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IVF and endometriosis-related symptom progression: insights from a prospective study

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BACKGROUND: A possible and neglected concern in women with endometriosis undergoing IVF is the potential risk of progression of the disease. We set up a prospective study mainly aimed at evaluating the impact of IVF on endometriosis-related symptoms.

MATERIALS AND METHODS: Women with surgical or echographic diagnosis of endometriosis and selected for IVF were included. In the month preceding the IVF attempt and at a second evaluation 3–6 months after the cycle, women who did not get pregnant underwent clinical assessment and transvaginal ultrasonography. Each patient was requested to complete a questionnaire on the presence, severity and modifications of endometriosis-related symptoms before and after the IVF cycle.

RESULTS: Overall, 64 patients completed the study protocol. The Biberoglu–Behrman Scores and the Verbal Rate Scales for dysmenorrhea, dispareunia and chronic pelvic pain did not worsen after the procedure. Other endometriosis-related symptoms also did not change. There was no modification in size and number of endometriomas and deep peritoneal nodules. The number (%) of women reporting general improvement and worsening were 14 (22%) and 7 (11%), respectively.

CONCLUSIONS: IVF does not expose women to a consistent risk of endometriosis-related symptoms progression.

Key words: endometriosis / IVF / endometriosis-related symptoms

Introduction

Of women with endometriosis, who wish for a child, a considerable proportion require IVF because of infertility (Adamson, 2005; Vercellini *et al*., 2009a). A possible and neglected concern in this field is the potential risk of progression of the disease due to IVF treatment. Indeed, controlled ovarian hyperstimulation (COH) leads to the development of multiple follicles and to a considerable rise in the serum estradiol concentration. Endometriosis is an estrogen-dependent disease and the number of ovulatory events has been claimed to play a critical role in the formation of ovarian endometriomas (Jain and Dalton, 1999; Missmer *et al*., 2004; Vercellini *et al*., 2009b, 2010). Overall, however, it cannot be excluded that IVF favors the progression of the disease (Garcia-Velasco and Somigliana, 2009).

Surprisingly, although the impact of endometriosis on IVF outcome has attracted the interest of researchers for two decades, scant attention has been paid to the impact of IVF on endometriosis progression. Noteworthy, the available evidence is contradictory. Three studies initially documented some cases of women, with deep peritoneal endometriosis, who experienced clinically significant progression of the disease following IVF (Renier *et al*., 1995; Govaertis *et al*., 1998; Anaf *et al*., 2000). However, a causal relationship has been questioned since these first reports (Govaertis *et al*., 1998). In a subsequent retrospective cohort study, D'Hooghe *et al*. showed that the rate of recurrence is in fact lower in women undergoing IVF compared with those treated with IUI. A prospective study of our group evaluating modifications of ovarian endometriomas did not show any increase in size of these lesions following IVF (Benaglia *et al*., 2010). Finally, in a retrospective cohort study also performed in our Institute, we failed to demonstrate any significant effect of ovarian responsiveness and number of IVF cycles on the rate of recurrences (Benaglia *et al*., 2010).

Overall, however, the question remains open and further evidence is warranted (Garcia-Velasco and Somigliana, 2009). Inline with this need, we herein report on a prospective study mainly aimed at evaluating the impact of IVF on endometriosis-related symptoms.

Materials and Methods

Women selected for IVF between January 2007 and December 2008 at the Infertility Unit of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico were considered for the study. Inclusion criteria were as follows: (i) surgical or echographic diagnosis of endometriosis, (ii) age <43 years at the time of IVF procedure and (iii) no previous COH cycles (including IVF or IUI). Exclusion criteria after recruitment were: (i) IVF cycle not performed, (ii) pregnancy and (iii) refusal to refer for second evaluation. Selected women were assessed before the IVF cycle and 3–6 months later. The study was approved by the local Institutional Review Board and all women gave written informed consent to participate.

In the month preceding the IVF attempt and at the second evaluation 3–6 months after the cycle, selected women underwent clinical assessment, vaginal and rectal examination, and transvaginal ultrasonography. They were interviewed about demographic characteristics, reproductive history, endometriosis-related symptoms, and surgical interventions or medical treatments for endometriosis. Each patient was requested to complete a questionnaire on the presence and severity of dysmenorrhea, deep dyspareunia and non-menstrual pelvic pain graded using a 0- to 3-point multidimensional categorical rating scale modified from that devised by Biberoglu and Berhman (1981). This scale defines dysmenorrhea according to the 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 the limitation of sexual activity. Moreover, the women were requested to grade the severity of dysmenorrhea, deep dyspareunia and non-menstrual pelvic pain using a verbal rating scale (VRS), with 0 indicating the absence of pain and 10 indicating the most pain possible. They were also interviewed about the presence of other endometriosis-related symptoms, including dischezia, proctorragia, unexplained vaginal bleeding and disuria. Furthermore, the women were asked to give a judgment regarding modifications of symptoms on a five grade scale (much improved/moderately improved/unchanged/moderately worsened/much worsened). This was requested for dysmenorrhea, dyspareunia, chronic pelvic pain, other symptoms and overall symptoms. Finally, during the post-IVF examination, women were also interviewed about recurrences occurring during the period between the two assessments. Recurrence was defined as the need to undergo surgery or to start a hormonal treatment interfering with spontaneous conception (oral contraceptives, progestins, GnRH analogs) in spite of a persisting pregnancy desire.

