combining these studies to draw an estimate on the risk of recurrence could not be done given the wide differences in durations of follow-up, definitions of recurrences and populations studied (Table 1). Noteworthy, when we plotted rates of recurrences with the mean/median duration of follow-up of the included studies, we found a highly significant correlation (Spearman coefficient Rho of 0.86,  $p=0.001$ ).

The selected studies did not systematically report on the specific forms of the disease detected at the time of recurrence (Table 2). This information was included in only four of them, corresponding to 24 recurrences (Govaerts *et al.*, 1998; Benaglia *et al.*, 2009; Coccia *et al.*, 2010; van der Houwen *et al.*, 2014a). Deep invasive lesions were diagnosed in 17 of them (71%, 95% CI: 52-86%). In the unique available study comparing the type of recurrences between women with endometriosis exposed and non-exposed to IVF, deep invasive lesions were documented in 13 (14%) and 8 (9%) women, respectively ( $p=ns$ ) (Coccia *et al.*, 2010).

Finally, correlation between ovarian responsiveness and risk of recurrence was specifically reported in four studies (D'Hooghe *et al.*, 2006; Benaglia *et al.*, 2009; Benaglia *et al.*, 2010; Seyhan *et al.*, 2018). D'Hooghe *et al.* (2006) and Seyhan *et al.* (2018) evaluated the impact of estrogens peak levels whereas Benaglia *et al.* (2009 and 2010) focussed on the number of oocytes retrieved. None of these studies identified any statistically significant association.



### ***Intrauterine insemination***

D'Hooghe *et al.* (2006) retrospectively identified 67 women operated for endometriosis stage III-IV who subsequently underwent intrauterine insemination (IUI) (n=17), IVF (n=39) or IUI+IVF (n=11). The cumulative risks of recurrences at 21 months in the three groups were 84%, 7% and 43%, respectively. The risk was significantly higher for women undergoing IUI or IUI+IVF compared to those receiving IVF ( $p=0.002$  for both). Subsequent evidence on this specific issue is not fully consistent. Coccia *et al.* (2010) failed to show significant differences according to the type of ART used: the rates of recurrence in women undergoing IUI (n=34), IVF (n=36) or IUI+IVF (n=20) were 18%, 19% and 25%, respectively ( $p=ns$ ). On the other hand, van der Houwen *et al.* (2014b) provided evidence in support of D'Hooghe's *et al.* results. Specifically, they presented data on women previously operated for endometriosis who subsequently performed IUI and compared the rate of recurrence between those performing IUI on natural cycle and then ovarian stimulation (n=45) to those receiving straight only IUI with ovarian stimulation (n=20). The cumulative risk of recurrence was 35% and 72%, respectively ( $p=0.03$ ). The adjusted Hazard Risk (HR) was 2.2 (95%CI: 0.9-5.3). Albeit indirect, this result supports a detrimental effect of ovarian stimulation.

### ***Comparative studies***

Two non-randomized studies compared women with endometriosis receiving IVF to a control group of women with the disease who did not receive ART (Coccia *et al.* 2010; Crochet *et al.*, 2016). Coccia *et al.* (2010) retrospectively identified 177 women who were operated for endometriosis and who were infertile and compared the rate of disease recurrence between those who did (n=90) and did not (n=87) undergo ART (both IVF and IUI). Forty recurrences were diagnosed, of whom 18 were recorded in the ART group (20%) and the remaining 22 in the non-ART group (25%) ( $p=ns$ ). The IVF group did not face a higher risk: ever users of IVF (i.e. combining women receiving IVF

and those receiving both IVF and IUI) had a recurrence rate of 19% (13 out of 70) (Coccia *et al.* 2010). A multivariate analysis to adjust for the differences in baseline characteristics among the study groups was not performed.

Albeit also comparative, insights from the study of Crochet *et al.* (2016) are difficult to interpret. These authors exclusively recruited women who were operated twice for endometriosis and compared modifications of the anatomical lesions at second surgery between women who had (n=21) and did not have (n=36) IVF in the interval between the two interventions. They actually failed to observe significant differences in the change of the ASRM score (Crochet *et al.*, 2016). Unfortunately, the study did not report whether women undergoing IVF were more or less likely to be operated.

