The impact of endometrioma size on ovarian responsiveness.

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ABSTRACT

Research question: Available evidence showed that the presence of ovarian endometriomas do not interfere with ovarian response to hyper-stimulation. However, the mean size of the endometriomas included in these studies is generally small and two recent investigations suggested that follicular development could be conversely impaired when focusing on larger endometriomas. However, these studies could not disentangle a clear threshold above which endometriomas could become detrimental.

Design: To identify this threshold, we retrospectively selected women without a history of surgery for ovarian cysts and who underwent IVF in the presence of unilateral endometriomas with a mean diameter between 20 to 49 mm. Selected women were divided into three endometrioma size categories: 20-29 mm (Group 1, n=23), 30-39 mm (Group 2, n=23) and 40-49 mm (Group 3, n=21). Recruitment for each category was censored at about 21 women to ensure equal statistical power for every group.

Results: The response to hyper-stimulation was equal or superior in the affected gonads in 8 women (35%, 95%CI: 16-57%), 7 women (30%, 95%CI: 13-53%) and 2 women (10%, 95%CI: 2-30%) in group 1, 2 and 3, respectively. The median [interquartile range] number of developed follicles in the affected and intact ovaries was 6 [3-7] and 5 [4-9] in group 1 (p=0.21), 4 [1-6] and 4 [3-7] in group 2 (p=0.08), 5 [3-7] and 7 [4-8] in group 3 (p=0.01), respectively.

Conclusion: The threshold to be used to distinguish between endometriomas that could and could not interfere with ovarian response is 4 cm in diameter.

KEY WORDS: endometrioma / IVF / hyper-stimulation

Introduction

The presence of ovarian endometriomas is not a stringent indication to surgery for infertile women scheduled for IVF (Practice Committee of ASRM, 2012; Dunselman *et al*., 2014; ETIC, 2019). In the past, some experts claimed that the presence of these cysts could hinder IVF, but the observation of the detrimental effects of surgery on the ovarian reserve led the scientific community to change his orientation. Indeed, ovarian response is halved in operated ovaries and, in 13-15% of cases, the ovarian reserve is totally compromised (Somigliana *et al*., 2015). In addition, the conservative approach is supported by the observation that the mere presence of endometriomas does not reduce the response to ovarian hyperstimulation (Somigliana *et al*., 2006; Benaglia *et al*., 2011; Almog *et al*., 2011; Esinler *et al*., 2012; Ashrafi *et al*., 2014; Filippi *et al*., 2014) and by the absence of clear evidence that these cysts could have a negative effect on oocytes quality (Somigliana *et al*., 2015; Sanchez *et al*., 2017; Takashima *et al*., 2017). More in general, there is no evidence that surgery could improve the rate of success of IVF (Brink Laursen *et al*., 2017; Nickkho-Amiry *et al*., 2018).

However, two recent studies re-opened the question (Coccia *et al*., 2014; Ferrero *et al*., 2017). These authors specifically evaluated women with large unilateral endometriomas undergoing IVF and, in contrast to previous evidence on unselected endometriomas, they observed a significant reduction of responsiveness to hyper-stimulation in the affected ovary compared to the contralateral intact one. Specifically, Coccia *et al*. (2014) evaluated 12 women with endometriomas larger than 3 cm and showed that the number of co-dominant follicles was 3.8 ± 2.5 and 4.7 ± 2.6, respectively ($p=0.024$). In the study from Ferrero *et al*. (2017) who focused on 26 women carrying endometriomas larger than 5 cm, the number of follicles was 2.0 ± 1.2 and 4.2 ± 1.7, respectively ($p<0.001$). Taken together, this evidence suggests that the size of the endometrioma may be relevant and that there may be a threshold in cyst diameter above which ovarian responsiveness could be affected. However, a precise threshold cannot be disentangled from the literature because of the small sample sizes of the available series and of the study design (only dichotomous analyses were

done) (Coccia *et al*., 2014; Ferrero *et al*., 2017). In our opinion, the clear definition of a minimum diameter above which endometriomas may be detrimental could be of clinical interest.

