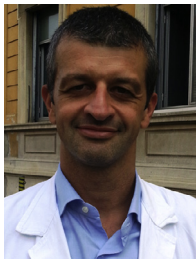




REVIEW



Ovarian stimulation and endometriosis progression or recurrence: a systematic review

**BIOGRAPHY**

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KEY MESSAGE

In women with endometriosis, IVF does not generally increase the risk of disease recurrence. There is evidence, however, that intrauterine insemination may increase this risk and that deep peritoneal lesions may progress in some cases, although further studies are needed to confirm the latter findings.

ABSTRACT

Available evidence on the impact of ovarian stimulation on the progression of endometriosis or its recurrence was systematically reviewed. Data from ovarian stimulation alone, or associated with intrauterine insemination (IUI) or IVF, were included. Sixteen studies were selected. Initial case reports ($n = 11$) documented some severe clinical complications. However, subsequent observational studies were more reassuring. Overall, five conclusions can be drawn: (i) IVF does not worsen endometriosis-related pain symptoms (moderate quality evidence); (ii) IVF does not increase the risk of endometriosis recurrence (moderate quality evidence); (iii) the impact of IVF on ovarian endometriomas, if present at all, is mild (low quality evidence); (iv) IUI may increase the risk of endometriosis recurrence (low quality evidence); (v) 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 assisted reproductive technology treatment to prevent endometriosis progression or recurrence. However, further evidence is required before being able to reach definitive conclusions. In particular, the potential effects on deep invasive endometriosis and the possible synergistic effect of stimulation and pregnancy are two areas that need to be explored further.

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KEYWORDS

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IVF
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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 at about 1–2% (*Eisenberg et al., 2018; Morassutto et al., 2016*) but the prevalence increases to 6–9% in infertile women seeking treatment with assisted reproductive technology (ART) (*CDC, 2014; Smith et al., 2015*). Reasons for the association between endometriosis and infertility are not clear, but adhesions and an inflammatory pelvic milieu may play a crucial role (*Somigliana et al., 2017*).

In recent years, ART treatment has become the first-line therapeutic approach to endometriosis-associated infertility (*Dunselman et al., 2014; Practice Committee of the American Society for Reproductive Medicine, 2012*). However, ART treatment is not without problems in this particular population (*Somigliana et al., 2015a, Somigliana and Garcia-Velasco, 2015b*). Of particular relevance is the possibility of disease progression or recurrence during or following treatment. Two main observations support this concern. Firstly, peripheral oestrogens that play a fundamental role in endometriosis progression (*Vercellini et al., 2014*) rise considerably during ovarian stimulation, reaching levels that are up to 10-fold higher than those observed in a physiologically natural cycle (*Macklon et al., 2006*). Secondly, as there is growing evidence that endometriomas may originate from ovulatory events (*Vercellini et al., 2010; Viganò et al., 2013*), the multiple ovulations that typically occur during ovarian stimulation could increase the risk of formation of endometriomas.

Overall, the possible impact of ovarian stimulation on endometriosis progression or recurrence is clinically relevant for both patient and physician but has received scant consideration in the literature, mainly because collecting evidence is methodologically complex. However, new evidence has emerged over the last decade and a systematic review of the literature on this issue is therefore timely and important.

MATERIALS AND 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 for surgery or initiation of medical therapy).

A literature overview was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*Moher et al., 2009*). This study was exempt from Institutional Review Board approval because previously published, anonymized data were used. Data for ovarian stimulation alone, for intrauterine insemination (IUI) or for IVF were all included. Conversely, studies reporting exclusively on pregnant cases were excluded because it is not possible to discriminate between the detrimental effects of ovarian stimulation and pregnancy. The primary search was conducted with MEDLINE, for 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 complications related to the oocyte 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 previous 10 years were consulted and their reference lists searched for potential additional studies. No attempt was made to contact authors for incomplete information or to identify unpublished studies or abstracts

submitted to national or international conferences. All of this research was conducted independently by two of the authors (ES and AB) and discordances were solved by discussion, including the other authors if necessary. The main measure used was the rate of recurrence. A binomial distribution model was used to calculate the 95% confidence interval (CI) of proportions.

The 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 classifies 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 categories: high, moderate, low and very low quality (*Balshem et al., 2011*).

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

Although the initial intention was to combine results into a meta-analysis, this was ultimately not possible 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, 16 publications were included.