Two studies aimed at overcoming the intrinsic difficulties of comparative studies using alternative methodological approaches (Benaglia *et al.*, 2010; van der Houwen *et al.*, 2014a). Benaglia *et al.* (2010) retrospectively identified 189 women with endometriosis who underwent IVF and actively investigated whether or not they had recurrences in the following years (the median time of follow-up was 34 months). Specifically, they evaluated the impact of the number of cycles and the responsiveness to ovarian stimulation, based on the assumption that if a detrimental effect of IVF did exist, a gradient effect (an increase in the rate of recurrence with the number of IVF cycles and the responsiveness to treatment) would have emerged. No gradient effect was found. The adjusted OR of recurrences was 0.92 (95% CI: 0.77-1.10) per cycle and 0.80 (95% 0.40-1.58) for normal responders compared to poor responders (Benaglia *et al.*, 2010). In the second study, van der Houwen *et al.* (2014a) hypothesized that, if a detrimental effect of IVF did exist, a lower risk of recurrences in women receiving long term down regulation with GnRH agonists prior to initiate the ovarian stimulation should be expected (ultralong protocol). They retrospectively recruited women with endometriosis who underwent IVF and compared the recurrence rate at 12 months between

women who did (n=68) and did not (n=45) receive the ultralong protocol. The adjusted OR for those who did receive this protocol was 0.95 (95%CI: 0.37-2.44) (van der Houwen *et al.*, 2014a).

### ***Pain symptoms modifications***

Endometriosis recurrence and pain symptoms modifications are frequently associated, but should be considered distinct aspects. Three independent prospective studies monitored pain symptoms during IVF cycles and all failed to observe detrimental effects (Benaglia *et al.* 2011; van der Houwen *et al.*, 2014c; Santulli *et al.*, 2016).

Specifically, Benaglia *et al.* (2011) evaluated women with endometriosis prior to initiating the cycle and re-evaluated those who failed to become pregnant 3-6 months later. Sixty-four women were eventually assessed. Before-after intra-patient comparisons of the severity of dysmenorrhea, dyspareunia and non-menstrual pelvic pain failed to document significant differences. General improvement or worsening of symptoms was reported by 14 (22%) and 7 (11%) women, respectively. The vast majority (n=43; 67%) subjectively judged their symptoms as unchanged (Benaglia *et al.*, 2011).

Van der Houwen *et al.* enrolled 75 women with a surgical diagnosis of endometriosis stage III-IV prior to initiate IUI (n=25), classical IVF (n=25) and IVF with an ultra-long protocol (n=25) (Van der Houwen *et al.*, 2014c). The rate of satisfaction did not differ among the three groups. For the whole cohort, the number (%) of women with improvement or deterioration of visual analogue scores (VAS) according the studied symptom were as follows: dysmenorrhea 7 (23%) and 8 (26%); dyspareunia 7 (14%) and 5 (10%); non-menstrual pain 9 (13%) and 10 (15%); dyschesia 8 (12%) and 9 (13%); and dysuria 4 (6%) and 4 (6%), respectively. Moreover, no statistically significant differences emerged when comparing the three different study groups (Van der Houwen *et al.*, 2014c).

Santulli *et al.* prospectively compared 102 women with endometriosis and 104 unaffected women during an IVF cycle (Santulli *et al.*, 2016). Four time-points were scheduled, i.e. prior to initiate oral contraceptive synchronization, during oral contraceptive synchronization, at the time of oocytes retrieval and three weeks later. At all time-points, the scores of dysmenorrhea, dyspareunia, non-menstrual pain, and gastrointestinal symptoms were higher in affected women. However, compared to the baseline evaluation, pain increased during IVF in the control group, but not in the endometriosis group. The authors also performed a subgroup analysis according to the phenotype (superficial endometriosis, ovarian endometriomas or deep invasive endometriosis) but failed to identify a subgroup that was more sensitive to the IVF effects (Santulli *et al.*, 2016).

