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The impact of IVF on deep invasive endometriosis

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ABSTRACT

Objective: Ovarian hyper-stimulation during IVF is associated with a significant raise in serum estrogens and one may expect detrimental effects on estrogen-dependent diseases such as endometriosis. However, available evidence from large case series of affected women performing IVF is generally reassuring with the possible exception of women carrying deep invasive lesions. On this basis we deemed important investigating more in depth whether women with deep invasive endometriosis could be a subgroup at higher risk of recurrence or disease progression during IVF.

Study design: Women with endometriosis who underwent IVF and who had a second evaluation after 3–6 months from a failed cycle were retrospectively reviewed. The main inclusion criteria were the presence of deep invasive endometriosis and/or a history of surgery for this form of the disease. The primary aim of the study was to determine the frequency of endometriosis-related complications in the interval between the two evaluations. Secondary aims were pain symptoms and lesion size modifications.

Results: Eighty-four women were ultimately selected: baseline ultrasound documented deep invasive lesions in 60 of them. One case of possible endometriosis-related complication was recorded, corresponding to a rate of 1.2% (95% CI: 0.05%–5.5%) for the whole cohort and 1.7% (95% CI: 0.08–7.6%) for the subgroup of women with ultrasound detected lesions. This rate appears similar to the reported frequency of endometriosis progression in women not receiving IVF. No significant modifications in pain symptoms or lesions size occurred.

Conclusions: Women with deep invasive endometriosis who underwent IVF do not seem to be exposed to a substantially increased risk of recurrence/disease progression. Larger evidence from independent groups is however required for a definitive conclusion.

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Introduction

In vitro fertilization (IVF) is a possible option for the treatment of infertile women with endometriosis [1,2]. However, IVF not only exposes women to the well-known general risks of the procedure but, also, to some specific endometriosis-related risks [3]. Of relevance here is the hazard of disease-progression during the procedure. Indeed, endometriosis is an estrogen-dependent disease and peripheral levels of estrogens increase up to 10-folds during ovarian hyper-stimulation. Given this premise, some harmful effects on the natural history of the disease could be expected. However, the available evidence does not generally

support this concern [4]. Several independent large case series failed to highlight major detrimental effects [5–10]. On the other hand, these reassuring data contrast with some case reports of severe complications [11–15]. The main characteristics of these cases are summarized in Table 1. Noteworthy, deep invasive peritoneal lesions (ie nodules infiltrating the peritoneum by >5 mm) [16] were highly common in these published cases, being present in at least 9 out of 13 affected women.

On these bases, we hypothesized that women with deep invasive endometriosis may be a subgroup of women who are more vulnerable to the potential detrimental effects of ovarian hyper-stimulation. To the best of our knowledge, only one study specifically reported evidence on deep lesions and failed to show detrimental effects. However, the evaluation of the lesions was a secondary finding, the number of included cases was extremely limited ($n = 9$) and the study did not focus on clinical complications [8]. Given the clinical relevance of the described cases, we deemed important exploring more in-depth this issue. To this aim, we

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Table 1
Case reports on the progression of endometriosis during IVF.

Authors, year (N. of cases)	Time from IVF to symptoms	Description	ASRM stage	DIE
Renier et al., 1995 (n = 1)	26 days	Left hydronephrosis and complete ureteral stenosis	n.r.	Yes
Govaerts et al., 1998 (n = 2)	2 months	Catamenial rectorrhagia		Yes
	2 months	Catamenial rectorrhagia		Yes
Anaf et al., 2000 (n = 4)	3 cycles	Rectorrhagia, severe digestive symptoms, subocclusion	IV	Yes
	3 cycles	Rectorrhagia, severe digestive symptoms, subocclusion	IV	Yes
	1 cycle	Rectorrhagia, severe digestive symptoms, subocclusion	IV	Yes
	7 cycles	Rectorrhagia, severe digestive symptoms, subocclusion	IV	Yes
Jun and Lathi, 2007 (n = 5)	During stimulation	Inreasing pelvic pain	II	nr
	During stimulation	Inreasing pelvic pain	IV	Yes
	During stimulation	Inreasing pelvic pain	II	nr
	During stimulation	Inreasing pelvic pain	nr	nr
	During stimulation	Inreasing pelvic pain	I	nr
Halvorson et al., 2012 (n = 1)	3 days	Hydropneumothorax	nr	Yes

DIE: Deep invasive endometriosis.

nr: not reported.