Case reports

The first evidence for possible detrimental effects of ovarian stimulation on endometriosis progression was published in the form of a case report. 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 oocyte retrieval. She recovered after distal resection of the ureter and bladder re-implantation. The histological examination revealed extensive

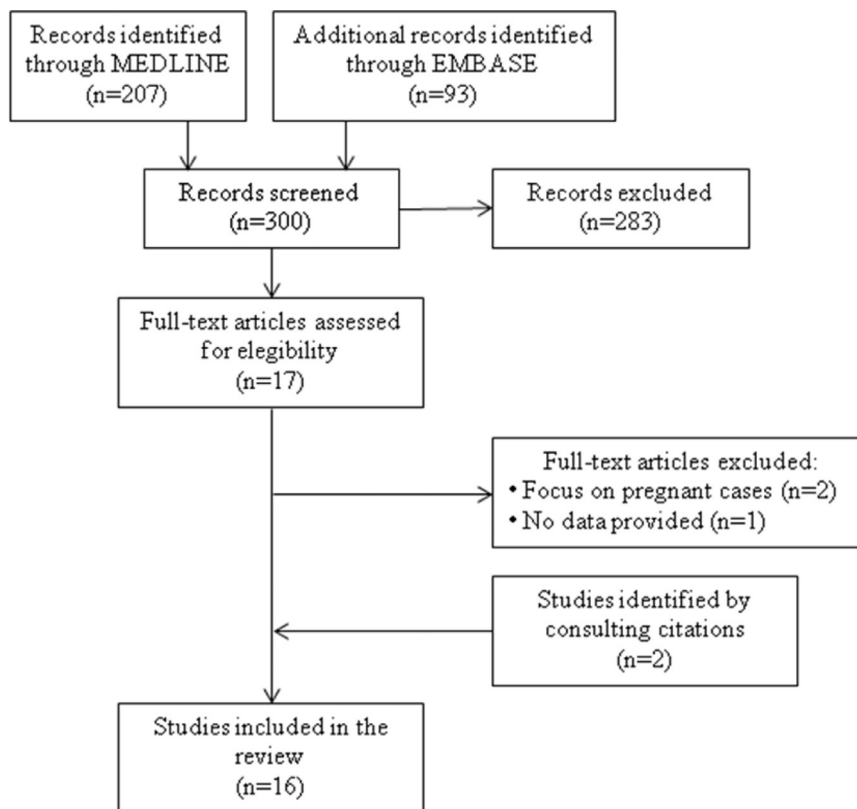


FIGURE 1 Flow chart of the study. Sixteen studies were ultimately included, of which four were case reports.

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.* (2000) described four women who required segmental bowel resection after IVF, as a result of sigmoid endometriosis causing severe stenosis of the lumen. 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 2230 and 2635 pg/ml). The time between stimulation and occurrence of symptoms was not clearly reported, but in at least one case symptoms occurred during stimulation. It should be noted that 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 of the degree of responsiveness to ovarian stimulation and 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 of ovarian hyperstimulation syndrome (OHSS) 3 days after the retrieval of 30 oocytes. She had considerable free fluid in the pouch of Douglas and severe bilateral hydrothorax that necessitated bilateral thoracenteses. She then recovered but, after achieving pregnancy with frozen embryos, she was diagnosed with congenital diaphragmatic agenesis and underwent surgical repair that revealed the local presence of endometriosis. On this basis, the authors reinterpreted the events that occurred at the time of IVF and opted for a final diagnosis of thoracic endometriosis syndrome rather than OHSS (Halvorson *et al.*, 2012).

No case reports were identified on endometriosis progression after ovarian stimulation (with or without IUI) without IVF.