### ***Lesions growth***

Superficial endometriosis cannot be monitored without performing a laparoscopy before and after the IVF cycle, a study design that is obviously ethically untenable. On the other hand, non-invasive diagnosis of ovarian endometriomas and deep invasive peritoneal lesions has become highly reliable (Guerriero *et al.*, 2016; Nisenblat *et al.*, 2016) and monitoring these lesions during IVF is feasible. Three studies reported data on US evaluation of ovarian endometriomas (Benaglia *et al.*, 2009; Benaglia *et al.*, 2011; Seyhan *et al.*, 2018), one of which provided data also on deep invasive lesions (Benaglia *et al.*, 2011).

Specifically, Benaglia *et al.* evaluated 48 women with a total of 70 ovarian endometriomas before and 3-6 months after a failed IVF cycle (women becoming pregnant were excluded) (Benaglia *et al.*, 2009). The median (interquartile range - IQR) volume of the cysts before and after the cycle was 3.9 (2.9-7.9) and 4.9 (2.4-9.9) ml, respectively (p=ns). Subgroup analyses according to the dimension of the cyst and the responsiveness to ovarian stimulation failed to identify a subgroup at

higher risk of significant growth. One woman was diagnosed with an additional endometrioma at the second evaluation (2.1%, 95%CI: 0.1-11.1%) (Benaglia *et al.*, 2009).

Two years later, the same study group performed a second study that focused on symptoms modification before and 3-6 months after a failed IVF cycle (this study was already discussed in the previous chapter) (Benaglia *et al.*, 2011). As secondary findings, the authors reported data also on endometriomas (35 women with 45 cysts) and deep invasive endometriosis (9 women with 10 lesions) modifications. The median (IQR) diameter of the endometriomas before and after the cycle was 20 (12-27) and 20 (17-27) mm, respectively (p=ns). The median (IQR) diameter of the deep lesions before and after the cycle was 10 (5-18) and 10 (5-18) mm, respectively (p=ns) (Benaglia *et al.*, 2011).

Finally, Seyhan *et al.* (2018) recently monitored ovarian endometrioma modification during the cycle using 3D ultrasound. Specifically, they evaluated the dimension of the cysts on the day of the initiation of ovarian stimulation and on the day of ovulation trigger in 25 women with 28 cysts. The volume increased from 22 (IQR: 12 - 30) mL to 25 (IQR: 11 - 37) mL (p<0.001), corresponding to a median increase of 14%. The authors showed a significant positive correlation between endometrioma growth and the baseline dimension of the endometriomas, but failed to detect any correlation with responsiveness to stimulation (Seyhan *et al.*, 2018).

### ***Summary of the evidence***

The main conclusions that can be drawn from this systematic review are summarized in Table 3. Overall, the available evidence is not of high quality, and further data is needed to depict a definitive and comprehensive scenario.

The impact of IVF on endometriosis-related pain symptoms and on ovarian endometriomas are the most properly studied issues. They were both investigated with at least two independent prospective studies. However, data is not fully consistent. Even if the observational studies on pain symptoms failed to identify detrimental effects (moderate quality evidence), one cannot exclude that pain worsening may occur in some particular cases. The five women experiencing pain worsening during ovarian stimulation described by Jun and Lathi (2007) support this possibility.

Considering endometriomas, IVF does not appear to markedly modify their dimension but data is not univocal. Indeed, two studies of the same study group did not report changes, while the third and independent one observed a mild but statistically significant increase in size. One can generally conclude that the impact of IVF on endometriomas dimension is modest, if any, but further evidence is needed and the quality evidence is inevitably rated as low.

Data on the unremarkable effects of IVF on the rate of recurrences and those on the detrimental effects of IUI are supported by independent studies but the study designs have some limitations (in particular, none was prospective) and data is not univocal for IUI. Quality of the evidence can ultimately be rated as moderate and low for IVF and IUI, respectively.

Finally, it is noteworthy that the possible progression of deep invasive endometriosis, which is actually the most worrying potential drawback of ovarian stimulation, is supported exclusively by case reports (very low quality evidence). Future data on this issue is needed.

