Impact of ovarian stimulation for IVF/ICSI on the size of endometriomas: monocentric retrospective study

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ABSTRACT

Objectives: To evaluate endometrioma diameter before and after controlled ovarian stimulation (COS) in infertile patients undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) and the impact of endometrioma growth on clinical pregnancy rate (CPR).

Methods: We performed a retrospective study of 52 patients with endometrioma undergoing IVF or ICSI at Tenon Hospital between February 2013 and May 2017. Each patient underwent transvaginal ultrasound before COS and was monitored by regular transvaginal ultrasound until the day of triggering of ovulation. Endometrioma diameter was measured at each ultrasound examination.

Results: Endometrioma mean diameter was not significantly higher after COS (30 mm [10-90] versus 26 mm [10-130], p=0.85). The CPR was slightly lower with increased endometrioma diameter (21.6% in patients with increased endometrioma diameter versus 23.5% in patients without increased endometrioma diameter, p=0.72), but the difference did not reach statistical significance.

Conclusion: Endometrioma diameter increased, but not significantly, in infertile patients undergoing COS for IVF/ICSI. The increase in endometrioma diameter did not seem to affect the CPR.

KEYWORDS

Endometriosis; endometrioma; controlled ovarian stimulation; IVF/ICSI; AMH.

Introduction

Endometriosis is a chronic, estrogen-dependent gynecological pathology defined by the presence of endometrial tissue outside the uterus. Its pathophysiology is incompletely understood. The incidence of endometriosis is estimated to be 6-10% in the female population of childbearing age ,but reaches up to 50% in the infertile female population [1,2].

Three anatomopathological entities have been described: superficial endometriosis, ovarian endometriosis defined by the presence of cysts (endometriomas), and deep endometriosis defined as infiltration of the subperitoneal space and/or organ. These three entities are often associated to varying degrees. The ovary is the most common site of endometriosis with a prevalence ranging from 30% to 50% [3–8].

The presence of an ovarian endometrioma larger than 20 mm may influence ovarian function [9]. The mechanisms involved are chronic inflammation by fibrosis and metaplasia, a significant decrease in the density of primordial follicles, and dysregulation of folliculogenesis [10-13]. However, the value of endometrioma treatment in the context of assisted reproductive techniques (ART) is debated. Indeed, surgery can reduce ovarian reserve through removal or destruction of the ovarian parenchyma [14–17]. Previous meta-analyses have shown a significant decrease in anti-Mullerian hormone (AMH) levels after unilateral cystectomy [18,19]. However, the presence of ovarian endometrioma does not seem to have an impact on *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) results. The discovery of an endometrioma during IVF should not prompt interruption of the attempt according to the new recommendations from the Haute Autorité de Santé and the Collège National des Gynécologues et Obstétriciens Français (CNGOF), but the level of evidence remains low (grade C) [20,21]. Nevertheless, few data are available on the impact of IVF/ICSI stimulation on the size of endometriomas. Benaglia et al. demonstrated that IVF was not associated with recurrence of endometriosis, which is defined by the need for surgery or hormonal treatment after an IVF attempt. In 6 out of 21 cases, the surgery after IVF was motivated by the development of an endometrioma with a diameter greater than 5 cm [22,23].

Given the inconsistencies in the literature, the primary objective of this retrospective study was to evaluate the impact of controlled ovarian stimulation (COS) for IVF/ICSI on the size of endometriomas. The secondary objective was to evaluate the impact of endometrioma growth during ovarian stimulation on clinical pregnancy rate (CPR).

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Methods

From February 2013 to May 2017, we conducted a retrospective study based on prospective data from the Gynecology-Obstetrics and Reproductive Medicine Department of Tenon Hospital. The study included infertile patients managed for IVF/ICSI with endometriosis and presenting with a 10 mm endometrioma. All patients had an ultrasound evaluation of endometriomas (number, size, mapping) before ovarian stimulation, during stimulation, and before ovulation was initiated. Patients who received endometrioma treatment by cystectomy, puncture, vaporization or alcoholization between the time of the first check-up ultrasound and the start of ovarian stimulation were excluded from the study. All patients agreed to participate in the study. The study protocol was validated by the ethics committee of the CNGOF (CEROG 2019-GYN-0101).