Case series and cohort studies

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

TABLE 1 CHARACTERISTICS OF THE STUDIES REPORTING ON ENDOMETRIOSIS RECURRENCE IN WOMEN RECEIVING ART TREATMENT

Study	Design	Type of ART	No. of women	No. of cycles	Inclusion	Recurrence	Follow-up duration ^a	Pregnancy included	Comparisons	Quality of evidence ^b
<i>Govaerts et al., 1998</i>	Retros.	IVF	143	311	Not defined	Bowell endometriosis	≤2 months	Yes	None	NA
<i>D'Hooghe et al., 2006</i>	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 = 39), IUI (n = 17) or IUI + IVF (n = 11)	6
<i>Benaglia et al., 2009</i>	Prosp.	IVF	48	48	US diagnosis of endometriomas	Increase in endometrioma size and number after 3–6 months	5 (3–6) months	No	Inpatient comparison in women failing to become pregnant (before and 3–6 months after IVF)	
<i>Coccia et al., 2010</i>	Retros.	IVF or IUI	90	NR	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
<i>Benaglia et al., 2010</i>	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
<i>Benaglia et al., 2011</i>	Prosp.	IVF	64	64	Previous surgery or US diagnosis	Need to undergo surgery or initiate medical treatment for endometriosis	4 (3–6) months	No	Inpatient comparison on the modification of symptoms and lesions	NA
<i>van der Houwen et al., 2014a</i>	Retros.	IVF	113	113	Previous surgery (stage III–IV)	Endometriosis at surgery within 1 year	12 months	Yes	Comparison between women treated with the long protocol and those receiving a protocol with GnRH antagonists	na
<i>van der Houwen et al., 2014b</i>	Retros.	IUI	65	245	Previous surgery (stage III–IV)	Recurrence or increase in patient's complaint within 1 year	12 months	Yes	Comparison between natural and stimulated IUI	8
<i>van der Houwen et al., 2014c</i>	Prosp.	IVF or IUI	75	50 + 25	Previous surgery (stage III–IV)	Not defined; the study monitored pain modifications	1 month		Comparison between women treated with IUI (n = 25), IVF (n = 25) or IVF with an ultra-long protocol (n = 25)	8
<i>Crochet et al., 2016</i>	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
<i>Santulli et al., 2016</i>	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
<i>Seyhan et al., 2018</i>	Prosp.	IVF	25	25	US diagnosis of endometriomas	Not defined; the study monitored endometrioma size during the cycle	2 weeks	Yes	Inpatient comparison of endometrioma dimension between the beginning and the end of the stimulation	na

ART = assisted reproductive technology; ASRM = American Society of Reproductive Medicine; NA = not available; NR = not relevant; US = transvaginal ultrasound.

^a Data are reported as mean ± SD or median [interquartile range] or median (range).

^b 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 RECURRENCE FOLLOWING OVARIAN STIMULATION (CATEGORICAL EVALUATION)

Study	Rate of recurrence		Description of recurrence
	No. of recurrences/total no. patients	% (95% CI)	
<i>Govaerts et al., 1998</i>	2/143	1.4 (0.4–4.9)	Two cases of bowel endometriosis. Intestinal resection was required in one of them.
<i>D'Hooghe et al., 2006</i>	11/67	16.4 (8.9–26.4)	Compared to initial surgery, ASRM score was increased in three, unchanged in five and decreased in three cases. In two cases, new deep endometriotic nodules were found.
<i>Benaglia et al., 2009</i>	1/48	2.1 (0.1–11.1)	One woman was diagnosed with one new additional endometrioma.
<i>Coccia et al., 2010</i>	18/90	20.0 (12.7–29.0)	Thirteen women had deep invasive endometriosis and five had ovarian endometriomas.
<i>Benaglia et al., 2010</i>	41/189	21.7 (16.2–27.9)	Twenty-one underwent surgery (stage III in six cases and stage IVF in 15 cases) and 20 received medical therapy.
<i>Benaglia et al., 2011</i>	0/64	0.0 (0.0–4.5)	NA
<i>van der Houwen et al., 2014a</i>	3/113	2.7 (0.6–6.8)	Two women had segmental colon resection for partial stenosis (one also has ureter reimplantation) and one had salpingectomy, adhesiolysis and cystectomy.
<i>van der Houwen et al., 2014b</i>	24/65	36.9 (26.0–48.9)	Thirteen women started hormonal therapy with oral contraceptives or GnRH agonists and nine had a surgical diagnosis. The remaining two did not receive any treatment.
<i>van der Houwen et al., 2014c</i>	1/75	1.3 (0.1–6.1)	Severe pain after oocyte retrieval requiring hospitalization.
<i>Santulli et al., 2016</i>	0/102	0.0 (0.0–2.9)	NA

ASRM = American Society of Reproductive Medicine; GnRH = gonadotrophin-releasing hormone; NA = not applicable.

Data on IVF prevailed but some evidence was also available for IUI (*Coccia et al., 2010; Crochet et al., 2016; D'Hooghe et al., 2006; van der Houwen et al., 2014c*). 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 10 studies (*Benaglia et al., 2009, 2010, 2011; Coccia et al., 2010; D'Hooghe et al., 2006; Govaerts et al., 1998; van der Houwen et al., 2014a, 2014b, 2014c; Santulli et al., 2016*). Results are summarized in **TABLE 2**. The rates varied from 0% to 37%. Combining these studies to reach an estimate on the risk of recurrence was not possible given the wide differences in duration of follow-up, definition of recurrence and populations studied (**TABLE 1**). It is noteworthy that when rates of recurrence were plotted with the mean/median duration of follow-up of the included studies, a highly significant correlation was found (Spearman's rank correlation coefficient, rho of 0.86, $P = 0.001$).