## **DISCUSSION**

Available evidence on the impact of ovarian stimulation and ARTs on endometriosis progression or recurrence is incomplete. None of the evidence could be graded as high quality. To note, this systematic review focused on observational studies and is consequently exposed to the risk of

publication bias. Some studies could have been missed because search filters for observational studies do not have the high sensitivity as search filters for RCTs. Moreover, the natural tendency of endometriosis to recur (Guo, 2009) complicates the interpretation of the findings because of the inherent difficulty of discerning between recurrences that are caused by stimulation and those that just coincidentally occurred after ARTs. Nonetheless, some notions have emerged and should deserve consideration in clinical practice. In particular, the reassuring data on the impact of IVF on endometriosis recurrence or pain-symptoms progression are supported by moderate quality evidence. Moreover, the impact on endometriomas' dimension (if any) may be clinically unremarkable. This information can be used to reassure affected women entering an IVF program who may be concerned by the theoretical risks of ovarian stimulation.

On the other hand, the insufficient data regarding deep invasive lesions is the most important scientific gap that needs to be covered in the future. These lesions are indeed particularly sensitive to oestrogens compared to other forms of the disease (Vercellini *et al.*, 2016). Evidence from case reports and the high rate of deep invasive lesions observed among recurrent cases (71%, 95% CI: 52-86%) fuel this concern. To date, however, evidence is too scanty to support a detrimental effect. To note, despite the small sample size (only 9 women), the prospective study from Benaglia *et al.* (2011) failed to document a significant growth of these lesions. Moreover, there is a clear contradiction between the worrying case reports on deep invasive endometriosis published in the literature and the reassuring evidence emerging from case-series and cohort studies for endometriosis in general. On these bases, prophylactic surgery in women with deep invasive endometriosis to prevent progression seems to us unsubstantiated and probably unwise. Surgery for deep invasive endometriosis is technically demanding and potentially harmful (Kondo *et al.*, 2011; Oliveira *et al.*, 2016). It could be justified only based on robust clinical evidence. In this regard, it is also worth noting that there is no evidence to support a benefit of prophylactic surgery in terms of pregnancy rate after ART (Somigliana and Garcia-Velasco, 2015; Darai *et al.*, 2017; Iversen *et al.*,

2017). Surgery may be currently considered to increase the chances of pregnancy only if IVF fails (Littman *et al.*, 2005).

The possible detrimental effects of IUI and the absence of effects of IVF is the most intriguing and unexpected finding of our review. Given the lower peripheral steroids and the lower number of developed follicles that are generally achieved in IUI compared to IVF cycles, the opposite findings would have been more logical. D'Hooghe *et al.* (2006) and van der Houwen *et al.* (2014b), who highlighted this increased risk, speculated that “*the monthly exposure to ovulation and retrograde menstruation is the basis for the increased risk of endometriosis recurrence, which might be facilitated by ovarian hyper-stimulation*”. If this is so, at least a similar effect for IVF should be expected, but this was not the case. To note, the available studies investigating the possible gradient effect between ovarian responsiveness (including oestrogens peak levels) and recurrence failed to identify any relation (D'Hooghe *et al.*, 2006; Benaglia *et al.*, 2009; Benaglia *et al.*, 2010; Seyhan *et al.*, 2018). An alternative explanation that refers to the origin of endometriomas can be suggested. Indeed, according to the ovulation theory, these cysts would develop from the corpus luteum invasion of endometriotic cells (Vercellini *et al.*, 2010), an event that can be possible only when the ovulation stigma occurs in correspondence of the implant. In fact, this correspondence may be more likely in IUI cycles because endometriotic implants cause a local inflammation and many molecules involved in endometriosis-related inflammation are also involved in the process of ovulation dehiscence (Gérard *et al.*, 2004; Somigliana *et al.*, 2012). Ovulation may be somehow guided to occur in the proximity of superficial implants. Conversely, in IVF, follicles are arbitrarily punctured and aspirated before spontaneous ovulation occurs. This interpretation is intriguing but speculative. One should at least disentangle whether the reported IUI-related recurrence is specific, i.e. mostly consisting in endometriomas rather than other lesions. Unfortunately, the available evidence did not differentiate between ovarian and non-ovarian lesions (D'Hooghe *et al.*, 2006; Coccia *et al.* 2010; van der Houwen *et al.*, 2014b). Finally, a third possible



interpretation of the increased risk in IUI cycles may be related to the confounding effect of time. Indeed, women who undergo IUI simply allow more time to pass than if they had moved straight to IVF. This passage of time (fertility interventions or not) would naturally result in a higher rate of recurrences.