Ultrasound of endometriomas

All patients underwent ultrasound examination, including antral follicle count (AFC), as part of infertility monitoring. The ultrasound diagnostic criteria for endometrioma were those used by the European Society of Radiology [24]. A Cochrane review by Nisenblat et al. highlighted the high performance of ultrasound for endometrioma diagnosis. To diagnose ovarian endometrioma, endovaginal ultrasound has a sensitivity of 93% (95% CI [0.87 ; 0.99] and a specificity of 96% (95% CI [0.92; 0.99]), while MRI has a sensitivity of 95% (95% CI [0.90 ; 1.00] and a specificity of 91% (95% CI [0.86 ; 0.97]) [25]. Ovarian endometriotic implants < 10 mm were not included. The endometrioma was evaluated by measuring its mean diameter: dmoy= d_1+d_2/2, where d_1 and d_2 were two perpendicular diameters of the endometrioma.

IVF-/ICSI: ovarian stimulation and ultrasound monitoring

Patients received controlled ovarian stimulation. Several protocols were used: I) daily long agonist protocol, II) short agonist protocol, III) antagonist protocol. In the long agonist protocol, ovarian stimulation began following blockage of the hypothalamic-pituitary axis, after verification of pituitary desensitization (E2<50 pg/ml). In the short agonist protocol, patients were pre-treated with an estrogen-progestin pill (Minidril, Pfizer holding, France) for at least 20 days, then simultaneously started the gonadotropin-releasing hormone (GnRH) agonist and a gonadotropin. In the antagonist protocol, ovarian stimulation with gonadotropin started on the second day of menstruation and the antagonist on the sixth day of stimulation. The initial dose of FSH ranged from 150 to 450 IU, determined according to the patient's profile (body mass index, age, AMH serum level and AFC) [26–29]. Oocyte retrieval was performed 36 hours following triggering of ovulation by administration of alpha chorionic gonadotropin (Ovitrelle 250 IU, Merk Serono, France). Monitoring of the growth of the antral follicles was done on the eighth day of stimulation and then every 48 hours to decide on the day of ovulation induction. The number of follicles and endometriomas observed and their diameter were recorded, for each ovary, in a computer program (Médifirst). The diameter of the endometrioma before stimulation was compared with its diameter on the day of ovulation induction.

Embryo transfer was performed on day 2-3 following oocyte retrieval as none of the patients included in the present study underwent blastocyte transfer. Embryos were evaluated according to the usual morphological criteria on the basis of the number of blastomeres, their size and the fragmentation rate [30–32]. Vaginal progesterone treatment was administered to support the luteal phase. Clinical pregnancy diagnosis was based on the presence of a gestational sac and an embryo with cardiac activity on ultrasound performed 5 weeks after oocyte retrieval.

Statistical analysis

The descriptive analysis was performed using percentage values for quantitative variables and medians for qualitative variables. The impact of IVF/ICSI ovarian stimulation on endometriomas was assessed by comparing, in each patient, the diameter of the largest endometrioma before and after stimulation. The secondary analysis evaluated the effect of increased endometrioma diameter on clinical pregnancy rate. These comparisons were made using the Chi-square and Wilcoxon tests. A $p < 0.05$ was considered significant. The statistical analysis was done using the R software.

Results

Epidemiological characteristics of the population and stimulation

Two hundred ninety-seven patients with ovarian endometrioma received ovarian stimulation as part of IVF/ICSI management during the study period. Of these patients, 234 were excluded either because of ovarian surgery (n=40) or because of absence of endometrioma evaluation before ovarian stimulation (n=194), while a further 11 patients were excluded because only one diameter of endometrioma was evaluated before stimulation, making it impossible to evaluate changes between two diameters, or beginning-of stimulation vs end-of-stimulation differences (11 patients). Fifty-two patients were finally included.