Studies including pregnant cases were excluded.

retrospectively selected women with deep peritoneal lesions and/or history of surgery for deep endometriosis who underwent IVF, and assessed the possible detrimental effects of ovarian hyperstimulation for IVF on this selected population.

Materials and methods

All women who underwent IVF cycles between January 2011 and March 2013 at the Infertility Unit of the Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milano were retrospectively reviewed. Inclusion criteria were: the presence of one or more deep endometriotic nodules, *i.e.* nodules infiltrating the peritoneum by >5 mm [16], and/or a history of surgical removal of deep invasive endometriosis; the availability of a follow-up evaluation 3–6 months after ovarian hyperstimulation; age ≤42 years; failed cycle (no pregnancy). Women could be enrolled only for one cycle. The first evaluation was systematically performed at the time of the basal clinical and sonographic evaluation that preceded the initiation of the IVF cycle. The second evaluation was performed before initiating the second cycle, except in drop-outs from IVF. In those cases, the evaluation was performed at our referral center for the general management of endometriosis. Data were thus extracted by reviewing clinical charts of the whole hospital, including the Infertility Unit, the Gynecological Unit, the outpatient center for endometriosis management and the obstetrical and gynecologic emergency department. The local institutional review board approved the study. A specific informed consent was not obtained because the study is retrospective. However, women referring to our units are routinely requested to provide an informed consent for their clinical data to be used for research purposes and those denying this consensus were excluded.

At our institution, women with endometriosis are systematically interviewed at every clinical evaluation about dysmenorrhea, inter-menstrual pelvic pain and dyspareunia using both a 11-point verbal rating scale (VRS) and the Biberoglu and Behrman (BB) scale [17]. The VRS grades pain from 0, indicating the absence of pain, to 10, indicating the worst possible pain. The BB scale defines dysmenorrhea according to loss of work efficiency and need for bed rest, non-menstrual pain according to various degrees of discomfort and use of analgesics, and deep dyspareunia according to limitation of sexual activity. The presence of other endometriosis-related symptoms, including dyschezia, proctorrhagia, unexplained vaginal bleeding and dysuria was also actively investigated. Women assuming hormonal therapy (oral contraceptives, progestins, GnRH analogues) before entering the IVF program were requested to discontinue the therapy during the IVF cycle but also to resume it immediately after the cycle in case of

failure. Moreover, women were interviewed about possible urgent events that occurred since the last visit, thus consenting to collect data on possible IVF-related complications and endometriosis recurrence/progression. The latter was defined as the need to undergo surgery or to start/change hormonal treatment. Finally, based on the policy of our hospital, a follow-up through phone contacts was systematically performed in women who did not attend the scheduled appointments and reasons for non-referral were recorded. Women reporting that they did not refer because of endometriosis or IVF-related complications could be included for the primary outcome.

Transvaginal ultrasound (US) was performed at every clinical evaluation. Seven sonographers with many years of experience in reproductive medicine performed all the evaluations. Deep nodules were defined as hypoechoic lesions with irregular outer margins and few blood vessels within and around the nodules at Doppler examination [18]. We included nodules that could be visualized at US in proximity with the uterine cervix, or behind the cervix (posterior compartment) or within the bladder wall (anterior compartment). No attempt was made to identify lesions located in other more distant sites. The dimensions of the nodules were measured in three orthogonal planes.

During the IVF cycle, women were monitored and managed according to a standardized clinical protocol as reported elsewhere [8]. Briefly, the regimen and the dose of gonadotropins were determined on an individual basis according to age, day 3 serum FSH, serum anti-mullerian hormone (AMH) and Antral Follicle Count (AFC). During the stimulation, women underwent serial transvaginal US and serum hormonal assessments when indicated. When leading follicles with a mean diameter >18 mm were visualized, human chorionic gonadotropin (hCG) was administered subcutaneously. Cycles could be cancelled because of low or hyper-response. Oocyte retrieval was performed transvaginally 36 h after the hCG injection. Embryo transfer was performed 48–72 h after the oocyte collection or, in properly selected subjects, at blastocyst stage.