From a clinical perspective, the alarmism on the possible detrimental effects of IUI is of debatable relevance. In fact, the clinical utility of IUI in infertile women with endometriosis is questionable for several reasons. Firstly, albeit debated, the recent NICE guideline does not consider IUI for the group of women with unexplained infertility (that includes also women with endometriosis stage I-II) (Bahadur *et al.* 2015; NICE, 2013). Secondly, specific evidence in favour of IUI for women with endometriosis is weak (Somigliana *et al.*, 2017). Last but not least, there is no rationale for IUI in women with endometriosis. The detrimental effects of the disease on fertility are mainly due to intraperitoneal effects, i.e. anatomic distortion due to adhesions and the development of an unfavourable peritoneal milieu that may affect gametes and early embryos (Somigliana *et al.*, 2017). In this context, IUI cannot be expected to provide any benefit.

The general reassuring scenario emerging from our review has important clinical implications but also warrants some pathogenic comments. Endometriosis is actually an oestrogen-dependent disease and the unremarkable effects of IVF is somehow surprising. There is strong evidence that oestrogens exposure may facilitate endometriosis growth. Accordingly, lowering serum oestrogens is still the crucial target of modern medical therapy of endometriosis (Vercellini *et al.*, 2016; Taylor *et al.*, 2017). This conceptual inconsistency is difficult to explain. On the other hand, the syllogism linking oestrogens dependence of endometriosis to a detrimental effect of IVF due to the marked raise in oestrogens is presumably too simplistic. In our opinion, the most plausible explanation is related to the duration of the exposure. Peripheral oestrogens do raise significantly during ovarian stimulation, reaching levels that are up to 10 folds higher (2-4,000 pg/ml) than those occurring in natural cycles. However, these levels are reached only for a few days

and, immediately after the oocytes retrieval, progesterone level typically raise considerably (Macklon *et al.*, 2006). It may be speculated that this may effectively and promptly counteract the previous short term detrimental effects of hyper-oestrogenism. To note, high-dose progesterone is also commonly prescribed after ovarian stimulation to support the luteal phase (van der Linden *et al.*, 2011).

In this study, we aimed exclusively at disentangling the possible effects of ovarian stimulation on endometriosis. We were not interested in the pregnancy-related effects on the disease and, therefore, we excluded studies reporting complications of endometriosis occurring during pregnancy in women conceiving with ARTs. This choice may be viewed as a limitation of our review, but was based on the difficulty (impossibility) to disentangle the effects of ovarian stimulation and those of pregnancy. On the other hand, it cannot be excluded that the mild (if any) effects of ovarian stimulation could be boosted by the additional effects of pregnancy. In other words, the ovarian stimulation might be a predisposing condition favouring the detrimental effects of pregnancy. Indeed, even if pregnancy is historically considered beneficial to endometriosis (McArthur and Ulfelder, 1965), in rare and still unexplained cases, the disease may unexpectedly and rapidly progresses leading to severe and potentially fatal complications such as spontaneous haemoperitoneum (Brosens *et al.*, 2016; Leone Roberti Maggiore *et al.*, 2016; Leone Roberti Maggiore *et al.*, 2017). In a systematic review of the literature on this frightful complication, Brosens *et al.* (2016) showed that 24 out of the 64 described cases (38%) occurred in women with endometriosis undergoing ovarian stimulation. It remains to be clarified whether this observation reflects a real detrimental effect of IVF or, conversely, whether it is just consequent to the fact that worse endometriosis cases require more frequently IVF (Vercellini *et al.*, 2018).