The median age of the patients was 31 years [range: 25-42] and they had a median body mass index of 20.5 kg/m^2 [range: 18-33]. Among the patients included, 10 were smokers (19%). The median AMH serum level was 2.1 ng/ml [range: 0.22-24], and the median AFC was 10 [range: 1-30]. The majority of the patients had primary infertility (n=38, 74%). Eleven patients (22%) had a history of ovarian surgery prior to ART management: one patient (2%) had undergone unilateral salpingo-oophorectomy, five patients (10%) a cystectomy, and five (10%) endometrioma fenestration with plasma energy vaporization (Table 1).

Controlled ovarian stimulation characteristics

Thirty-two patients (62%) underwent IVF and 20 patients (38%) ICSI. The stimulation protocols were a GnRH agonist protocol in 58% of cases (long agonist protocol in 40.5% (n=21) and short agonist in 17.5% (n=9)) and a GnRH antagonist protocol in 22 patients (42%).

The median duration of stimulation was 11 days [range: 8-18]. The median dose of gonadotropins used was 3300 IU [range: 1500-7200] and the median number of mature follicles

Table 1 Epidemiological characteristics of the study population.

Characteristics	Patients (n=52)
Age, median (years) [range]	31 [25-42]
BMI, median (kg/m^2) [range]	20.5 [18-30]
Smoker, n (%)	10 (19)
AMH, median serum level (ng/ml) [range]	2.1 [0.22-23.9]
AFC median [range]	10 [1-30]
Infertility, n (%)	
Primary	38 (74)
Secondary	14 (26)
Previous ovarian surgery, n (%)	
Cystectomy	5 (10)
Endometrioma fenestration	5 (10)
Unilateral oophorectomy	0 (0)
Unilateral salpingo-oophorectomy	1 (2)

BMI: Body mass index; AMH: Anti-Mullerian hormone; AFC: antral follicle count

Table 2 Results of controlled ovarian stimulation.

Characteristics	Stimulation
Assisted reproductive technique (n%)	
IVF	32 (62)
ICSI	20 (38)
Protocol type n (%)	
Long agonist	21 (40.5)
Short agonist	9 (17.5)
Antagonist	22 (42)
Median duration of stimulation (days) [range]	11 [8-18]
Median dose of gonadotropins (IU) [range]	3300 [1500-7200]
Stimulation response n [range]	
Number of mature follicles ≥ 16 mm	4 [2-18]
Number of oocytes retrieved	7 [0-21]
Number of fresh embryos transferred	1 [0-2]

IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection

Table 3 Distribution of endometriomas and endometriosis lesions in the study population.

Characteristics	Endometrioma (n=60)
Endometrioma size n (%)	
< 30 mm	28 (54)
30 to 60 mm	20 (38)
> 60 mm	4 (8)
Location of endometriomas, n (%)	
Unilateral	44 (84.5)
Bilateral	8 (15.5)
Deep endometriosis lesion n (%)	
Torus uterinum	31 (59)
Uterosacral ligaments	32 (62)
Fallopian tubes	14 (27)
Colorectum	25 (48)
Vagina	9 (17)
Parametrium	7 (13)
Bladder	2 (4)

≥ 16 mm observed was 4 [range: 2-18]. The median number of oocytes retrieved was 7 [range: 0-21], and the median number of fresh embryos transferred was 1 [range: 0-2] (Table 2).

Characteristics of endometriomas

Forty-four patients (84.5%) had unilateral endometrioma and 8 patients (15.5%) bilateral endometrioma. Endometrioma size was small (<30 mm) in the majority of the patients (n=28, 54%), while in 20 patients (38%) the size was between 30 mm and 60 mm, and in four patients (8%) over 60 mm. Endometriosis lesions most frequently associated with endometrioma involved the utero-sacral ligaments (n=32, 62%), torus uterinum (n=31, 59%), colon-rectum (n=25, 48%) and fallopian tubes (n=14, 27%) (Table 3).