The primary aim of the study was to determine the frequency of endometriosis-related complications in women with deep invasive lesions who underwent ovarian hyperstimulation for IVF. Recurrent or progressive cases were considered as complications. They were generally defined the need to undergo surgery or to start or change hormonal treatment. A stringent definition of complication was not stated *a priori* given the wide and complex spectrum of the possible clinical conditions reported in the literature (Table 1). Secondary endpoints included the modification of pain symptoms and nodule dimensions. The planned sample size (at least 70 women) was based on the assumption that the risk of progression

of endometriosis in women who do not undergo IVF is about 2%. This rate was arbitrarily postulated based on an expected 10% annual risk of recurrence [19] (that actually corresponds to 2.5–5% at 3–6 months) that was halved considering that a consistent proportion of women (about half in our population) was assuming hormonal therapies, a treatment that is known to markedly reduce the risk of recurrences [20]. The sample size was calculated setting type I and II errors at 0.05 and 0.20, and considering as clinically important a fourfold increase in the recurrence/progression rate compared with expected event rate (>8% instead of 2%). Statistical analyses were performed using the Statistical Package for Social Sciences 23.0 (SPSS Inc., Chicago, IL, USA). Probability values below 0.05 were considered statistically significant. The 95% confidence interval (95%CI) of proportions was calculated using a binomial distribution model. Modifications of symptoms and dimension of lesions over time (within-patient comparisons) were tested using the paired non-parametric Wilcoxon test or the McNemar test, as appropriate.

Results

Eighty-four women were selected. Baseline characteristics of these women are shown in Table 2. Fifty women who were diagnosed with deep invasive endometriosis at baseline evaluation did not undergo previous surgery for this disease form. The remaining 34 participants underwent previous surgical excision of deep invasive lesions, and in ten of them surgery was reported to be incomplete. Lesions could actually be documented in all these latter cases, whereas no lesions could be detected in the 24 women who received complete surgery. Overall, 60 women (71%) entered IVF carrying US detectable deep invasive lesions, and another 24 (29%) had a history of surgery for deep nodules, but a negative baseline US for these lesions before starting ovarian hyperstimulation. Endometriotic nodules were identified in the posterior and anterior compartments in 58 and 2 women, respectively. IVF outcome for the whole cohort is shown in Table 3. The distribution of the type of protocols of hyperstimulation reflects our routine practice as described in previous studies [7,8]. The median time between the IVF cycle and the second evaluation was 4 (range 3–6) months.

One woman was admitted to the hospital after the IVF cycle. This patient carried a rectovaginal non-operated nodule of 15 mm. She had previously undergone surgery for the removal of a right inguinal endometriotic lesion. Pre-IVF urinary tract US, barium enema and colonoscopy were unremarkable. She was treated with a flare-up protocol and hMG 300 IU daily for 10 day. Six oocytes were retrieved, of whom 5 were in metaphase II. The day after oocytes retrieval, the patient was admitted to the gynecological division because of severe pelvic and left lumbar pain. Transvaginal US was unremarkable (apart from the expected enlarged ovaries and the

Table 2
Baseline characteristics of studied population (n=84).

Characteristics	Mean ± SD, Median (IQR) or Number (%)
Age (years)	33.6 ± 3.6
Smoking	15 (18%)
Duration of infertility (years)	2 (1–3)
Previous pregnancies	14 (17%)
Previous surgery for endometriosis	41 (48%)
Previous surgery for deep endometriosis	34 (40%)
Patients on hormonal therapy	42 (50%)
BMI (Kg/m ²)	21.3 ± 2.2
Day 3 serum FSH (IU/mL)	9.3 ± 5.1
AMH (ng/ml)	1.58 (0.64–2.92)
CA-125 (IU/mL)	39.2 (26–65.4)
Concomitant male factor	29 (35%)

Table 3
Characteristics of the IVF cycles in the studied population (n=84).

Characteristics	Mean ± SD, Median (IQR) or Number (%)
Stimulation protocol	
Long protocol	24 (29%)
GnRH antagonist	33 (39%)
Flare up	27 (32%)
Cancelled cycle	
Poor response	6 (4%)
Hyper response	3 (7%)
Total dose of FSH used (IU)	3,357 ± 1,621
Duration of hyper-stimulation (days) ^a	11 ± 3
Number of oocytes retrieved ^a	5.5 (2–9)
Number of suitable oocytes	3 (1–6)
Fertilization technique ^b	
IVF	28 (47%)
ICSI	33 (53%)
Number of cleavage stage embryos ^c	3 (1–4)
Number of top quality embryos ^c	1 (0–2)

SD: Standard Deviation. IQR: Interquartile Range.