In this regard, it has also to be pointed out that, independently of disease progression or pain symptom recurrence after ovarian stimulation, performance of IVF in infertile women with severe, deep endometriosis poses an ethical issue, because most of these women would not get pregnant

without this technique. Therefore, as IVF is an active medical intervention, discussion of its potential harms should not be limited to the impact on endometriosis, but should address also possible obstetrical sequelae, including not only spontaneous haemoperitoneum, but also the increased risk of placenta praevia and the reportedly high complication rate associated with a caesarean delivery in women with severely distorted abdomino-pelvic anatomy (Vercellini *et al.*, 2018). This appears important because, when thoroughly informed, some women may even decide not to undergo IVF (Somigliana *et al.*, 2015b).

## **CONCLUSIONS**

Even if there is growing agreement on the central role of ARTs in the management of endometriosis-related infertility, several issues remain disputed. Of particular relevance is the relative role of surgery and ART. In general, definitive evidence is not available and a shared decision-making approach with the woman is mandatory. The counselling should be comprehensive and exhaustive and the reassuring evidence emerging from this review should be part of this discussion. Nonetheless, the debate on the detrimental effects of ovarian stimulation on endometriosis progression is yet open. In particular, the potential effects on deep invasive endometriosis and the possible synergic effects of pregnancy are two arguments that need to be urgently explored.

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**Figure legend**

**Figure 1:** Flow chart of the study. Sixteen studies were ultimately included, of whom four were case reports.



Table 1. Characteristics of the studies reporting on endometriosis recurrence in women performing ART

Study	Design	Type of ART	M	N	Inclusion	Recurrence	Follow-up duration <sup>a</sup>	Pregnancy included	Comparisons	Quality of evidence <sup>b</sup>
Gevaerts et al., 1998	Retros	IVF	143	311	Not defined	Bowel endometriosis	5.2 months	Yes	None	na
D'Hoyghs et al., 2006	Retros	IVF or IUI	67	122 +78	Previous surgery (stage III-IV)	Endometriosis at surgery or endometriomas at US	10 (0-46) months	Yes	Comparison among women receiving IVF (n=59), IUI (n=17) or IUI+IVF (n=11)	6
Benaglia et al., 2009	Prosp.	IVF	48	48	US diagnosis of endometriomas	Increase in endometriosis size and number after 3-6 months	5 (3-6) months	No	Intra-patient comparison in women failing to become pregnant (before and 3-6 months after IVF)	na
Cocchia et al., 2010	Retros	IVF or IUI	50	n.r.	Previous surgery	Endometriomas or nodules detected at US	69 ± 42 months	Yes	Comparison with a cohort of operated women who did not undergo ART (n=87)	7
Benaglia et al., 2010	Retros	IVF	189	481	Previous surgery	Need to undergo surgery or initiate medical treatment for endometriosis	34 [21-52] months	Yes	Comparison according to the number of cycles and ovarian responsiveness (poor responders vs. normo-responders)	8
Benaglia et al., 2011	Prosp.	IVF	64	64	Previous surgery or US diagnosis	Need to undergo surgery or initiate medical treatment for endometriosis	4 (3-6) months	No	Intra-patient comparison on the modification of symptoms and lesions	na
van der Houwen et al., 2014a	Retros	IVF	113	113	Previous surgery (stage III-IV)	Endometriomas at surgery within 1 year	12 months	Yes	Comparison between women treated with the long protocol and those receiving a post-coal with GnRH antagonists	na
van der Houwen et al., 2014b	Retros	IUI	65	245	Previous surgery (stage III-IV)	Recurrence or increase in patients' complaint within 1 year	12 months	Yes	Comparison between natural and stimulated IUI	8
van der Houwen et al., 2014c	Prosp.	IVF or IUI	75	50 + 28	Previous surgery (stage III-IV)	Not defined. The study monitored pain modifications	1 month	Yes	Comparison between women treated with IUI (n=24), IVF (n=25) or IVF with an ultralong protocol (n=25)	8
Crochet et al., 2016	Retros	IVF	21	50	Previous surgery	Not defined. Second surgery was an inclusion criterion. The study evaluated changes in ASRM score	25 months	Yes	Comparison with a cohort of women also operated twice but who did not undergo IVF (n=36)	6
Sentilli et al., 2016	Prosp.	IVF	102	102	Previous surgery or imaging-based diagnosis	Need for surgical or medical therapy. The study mainly monitored pain modifications	3 weeks	Yes	Comparison with a control group of women without endometriosis (n=104)	na
Seylan et al., 2018	Prosp.	IVF	25	25	US diagnosis of endometriomas	Not defined. The study monitored endometrioma size during the cycle	2 weeks	Yes	Intra-patient comparison of endometrioma dimensions between the beginning and the end of the stimulation	na