Ovarian reserve before IVF/ICSI and response to stimulation

The AMH serum level was similar in patients with unilateral endometrioma compared with those with bilateral endometrioma (2.13 ng/ml [range: 0.22-23.9] vs 2.12 ng/ml [range: 0.22-14], p=0.69). AMH serum level was 2.95 ng/ml [range: 0.22-23.9] in patients with endometrioma < 30 mm, 1.39 ng/ml [range: 0.22-14] in patients with endometrioma measuring between 30 and 60 mm, and 1.43 ng/ml [range: 0.91-2.85] in those with endometrioma > 60 mm (p=0.25). The AFC was similar in patients with unilateral and bilateral endometrioma: 10 [range: 3-30] and 10 [range: 1-15], respectively (p=0.62), and it did not differ according to the size of the endometrioma: 8.5 [range: 1-15] in patients with endometrioma > 60 mm, 10 [range: 3-30] in patients with endometrioma < 30 mm, and 10.5 [range: 3-20] in patients with endometrioma measuring between 30 and 60 mm, p=0.77. Ovarian response to COS did not seem to be affected by bilateral endometriomas, as the number of mature follicles was 5 [range: 2-18] in patients with unilateral endometrioma and 3.5 [range: 1-18] in those with bilateral endometrioma (p=0.78). No significant differences were found in the number of retrieved oocytes in the unilateral endometrioma group compared with the bilateral endometrioma group (median value: 7 [range: 1-19] and 7.5 [range: 2-21], respectively (p=1)). The number of retrieved oocytes in patients with endometrioma > 60 mm was 4.5 [range: 0-28], which was lower than the 7.5 [range: 1-21] recorded in patients with endometrioma < 30 mm and the 6.5 [range: 2-17] in patients with endometrioma measuring between 30 and 60 mm, but without the difference reaching significance (p=0.32).

The duration of ovarian stimulation in patients with unilateral endometrioma was 11 days [range: 8-18] versus 12 days in patients with bilateral endometrioma [range: 11-16] (p=0.15), and the total dose of gonadotropins used was 3275 IU for unilateral endometrioma [range: 1000-7200] and 4500 IU for bilateral endometrioma [range: 1800-6000] (p=0.36). The gonadotropin dose was 3700 IU [range: 2000-4200] in patients with endometrioma > 60 mm, 2612 IU [range: 1500-7200] in patients with endometrioma < 30 mm, and 4087 IU [range: 1500-6000] in patients with endometrioma measuring between 30 and 60 mm (p= 0.14). The number of COS days was 13 [10-16] in patients with endometrioma > 60 mm, 11 [8-16] in patients with endometrioma < 30 mm, and 11 [9-18] in patients with endometrioma between 30 and 60 mm (p=0.40) (Tables 4 and 5).

Table 4 Ovarian reserve and response to controlled ovarian stimulation according to unilateral and bilateral endometrioma.

	Unilateral endometrioma (n=44)	Bilateral endometrioma (n=8)	p
AFC, median [range]	10 [3-30]	10 [1-15]	0.62
AMH, median serum level (ng/ml) [range]	2.13 [0.22-23.9]	2.12 [0.22-14]	0.69
Median duration of ovarian stimulation (days) [range]	11 [8-18]	12 [11-16]	0.15
Median dose of gonadotropins (IU) [range]	3275 [1000-7200]	4500 [1800-6000]	0.36
Number of follicles, median [range]	5 [2-18]	3.5 [1-18]	0.78
Oocytes retrieved, median number [range]	7 [1-19]	7.5 [2-21]	1

AFC: antral follicle count; AMH: Anti-Mullerian hormone

Table 5 Ovarian reserve and response to controlled ovarian stimulation according to endometrioma size.