Ovarian endometrioma was defined as a round-shaped cystic mass with a minimum diameter of 1 cm, with thick walls, regular margins, homogeneous low echogenic fluid content with scattered internal echoes and without the observation of papillary proliferations (Savelli, 2009). Deep endometriosis was diagnosed based on both clinical examination and transvaginal sonography. The deep endometriotic implants were defined as the presence of hypoechoic nodules with irregular outer margins and few blood vessels within and around the nodules at Doppler examination. We included nodules that could be visualized by ultrasound in proximity with the uterine cervix, or behind the cervix or within the bladder wall (Savelli, 2009). The dimension of the nodules and the endometriomas was calculated as the mean of three perpendicular diameters. Participating women who were operated for endometriosis were requested to provide the copy of the surgical charts in order to obtain endometriosis stage according to the revised American Society for Reproductive Medicine (ASRM) classification (rASRM, 1997). If operated more than once, the reported stage referred to the last intervention.

Patients selected for IVF were monitored and managed according to a standardized clinical protocol as reported elsewhere (Somigliana *et al.*, 2008). Briefly, the dose of gonadotrophins was determined on an individual basis according to the characteristics of the patients: age, number of interventions for endometriosis and ecographic characteristics of the ovaries indicating the number of antral follicles. Patients underwent serial transvaginal ultrasound and hormonal monitoring during hyperstimulation. When three or more leading follicles with a mean diameter >18 mm were visualized, 250 mg of recombinant hCG was administered s.c. Oocyte retrieval was performed transvaginally 36 h after the hCG injection. Embryo transfer was performed 48–72 h after the oocyte collection. Cycles could be cancelled because of poor or hyper-response.

Data analysis was performed using the Statistics Package for Social Sciences (SPSS 18.0, Chicago, IL). Paired Student's *t*-test, Wilcoxon test and MacNemar test were used to compare continuous and categorical variables, respectively. A *P*-value <0.05 was considered as statistically significant. Continuous data were reported as mean ± SD, median (interquartile range, IQR) or median (range) as appropriate. The sample size was estimated stating as clinically relevant a 2-fold increase in the rate of women reporting moderate–severe dysmenorrhea on the Biberoglu and Behrman scale (Biberoglu and Berhman, 1981) and setting the conventional type I and type II error of 0.05 and 0.20. On these bases and hypothesizing a rate of drop-out due to pregnancy or refusal to refer of ~30%, we calculated that the sample size should include about 90 women.

Results

For the study, 89 patients were recruited. The IVF cycles led to viable pregnancies in 18 cases (20%). No patients were lost at follow up. There were seven women (8%) who refused to refer for the second evaluation for personal reasons. None of these latter cases reported any endometriosis-related complications on a phone interview. Overall, 64 patients completed the study protocol. Data reported hereafter refer to this cohort.

Baseline clinical characteristics and IVF outcome of the selected women are shown in Tables I and II, respectively. Oocyte retrieval was performed in 56 cases (88%). The endometrioma was never

Table I Baseline clinical characteristics of the women who completed the study (*n* = 64).

Characteristics	Mean ± SD or number (%)
Age at IVF (years)	35.2 ± 3.3
Duration of infertility (years)	3.0 ± 1.8
Previous pregnancies	8 (12%)
BMI (kg/m^2)	21.4 ± 2.6
Day 3 serum FSH (IU/l)	10.8 ± 6.5
AMH (ng/ml)	1.3 ± 1.8
Age at first surgery (years)	31.4 ± 4.7
Number of interventions for endometriosis	
None	5 (8%)
I	40 (62%)
≥2	19 (30%)
rASRM classification[a]	
I–II	8 (14%)
III	25 (42%)
IV	27 (46%)

[a]Data refers to operated patients (*n* = 60).

Table II Characteristics of IVF cycles in the women who completed the study ($n = 64$).