US, Transvaginal Ultrasound; ASRM, American Society of Reproductive Medicine. <sup>a</sup> Data is reported as mean ± SD or Median [interquartile range] or Median (range) <sup>b</sup> based on the Newcastle-Ottawa scale (Wells et al., 2000). Evidence was considered low, moderate and high quality for scores of 0-4, 5-6 and 7-9, respectively.

Table 2. Rate of recurrences following ovarian stimulation (estrogenical evaluation).

Study	Recurrences per patient		Type or recurrences
	N. / tot	% (95%CI)	
Govaerts et al., 1998	2 / 143	1.4% (0.4-4.9%)	Two cases of bowel endometriosis. Intestinal resection was required in one of them.
D'Hooghe et al., 2006	11 / 67	16.4% (8.9-26.4%)	Compared to initial surgery, ASRM score was increased in 3, unchanged in 5 and decreased in 3 cases. In 2 cases, new deep endometriotic nodules were found.
Benaglia et al., 2009	1 / 48	2.1% (0.1-11.1%)	One woman was diagnosed with one new additional endometrioma.
Cocchia et al., 2010	18 / 90	20.0% (12.7-29.0%)	Thirteen women had deep invasive endometriosis and 5 had ovarian endometriomas.
Benaglia et al., 2010	41 / 189	21.7% (16.2-27.9%)	Twenty-one underwent surgery (stage II) in 6 cases and stage IVF in 15 cases) while 20 received medical therapy.
Benaglia et al., 2011	0 / 64	0.0% (0.0-4.5%)	n.a.
van der Houwen et al., 2014a	3 / 113	2.7% (0.6-6.3%)	Two women had segmental colon resection for partial stenosis (one had also ureter reimplantation) and one had salpingectomy, oophorectomy and cystectomy.
van der Houwen et al., 2014b	34 / 65	56.9% (36.6-68.9%)	Thirteen women started hormonal therapy with oral contraceptives or GnRH agonists and 9 had a surgical diagnosis. The remaining 2 did not receive any treatment.
van der Houwen et al., 2014c	1 / 75	1.3% (0.1-6.1%)	Severe pain after oocyte retrieval requiring hospitalization.
SawallH et al., 2016	0 / 102	0.0% (0.0-2.9%)	n.a.

ASRM: American Society of Reproductive Medicine

n.a.: not applicable

Table 3. Summary of the evidence

Main conclusions	Level of the evidence <sup>a</sup>	Main publications
IVF does not worsen endometriosis-related pain symptoms.	Moderate	Jen and Luthi, 2007; Benaglia <i>et al.</i> , 2011; Santulli <i>et al.</i> , 2016; van der Houwen <i>et al.</i> , 2014c
IVF does not increase the risk of recurrence	Moderate	Benaglia <i>et al.</i> , 2010; Cecchi <i>et al.</i> , 2010; van der Houwen <i>et al.</i> , 2014a
The impact of IVF on ovarian endometriosis is mild, if any.	Low	Benaglia <i>et al.</i> , 2009; Benaglia <i>et al.</i> , 2011; Seyhan <i>et al.</i> , 2017
IVF increases the risk of recurrence	Low	Trifirovic <i>et al.</i> , 2006; Cecchi <i>et al.</i> , 2010; van der Houwen <i>et al.</i> , 2014b
Deep invasive endometriosis may progress with ovarian stimulation.	Very low	Reiner <i>et al.</i> , 1995; Anaf <i>et al.</i> , 2010; Halverson <i>et al.</i> , 2012

The conclusions are presented in decreasing order of reliability.

Level of evidence was judged in a semi-quantitative manner based on the literature and consensus.

IVF: in vitro fertilization; IUI: intrauterine insemination

<sup>a</sup> Level of evidence was based on the GRADE guidelines (Halpern *et al.*, 2011)