	Endometrioma < 30 mm (n=28)	Bilateral endometrioma (n=8) (n=20)	Bilateral endometrioma (n=8) (n=4)	p
AFC median [range]	10 [3-30]	10.5 [3-20]	8.5 [1-15]	0.77
AMH, median serum level (ng/ml) [range]	2.95 [0.22-23.9]	1.39 [0.22-14]	1.43 [0.91-2.85]	0.25
Median duration of stimulation (days) [range]	11 [8-16]	11 [9-18]	13 [10-16]	0.40
Median dose of gonadotropins (IU) [range]	2612 [1500-7200]	4087 [1500-6000]	3700 [2000-4200]	0.14
Number of follicles ≥ 16 mm, median [range]	4.5 [2-15]	4.5 [2-18]	3 [2-5]	0.47
Oocyte retrieved, median [range]	7.5 [1-21]	6.5 [2-17]	4.5 [0-28]	0.32

AFC: antral follicle count; AMH: Anti-Mullerian hormone

Change in endometrioma size after controlled ovarian stimulation and clinical pregnancy rate

The mean diameter of the endometrioma before and after COS was 26 mm [range: 10-130] and 30 mm [range: 10-90], respectively (p=0.85). An increase in endometrioma size was noted in 62% of the patients after COS.

For the analysis of the CPR, seven patients were excluded due to no embryo transfer after COS (five culture failures, one fertilization failure, and one absence of oocyte retrieved). Thus, the population for the secondary analysis consisted of 45 patients. The CPR was 21.6% (n=6) in patients showing endometrioma growth and 23.5% (n=4) in patients with stable endometrioma diameter (p=0.72).

Discussion

In our study, endometrioma diameter in infertile patients increased, but non-significantly, after COS for IVF/ICSI. As regards the impact of COS for IVF on endometrioma growth, literature data are scarce. Benaglia et al. evaluated the effect of stimulation on the size of endometriomas in two studies. In the first study, endometrioma volume was evaluated by 2-dimensional ultrasound in 48 patients, comparing the value one month before ovarian stimulation with that recorded 3-6 months after stimulation. This study did not show any significant difference (volume 3.9 ml [2.9-7.9] versus 4.9 ml [2.4-9.9]) [33]. In the second study, they also found no significant difference (p=0.51) when comparing endometrioma median diameters (where diameter is defined as the average of three perpendicular diameters on 2-dimensional ultrasound) [34]. In contrast, a recent prospective study by Seyhan et al. showed an increase in endometrioma volume on 3-dimensional ultrasound in 25 patients stimulated for IVF (22.2 ml [12-30] versus 24.99 ml [11.2-37.4], p=0.001). Volume was measured on the first day of gonadotropin stimulation and on the day of ovulation induction. The results were similar when comparing endometrioma median diameter at the same time points (37.5 mm [29.5-40.7] vs 40.5 mm [30.4-43.5], p<0.001) [35]. Our results are in accordance with those of Benaglia et al., whose studies showed no statistical difference in endometrioma diameter after COS. Although the results of Seyhan's study showed a significant increase in endometrioma size after COS, some issues deserve to be underlined. First, their study included 28 endometriomas from only 25 patients, and therefore showed a low incidence of bilateral endometriomas. In addition, the increase in endometrioma diameter after ovarian stimulation was significant but amounted to only 3 mm (37.5 mm before stimulation and 40.5 mm after ovarian stimulation); this corresponds to a less than 10% increase in endometrioma size, which could be linked to the simple intrinsic variability of the ultrasound. The 3-dimensional ultrasound described as efficient in the evaluation of en-

dometriomas also presents intra- and inter-observer variability [36]. The sole parameter that might explain the discrepancy of our results with those of Seyhan et al. is the inclusion of patients with smaller endometriomas in the present study (26 mm vs 37.5 mm) [35]. Finally, in a systematic review, Somigliana et al. reported that the impact of IVF on ovarian endometriomas is mild but also underlined the low quality of the evidence [17].