Characteristics	Mean ± SD or number (%)
Protocol of stimulation	
Long protocol	26 (41%)
GnRH antagonist	18 (28%)
Short protocol	20 (31%)
Cancelled cycles	
Poor response	8 (12%)
Hyper response	0 (0%)
Dosage of rFSH/day (IU)	3356 ± 1220
Duration of stimulation (days)[a]	10.5 ± 2.3
Serum estradiol at the time of hCG injection (pg/ml)[a]	1645 ± 883
Number of follicles >15 mm[a]	4.8 ± 2.5
Number of oocytes retrieved[a]	4.2 ± 3.3
Number of embryos obtained and transferred[b]	1.7 ± 0.7
Ovarian hyperstimulation syndrome	0 (0%)

[a]Data refers to patients performing oocyte retrieval ($n = 56$).
[b]Data refers to patients performing embryo transfer ($n = 34$). According to the new Italian legislation, all embryos obtained have to be transferred.

Table III Influence of IVF on endometriosis-related symptoms.

Symptoms	Pre-IVF	Post-IVF	*P*
Dysmenorrhea			
BB-scale			0.21
0	25 (39%)	21 (33%)	
1	22 (34%)	29 (45%)	
2–3	17 (27%)	14 (22%)	
VRS-scale	3.7 ± 3.3	3.8 ± 3.3	0.78
Dyspareunia			
BB-scale			0.08
0	44 (69%)	44 (69%)	
1	11 (17%)	16 (25%)	
2–3	9 (14%)	4 (6%)	
VRS-scale	1.6 ± 2.6	1.4 ± 2.4	0.25
Pelvic pain			
BB-scale			0.16
0	35 (55%)	38 (59%)	
1	21 (33%)	23 (36%)	
2–3	8 (12%)	3 (5%)	
VRS-scale	2.0 ± 2.8	1.4 ± 2.2	0.03
Other symptoms	15 (23%)	13 (20%)	0.69

BB scale, Biberoglu and Behrman scale; VRS scale, verbal rating scale.

accidentally punctured. None of these 56 women developed pelvic inflammatory disease after the procedure. The median (range) time between IVF and the second evaluation was 4 (3–6) months.

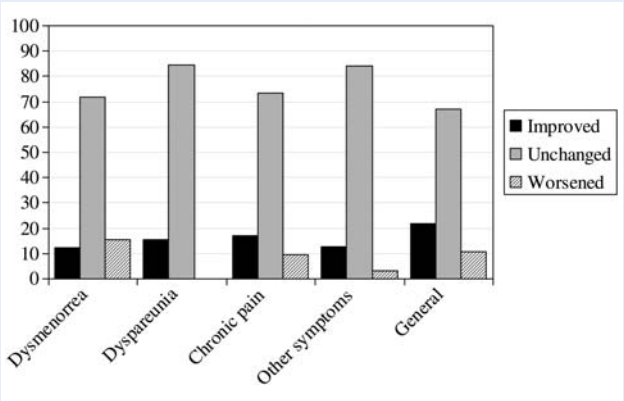

Figure 1 Modification of symptoms after IVF cycles. Recruited women were asked to give a judgment regarding modifications of symptoms after IVF on a five grades scale (much improved/moderately improved/unchanged/moderately worsened/much worsened). This was requested for dysmenorrhea, dyspareunia, chronic pelvic pain, other symptoms and overall. Results are presented in the graph after grouping the data into three categories: (1) improved (black bars), (2) unchanged (grey bars) and (3) worsened (grey stripes).

During this interval, no women had to undergo surgery for endometriosis and/or had to initiate specific medical treatments to control the disease [0.0%, 95% confidence interval (CI): 0.0–4.5%]. The modifications of endometriosis-related symptoms are shown in details in Table III. No statistically significant differences emerged with the exception of the VRS score of chronic pelvic pain that improved after IVF. The number (%) of women reporting improvement and worsening of dysmenorrhea, dyspareunia, chronic pelvic pain and other symptoms were 8 (12%) and 10 (16%), 10 (16%) and 0 (0%), 11 (17%) and 6 (9%), and 8 (12%) and 2 (3%), respectively. Those reporting general improvement and worsening were 14 (22%) and 7 (11%), respectively. These results are illustrated in Fig. 1.

Ovarian endometriomas were detected in 35 women (55%), and 45 cysts were available for analysis. The median (IQR) diameter of these lesions before and after the IVF cycle was 20 (12–27) and 20 (17–27) mm, respectively ($P = 0.51$). Deep nodules were observed in nine women (14%) who were carrying 10 lesions. The median (range) diameter of the nodules before and after the IVF cycle was 10 (5–18) and 10 (5–18) mm, respectively ($P = 1.00$). We did not detect the development of new endometriomas or new deep nodules after the procedure.