These 10 studies did not systematically report on the specific form of the disease detected at the time of recurrence (**TABLE 2**). This information was included in only four of them, corresponding to 24 recurrences (*Benaglia et al., 2009; Coccia*

et al., 2010; Govaerts et al., 1998; van der Houwen et al., 2014a). Deep invasive lesions were diagnosed in 17 of them (71%, 95% CI: 52–86). In the single included study comparing the type of recurrence between women with endometriosis exposed ($n = 90$) and non-exposed ($n = 87$) to IVF, deep invasive lesions were documented in 13 (14%) and 8 (9%) women, respectively (not statistically significant) (*Coccia et al., 2010*).

Finally, correlation between ovarian responsiveness and risk of recurrence was specifically reported in four studies (*Benaglia et al., 2009, 2010; D'Hooghe et al., 2006; Seyhan et al., 2018*). *D'Hooghe et al. (2006)* and *Seyhan et al. (2018)* evaluated the impact of peak oestrogen concentration whereas *Benaglia et al. (2009, 2010)* focused 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 who had surgery 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 recurrence 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 with 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 treatment 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. On the other hand, *van der Houwen et al. (2014b)* provided evidence in support of the results from *D'Hooghe et al. (2006)*. Specifically, they presented data on women who had previously had surgery for endometriosis who subsequently underwent IUI and compared the rate of recurrence between those receiving IUI on a natural cycle and then ovarian stimulation ($n = 45$) to those receiving only straight 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 treatment (*Coccia et al., 2010; Crochet*

et al., 2016). *Coccia et al. (2010)* retrospectively identified 177 women who had surgery 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 treatment (both IVF and/or IUI). A total of 40 recurrences were diagnosed, 18 in the ART group (20%) and the remaining 22 in the non-ART group (25%) (not statistically significant). The IVF group did not face a higher risk: all users of IVF (i.e. combining women receiving IVF and those receiving both IVF and IUI, $n = 70$) had a recurrence rate of 19% (13/70) (*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 had surgery 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 failed to observe any significant difference in the change in the ASRM score (*Crochet et al., 2016*). Unfortunately, the study did not report whether women undergoing IVF were more or less likely to have surgery.

Two studies aimed to overcome the intrinsic difficulties of comparative studies by 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 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 emerge. 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% CI: 0.40–1.58) for normal responders compared with poor responders (*Benaglia et al., 2010*). In the second study, *van der*

Houwen et al. (2014a) postulated 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 initiation of ovarian stimulation should be expected (ultra-long 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 ultra-long 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 symptom modification

Endometriosis recurrence and pain symptom modification 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; Santulli et al., 2016; van der Houwen et al., 2014c*).

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 dysmenorrhoea, 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 majority ($n = 43$; 67%) subjectively judged their symptoms as unchanged (*Benaglia et al., 2011*).

Van der Houwen et al. (2014c) enrolled 75 women with a surgical diagnosis of endometriosis stage III–IV prior to initiating IUI ($n = 25$), classical IVF ($n = 25$) and IVF with an ultra-long protocol ($n = 25$). The rate of satisfaction did not differ among the three groups. For the whole cohort, the number (%) of women with improvement and deterioration of visual analogue scores according to the studied symptom were as follows: for dysmenorrhoea (affecting 31 women), improvement and worsening was observed in 7 (23%) and 8 (26%) women, respectively. For dyspareunia (49 women), this occurred in 7 (14%) and 5 (10%) women, respectively; for non-menstrual pain (69 women)

this occurred in 9 (13%) and 10 (15%) women, respectively; for dyschesia (68 women) this occurred in 8 (12%) and 9 (13%) women, respectively; and for dysuria (69 women) this occurred in 4 (6%) and 4 (6%) women, respectively. Moreover, no statistically significant differences emerged when comparing these modifications within the three study groups separately (*Van der Houwen et al., 2014c*).

Santulli et al. (2016) prospectively compared 102 women with endometriosis and 104 unaffected women (control group) during an IVF cycle (*Santulli et al., 2016*). Four time-points were scheduled: prior to initiation of oral contraceptive synchronization, during oral contraceptive synchronization, at the time of oocyte retrieval and 3 weeks later. At all time-points, the scores for dysmenorrhoea, dyspareunia, non-menstrual pain and gastrointestinal symptoms were higher in affected women. However, compared with 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 effects of IVF (*Santulli et al., 2016*).