Similarly, endometrioma growth did not appear to have an impact on the CPR in our study. A study comparing patients with endometriomas (n=85) to patients with simple cysts (n=83) showed a negative effect of endometriosis disease itself on COS response (gonadotropin consumption, number of oocytes retrieved, implantation rate) rather than a negative effect of endometrioma volume [37]. Moreover, in an animal model, Kaplan et al. suggested multifactorial origins with a deleterious effect of endometrioma on ovarian function [38]. This would involve the size of the endometrioma but also the number of endometriotic cysts and the presence of adhesions associated with the cysts [38]. However, there are no data available in the literature on the effect of endometrioma growth on IVF outcomes. On the one hand, the only slight increase in the diameter of the endometriomas (4 mm) after stimulation could explain our result. On the other, the fact that most endometriomas remained smaller than 40 mm (n = 36, 60%) after ovarian stimulation (vs 38 patients with endometrioma smaller than 40 mm before stimulation) could also be an explanation. In this sense, Takashima's study evaluating the impact of endometriomas smaller than 40 mm on IVF results suggested that these endometriomas could be associated with a low ovarian reserve without affecting pregnancy outcomes [39].

The clinical pregnancy rates observed in our study (21.6% in patients with endometrioma growth after ovarian stimulation versus 23.5% in the remaining patients) are consistent with the results usually observed in IVF/ICSI in the presence of endometrioma. A literature review of 11 studies investigating IVF/ICSI in patients with endometrioma found pregnancy rates ranging from 20 to 51.5% [40]. Although the sample size of our population was relatively small, when comparing endometriomas smaller than 30 mm and those measuring between 30 and 60 mm vs endometriomas larger than 60 mm, the AFC and the AMH were found to be comparable. The response to stimulation (gonadotropin dose, number of mature follicles, and number of oocytes retrieved) was also similar. So far, no data in the literature are available on this specific issue. However, a study by Ferrero et al. showed that endometriomas with a diameter greater than 50 mm COS significantly reduced responsiveness to COS (number of dominant follicles and oocytes retrieved) ($p<0.01$), suggesting that the response to stimulation may be poorer for endometriomas larger than 5 cm compared with smaller endometriomas [41]. These data support the CNGOF guidelines recommending expectant management for endometriomas smaller than 6 cm in the context of ICSI/IVF [21].

As previously mentioned, in the current study, AMH level decreased with increasing endometrioma size while AFC was not affected. Our results are in contrast with those of Marcellin et al. which suggested that serum AMH increased with endometrioma size [42]. However, Karadag et al. recently reported decreased AMH levels in patients with endometrioma and a negative correlation between endometrioma size and AMH levels [43]. In a meta-analysis of 17 series, Muzii et al. confirmed that endometrioma was associated with a significant decrease in AMH compared with healthy patients or patients with non-endometriosis benign ovarian cysts [44]. Finally, previous studies underlined that AFC was a better predictive factor of IVF/ICSI results than AMH serum level [45,46].

However, our study has several limitations. First, it is a retrospective study; the fact that we were unable to include all the patients with endometrioma managed at our center, due to a lack of information on endometrioma size before or at the end of stimulation, is a potential bias. Second, the limited number of patients in our study may explain the absence of any significant difference. Third, the stimulation monitoring protocol in our center did not include systematic ultrasound either before the start of treatment or on the first day of stimulation, as is instead described in the Benaglia and Seyhan studies. Thus, the increase, not significant, in the size of the endometriomas could be related in this case to the natural evolution of endometriosis over time and therefore be independent of stimulation. However, Benaglia et al. have shown that time has no negative effect on ovarian response to stimulation in patients with endometrioma at any time interval (less than or greater than 12 months) [47].

Conclusion

Despite some limits of the present retrospective study, our results indicate that ovarian stimulation in infertile patients with endometrioma was associated with an insignificant increase in the diameter of the endometrioma. Moreover, even in the subpopulation with endometrioma growth, endometriomas size does not seem to have an impact on clinical pregnancy rate. This crucial information should reassure patients who need IVF/ICSI.

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