Discussion

Initial data regarding the impact of IVF on endometriosis-related symptoms was frightening. Seven cases of rapid and life-threatening progression of deep peritoneal endometriosis were reported, thus suggesting a detrimental effect (Renier *et al.*, 1995; Govaertis *et al.*, 1998; Anaf *et al.*, 2000). In contrast, the first available cohort study on this issue reported reassuring data (D'Hooghe *et al.*, 2006). Using electronic patients' files, these authors documented that the rate of endometriosis recurrence was higher in women who

underwent IUI when compared with those treated with IVF. The 36 months cumulative recurrence rate in women undergoing IUI ($n = 17$), IUI + IVF ($n = 11$) and IVF ($n = 39$) was 70, 43 and 7%, respectively (D'Hooghe *et al*., 2006). Assuming that IUI exposes women to a lower risk, these results indirectly support the view that IVF is not detrimental.

Two subsequent studies from our group added further comforting data. In the first one, we specifically recruited women who underwent IVF with ovarian endometriomas (Benaglia *et al*., 2010). Selected patients who failed to become pregnant were scanned again 3–6 months later to evaluate the modification of the dimension of the cysts; 48 women completed the study protocol. The median (IQR) of the diameter of the cysts before and after the IVF cycle was 20 (18–25) and 21 (17–27) mm, respectively ($P =$ not significant). In a second study, we retrospectively recruited 189 women with endometriosis and who underwent IVF cycles in our Unit (Benaglia *et al*., 2010). Of these, 41 (22%) had a diagnosis of endometriosis recurrence. The 36 months cumulative recurrence rate was 20%. To evaluate the impact of IVF, we analyzed the rate of recurrences according to the number of cycles and ovarian responsiveness. These two variables were expected to influence the rate of recurrence if IVF had a detrimental impact on the progression of the disease. Our results did not support this possibility. The number of IVF cycles and the responsiveness to ovarian hyperstimulation were not associated with the risk of disease recurrence. The adjusted OR for recurrences according to the number of started cycles was 0.92 (95% CI: 0.77–1.10) per cycle ($P = 0.35$). The adjusted OR for recurrences in women with intact versus compromised ovarian reserve was 0.80 (95% CI: 0.40–1.58), ($P = 0.52$) (Benaglia *et al*., 2010).

Overall, albeit somehow contradictory, available data from the literature were thus reassuring. We however considered it worthwhile to further investigate this issue considering that the two cohort studies were retrospective and that the conclusions were based on indirect evidence (D'Hooghe *et al*., 2006; Benaglia *et al*., 2010). Moreover, the unique prospective study focused exclusively on ovarian endometriomas (Benaglia *et al*., 2010), and the impact on endometriosis-related symptoms was not previously investigated. In the present study, we report—for the first time—comforting data also on this aspect. We indeed documented that ovarian hyperstimulation during IVF cycles does not markedly worsen endometriosis-related symptoms. Furthermore, this study confirmed previous reassuring data regarding endometriotic lesions since both endometriomas and deep nodules were unchanged after the procedure.

Some limits of the study should be considered. Firstly, a possible concern is the time point for the second evaluation. It can be argued that a 3–6 month period is too short to exclude long-term detrimental effects. On the other hand, endometriosis-related symptoms may develop *per se* over time. If a longer follow-up period was decided and a significant worsening was detected, the interpretation of the results would have been more demanding. It has however to be recognized that the present study cannot rule out the possible long-term effects of ovarian hyperstimulation on the modifications of endometriosis-related symptoms. Albeit unlikely, one may indeed argue that IVF may have a detrimental impact where the effects are not immediate but would become evident several months later. Secondly, the lack of a control group did not allow us to exclude a placebo effect. Women may fear IVF-related progression of endometriosis and this may translate into an overestimation of the harmful effects of the procedure. However, the lack of any evidence of a detrimental impact allows us to exclude a role of this placebo effect. Thirdly, we cannot rule out that women who dropped out were those who experienced some deleterious effects. This is, however, unlikely since excluded women were contacted by phone and they denied endometriosis-related symptoms as a reason for drop out. Finally, a further possible limitation is related to the sample size that is not sufficiently large to allow for reliable subgroup analyses. For instance, the possibility of a harmful impact on women with deep nodules cannot be definitely excluded since these lesions were detected in only nine cases. This is an important point, given the above-mentioned case reports of a detrimental effect of IVF on these specific lesions (Renier *et al*., 1995; Govaertis *et al*., 1998; Anaf *et al*., 2000).

Conclusion

Based on the available data from the literature and from the present study, it can be inferred that IVF does not expose women to consistent risk of progression of endometriosis-related symptoms. The impact on endometriotic lesions remains however to be fully clarified. Further evidence in particular is required for the specific group of women with deep peritoneal lesions.

Authors' roles

L.B. and G.R. designed the study. E.S., C.S. and G.S. collected and analyzed the data. L.B. and E.S. wrote manuscript. L.F. supervised the study. All authors critically revised the manuscript and approved the final version.

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