^a Data referring to patients who underwent oocytes collection (n = 75).

^b Data referring to patients who retrieved oocytes (n = 61).

^c Data referring to patients who obtained embryos (n = 56).

unchanged rectovaginal nodule) but computer tomography showed a narrowed left ureter, that was adherent to a 7 cm left ovary with multiple corpora lutea, and a mild ectasia of the renal pelvis of 1 cm. An expectant management with close monitoring of the renal function and the renal pelvic ectasia was decided. Both symptoms and radiologic signs regressed in two weeks. No other episodes occurred in the following months. The woman returned for the transfer of her embryos (that were frozen because of the pain symptoms), did not achieve pregnancy and then refused to undergo new hyper-stimulation cycles. No other women underwent surgery or had to initiate/modify hormonal treatments. No patient developed de-novo endometriotic lesions after the IVF cycle. On these bases, we extrapolated a rate of complication of 1.2% (95%: 0.05%–5.5%) (1 out of 84) for the whole cohort and 1.7% (95%CI: 0.08–7.6%) (1 out of 60) for the subgroup of women with US detectable lesions.

Table 4 shows the modifications of deep endometriosis related pain symptoms before and after IVF. More than half of recruited women presented endometriosis-related symptoms either before

Table 4
Modification of pain symptoms in studied population (N = 84).

Symptoms	Before IVF	After IVF	p
Dysmenorrhea			
BB scale			0.3
0	32 (38%)	26 (31%)	
1	12 (14%)	13 (15%)	
2–3	40 (48%)	45 (54%)	
VRS scale	5 (0–8)	6 (0–8)	0.3
Dyspareunia			
BB scale			0.4
0	28 (33%)	32 (38%)	
1	25 (30%)	23 (27%)	
2–3	31 (37%)	29 (35%)	
VRS scale	1 (0–6)	2 (0–6)	0.1
Intermenstrual pelvic pain			
BB scale			0.3
0	33 (39%)	29 (35%)	
1	22 (26%)	22 (26%)	
2–3	29 (35%)	33 (39%)	
VRS scale	3 (0–5)	2 (0–6)	0.4

BB: Biberoglu-Behrman Scale. VRS: Verbal Rating Scale. VRS is reported as median (interquartile range).

and after IVF, without significant modifications after ovarian stimulation as compared to baseline. Finally, in the 35 patients who underwent serial sonographic evaluations, the mean diameter of the endometriotic nodules was 19 ± 6 mm before IVF and 18 ± 7 mm after IVF ($p = 0.60$).

Comment

In our experience IVF was a safe procedure for women with deep invasive endometriosis. Only one woman was admitted to the hospital for a condition of hydronephrosis presumably related to deep invasive endometriosis, corresponding to a rate of 1.2% (considering the whole cohort) or 1.7% (considering exclusively women carrying US detectable lesions). This rate is in line with the expected 2% rate of endometriosis progression of over a 3–6-month period in women not receiving IVF and significantly below the threshold of 8% stated as clinically important in our sample size justification (the upper limits of the 95% CIs were $<8\%$ for both calculations). The safety of the procedure is also supported by our secondary analyses, *i.e.* the absence of relevant effects on symptoms and lesions dimension.

The observed case of endometriosis progression deserves some additional comments. Given the regression of the symptoms with expectant management, the interpretation of this case remains unclear. A ureteral stricture caused by the enlargement of an undetected deep endometriotic nodule under the stimulation effects of enhanced peripheral estrogens seems unlikely. Indeed, even if it is plausible that a deep nodule of the broad ligament could be missed at baseline evaluation (this diagnosis can be challenging), it is noteworthy that both the US and the computer tomography done at the time of the complication did not detect ureteral nodules. Moreover, symptoms regressed over a couple of weeks concomitantly to the progressive decrease in the size of the ipsilateral ovary. This observation argues against a rapid growth of a nodule, a condition that is likely to be irreversible. In our opinion, the most plausible explanation is a transient kinking of the ureter course consequent to the local traction of the enlarged and adherent ovary that was firmly adherent to the broad ligament. The growth of the ovary could have caused some tractions on a fibrotic area involving the ovary, the broad ligament and the ureter, actually pulling the ureter and causing a temporary narrowing of the lumen.