Lesion growth

Superficial endometriosis cannot be monitored without performing a laparoscopy before and after the IVF cycle, a study design that is 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; Nisenblatt et al., 2016*) and monitoring these lesions during IVF is feasible. Three studies reported data on transvaginal ultrasound evaluation of ovarian endometriomas (*Benaglia et al., 2009, 2011; Seyhan et al., 2018*), one of which also provided data on deep invasive lesions (*Benaglia et al., 2011*).

Benaglia et al. (2009) 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). 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 (not statistically significant). 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).

Two years later, the same group performed a second study that focused on symptom modification before and 3–6 months after a failed IVF cycle (Benaglia *et al.*, 2011). As a secondary finding, the authors also reported data on the modification of endometriomas (35 women with 45 cysts) and deep invasive endometriosis (9 women with 10 lesions). The median (IQR) diameter of the endometriomas before and after the cycle was 20 (12–27) and 20 (17–27) mm, respectively (not statistically significant). The median (IQR) diameter of the deep lesions before and after the cycle was 10 (5–18) and 10 (5–18) mm, respectively (not statistically significant) (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.

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 were the issues studied in most detail, both being investigated with at least two independent prospective studies. However, the data are not fully consistent. Even if the observational studies on pain symptoms failed to identify detrimental effects (moderate quality evidence), it cannot be excluded that there may be a worsening of pain in some particular cases. The five women experiencing pain worsening during ovarian stimulation described by Jun and Lathi (2007) support this position.

Considering endometriomas, IVF does not appear to modify their dimension markedly but the data are not unequivocal. Indeed, two studies by the same study group did not report changes, while a third, independent, study observed a modest but statistically significant increase in size. It can be generally concluded that the impact of IVF on the dimensions of endometrioma is minimal, if present at all, but the quality of evidence is low and further evidence is needed.

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 are not unequivocal 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, the most worrying potential drawback of ovarian stimulation, is supported exclusively by case reports (very low quality evidence). Further data on this issue are needed.

DISCUSSION

Available evidence on the impact of ovarian stimulation and ART treatment on endometriosis progression or recurrence is incomplete. None of the evidence could be graded as high quality. It should be noted that 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 of search filters for randomized controlled trials. Moreover, the natural tendency of endometriosis to recur (Guo, 2009) complicates 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 ART treatment. Nonetheless, some ideas have emerged that deserve consideration in clinical practice. In particular, the reassuring data on the limited impact of IVF on endometriosis recurrence or pain symptom progression are supported by moderate quality evidence. Moreover, the impact (if any)

TABLE 3 SUMMARY OF THE EVIDENCE

Main conclusions	Level of the evidence ^a	Main publications
IVF does not worsen endometriosis-related pain symptoms.	Moderate	Jun and Lathi, 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; Coccia <i>et al.</i> , 2010; van der Houwen <i>et al.</i> , 2014a
The impact of IVF on ovarian endometriomas is mild, if any.	Low	Benaglia <i>et al.</i> , 2009, 2011; Seyhan <i>et al.</i> , 2017
IUI increases the risk of recurrences.	Low	D'Hooghe <i>et al.</i> , 2006; Coccia <i>et al.</i> , 2010; van der Houwen <i>et al.</i> , 2014b
Deep invasive endometriosis may progress with ovarian stimulation.	Very low	Renier <i>et al.</i> , 1995; Anaf <i>et al.</i> , 2010; Halvorson <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 common sense.

IUI = intrauterine insemination.

^a Level of evidence was based on the GRADE guidelines (Balshem *et al.*, 2011).

on the dimension of endometriomas may also be clinically unremarkable. This information can be used to reassure women with endometriosis entering an IVF programme who may be concerned by the theoretical risks of ovarian stimulation.