Overall, our results are in line with those emerging from large case series of women with endometriosis in general. Indeed, several independent authors failed to highlight detrimental effects in affected women undergoing IVF [5–10]. Our results actually extend this reassuring conclusion to the population of women with a diagnosis of deep invasive endometriosis. On the other hand, caution in the interpretation of our findings is warranted in light of the inconsistency with the previously published case reports (Table 1). A publication bias is plausible for these cases but we cannot exclude that progression may occur in a minority of women with some peculiar clinical characteristics. Our findings have two clinical implications. Firstly, physicians engaged in ART should inform women with deep invasive endometriosis that the disease may worsen during ovarian hyper-stimulation but can also be reassuring on this regard, explaining in particular that this event is rare. Secondly, our findings argue against prophylactic surgery in women with deep invasive endometriosis scheduled for IVF. Based on our findings, systematically removing these lesions exclusively based on a hypothetical risk of progression seems unjustified. Exposing women to the risks and costs of a demanding surgery only for the purpose of preventing IVF-related deep endometriosis progression and complications seems unwise. Surgery may be considered before IVF, but the decision should be based on a comprehensive evaluation that does not consider the potential prevention of disease progression as the main indication [3].

Some limitations of our study should be acknowledged. Firstly, the study is retrospective and the quality of the information is inevitably sub-optimal. For instance, while data on pain symptoms was systematically and prospectively ascertained in our hospital, a precise measurement of deep lesions on three orthogonal planes was not (this information was available in the two assessments in only 35 women). Moreover, drop-outs could be negatively biased (*i.e.* women experiencing worsening of symptoms could be more likely to give up). On the other hand, it has to be underlined that we were mainly interested in demanding clinical complications. This latter outcome was actually not exposed to a significant risk of under-reporting because data was actively obtained for the whole hospital, including the Infertility Unit, the Gynecological Unit and the Emergency department. Moreover, women who did not return to the scheduled appointments were systematically called by phone to investigate the reasons, thus allowing to rule out severe complications. Secondly, one could question the decision to include also women with a history of surgery for deep invasive endometriosis but without US detectable lesions. This choice was based on the idea that deep invasive endometriosis is a multifocal recurrent disease and that the diagnosis of deep lesions may be in some cases challenging [21]. Some lesions could actually be overlooked during surgery or could have recurred but not identified postoperatively. In this regard, it has to be underlined that, the results were substantially similar when we repeated the analyses including only women with ultrasound detectable lesions. Thirdly, even if our sample size allowed us to draw a conclusion for the whole group of women with deep invasive endometriosis, subgroup analyses based on the characteristics of the lesions could not be performed. Further evidence taking into consideration the dimension, the multifocality and the precise location of the lesions is needed. To note, one cannot exclude that the demanding cases reported in Table 1 could have occurred in women with most severe forms of the disease. Unfortunately, our study cannot rule out this possibility. Indeed, most women in our cohort were poorly symptomatic. For instance, clinically relevant dyspareunia, a typical symptom of deep peritoneal endometriosis, was present in only one third of our patients (Table 4). Fourthly, a follow-up period of 3–6 months could be considered too short to identify every possible complication. However, such a short period has been chosen in order to focus our attention only to events that could be strictly related to IVF and ovarian hyper-stimulation, minimizing the possible influence of other confounding factors. To note, all the cases of progression of deep endometriosis after IVF described in literature occurred within three months after ovarian hyperstimulation (Table 1). Finally, we inevitably lack a definite histological diagnosis of endometriosis. However, this limitation is unlikely to play a relevant confounding effect since the accuracy of transvaginal sonographic diagnosis of deep invasive endometriosis is high, at least for distal localizations [22,23].

In conclusion, our study suggests that women with deep invasive endometriosis who undergo IVF are not exposed to a substantial increase in the risk of recurrence or disease progression. However, given that demanding complications may occur in some particular patients, further large studies are required for a definitive conclusion.

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