On the other hand, the insufficient data regarding deep invasive lesions are the most important scientific gap that needs to be covered in the future. These lesions are indeed particularly sensitive to oestrogens compared with other forms of the disease (Vercellini *et al.*, 2016). Evidence from case reports and the high proportion 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. Notably, the prospective study from Benaglia *et al.* (2011) failed to document any significant growth of these lesions, although the sample size was small (only nine women). 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 this basis, the need for prophylactic surgery in women with deep invasive endometriosis to prevent progression seems to be unsubstantiated and is probably unwise. Surgery for deep invasive endometriosis is technically demanding and potentially harmful (Kondo *et al.*, 2011; Oliveira *et al.*, 2016) and should only be justified based on robust clinical evidence. In this regard, it is also worth noting that there is no evidence to support benefit from prophylactic surgery in terms of pregnancy rate after ART treatment (Darai *et al.*, 2017; Iversen *et al.*, 2017; Somigliana and Garcia-Velasco, 2015b). Currently, surgery to increase the chance of pregnancy should only be considered 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 this review. Given the lower peripheral steroids and the lower number of developed follicles that are generally achieved in IUI compared with IVF cycles, the opposite findings might have been expected. 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 hyperstimulation'. If this is so, at least a similar effect for IVF should be expected, but this was not the case. It should be noted that the included studies investigating a possible gradient effect between ovarian responsiveness (including oestrogen peak concentrations) and recurrence failed to identify any relationship (Benaglia *et al.*, 2009, 2010; D'Hooghe *et al.*, 2006; Seyhan *et al.*, 2018). An alternative explanation that references the origin of endometriomas can be proposed. Indeed, according to the ovulation theory, these cysts would develop from the invasion of the corpus luteum with endometriotic cells (Vercellini *et al.*, 2010), an event that is only possible when the ovulation stigma occurs in correspondence with 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 somehow be 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. It should at least be clarified whether the reported IUI-related recurrence is specific, i.e. mostly consisting of endometriomas rather than in other lesions. Unfortunately, the available evidence did not differentiate between ovarian and non-ovarian lesions (Coccia *et al.*, 2010; D'Hooghe *et al.*, 2006; 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 surrounding 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 (including 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 due mainly 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.

Endometriosis is an oestrogen-dependent disease and the unremarkable effect of IVF is, therefore, somewhat surprising. There is strong evidence that oestrogen exposure may facilitate endometriosis growth. Accordingly, lowering serum oestrogen is still the target of modern medical therapy for endometriosis (Taylor *et al.*, 2017; Vercellini *et al.*, 2016). This conceptual inconsistency is difficult to explain, but on the other hand, the syllogism linking the oestrogen dependence of endometriosis to a detrimental effect of IVF due to the marked rise in oestrogens is presumably too simplistic. In our opinion, the most plausible explanation is related to the duration of exposure. Peripheral oestrogens do rise considerably during ovarian stimulation, reaching concentrations that are up to 10-fold higher (2000–4000 pg/ml) than those occurring in natural cycles. However, these concentrations are reached for only a few days and, immediately after oocyte retrieval, progesterone concentrations typically rise considerably (Macklon *et al.*, 2006). It may be that this could effectively and promptly counteract the previous short-term detrimental effect of hyper-oestrogenism, particularly as high-dose progesterone is also commonly prescribed after ovarian stimulation to support the luteal phase (van der Linden *et al.*, 2011).

This study aimed to exclusively disentangle the possible effects of ovarian stimulation on endometriosis. The pregnancy-related effects on the disease were not of interest and so studies reporting complications of endometriosis occurring during pregnancy in women conceiving following ART treatment were

excluded. This choice may be viewed as a limitation of this review, but it was based on the difficulty (impossibility) of distinguishing the effects of ovarian stimulation and those of pregnancy. On the other hand, it may be the case that the mild (if any) effects of ovarian stimulation could be boosted by the additional effects of pregnancy. In other words, ovarian stimulation might provide conditions in which the detrimental effects of pregnancy are enhanced. 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 progress, leading to severe and potentially fatal complications in pregnancy such as spontaneous hemoperitoneum (Brosens et al., 2016; Leone Roberti Maggiore et al., 2016, 2017). In a systematic review of the literature on this serious 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 women with worse endometriosis require IVF treatment more frequently (Vercellini et al., 2018).

In this regard, it should also 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 conundrum, 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 also address possible obstetrical sequelae, including not only spontaneous hemoperitoneum, 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 is important because, when thoroughly informed, some women may decide not to undergo IVF (Somigliana and Garcia-Velasco, 2015b).

Even if there is growing agreement on the central role of ART 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 patient is mandatory. The counselling should be comprehensive and exhaustive and the reassuring evidence emerging from this review should be part of the discussion. Nonetheless, the debate on the detrimental effects of ovarian stimulation on endometriosis progression is still open. In particular, the potential effects on deep invasive endometriosis and the possible synergistic effects of pregnancy are two arguments that need to be explored urgently.

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