To shed more light on this issue, we designed a multicenter study comparing ovarian response during IVF in the affected and contralateral intact gonads in women with unilateral lesions of different and pre-specified sizes. Specifically, we studied three different groups of women carrying endometriomas with a mean diameter of 20-29 mm, 30-39 mm and 40-49 mm.

Materials and methods

Women who underwent IVF at the Infertility Unit of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan and at the Clinica de Reprodución Assistida - IVI of Madrid between January 2014 and December 2018 were retrospectively reviewed. Inclusion criteria were the following: 1) presence of unilateral endometrioma with a mean diameter between 2 and 5 cm, 2) no previous ovarian surgery 3) normal response to ovarian hyper-stimulation in the intact ovary; the arbitrary threshold used to define a normal response was the presence of at least 3 follicles with a mean diameter ≥ 11 at the time of trigger. Exclusion criteria were the following: 1) presence of non endometriotic ovarian cysts (including cases of doubtful endometriomas), 2) presence of multiple endometriomas (multilocular endometriomas could conversely be included), 3) cancelled retrieval for any reason. Women could be included only for one cycle (their fist cycle fulfilling selection criteria). The study was approved by the local Institutional Review Boards. A specific informed consent was not requested since this is a retrospective study.

Women were monitored and treated according to the standards of care of the involved units (Benaglia *et al*., 2017; Pacheco *et al*., 2018). In both centers, the total number of follicles with e mean diameter above ≥ 11 mm was systematically recorded separately for the two ovaries at the

time of ovulation trigger. The presence of ovarian endometriomas was recorded at basal assessment, ie prior to initiate the cycle. They were defined as round-shaped cystic masses with thick walls, regular margins and homogeneous low echogenic fluid content with scattered internal echoes (Savelli, 2009). To rule out functional cysts, the presence of endometriomas had to be documented on at least one previous ultrasound scan performed at least two months before the IVF cycle. Atypical or doubtful cases were excluded. The diameter of the endometriomas used for the analysis was assessed prior to initiate the hyper-stimulation and was calculated as the mean of three perpendicular diameters.

Included cases were divided into three endometrioma size categories: 20-29 mm (Group 1), 30-39 mm (Group 2) and 40-49 mm (group 3). Recruitment was done backwards and stopped once a sufficient number of cases per group was reached. The primary outcome of the study was the total number of developed follicles in the two gonads. The sample size (at least 21 per group) was decided claiming as clinically relevant demonstrating that the response to hyper-stimulation was equal or superior in the affected gonad in less than 30% of cases with a 95% Confidence Interval (95%CI) of this estimate below 20% (so that the inferior limit of the 95%CI would be >50%) (*http://www.openepi.com/SampleSize/SSPropor.htm*). Data analyses were done using the Statistical Package for Social Science (SPSS 23.0, IL, USA). A binomial distribution model was used to calculate the 95%CI of proportions. Baseline characteristics among groups were compared using the ANOVA test, the non-parametric Wilcoxon test for unpaired data and the Fisher Exact test, as appropriate. The number of developed follicles in the two ovaries was reported as median [interquartile range - IQR] and compared using the Mann-Whitney test. A subgroup analysis to evaluate the possible effect of the magnitude of ovarian responsiveness was preplanned. To this aim, groups were dichotomized according to the median number of follicles developed in the intact gonad.

Results

Overall, 67 women were included: 23 in group 1, 23 in group 2 and 21 in group 3. Baseline characteristics of the included subjects are shown in Table 1. No significant differences were found among groups. Table 2 shows IVF outcome. A statistically significant difference emerged for the protocol of ovarian hyper-stimulation (women in group 2 were more frequently prescribed protocols with GnRH agonists) and for the cumulative chances of live birth (lower in group 2).

The response to hyper-stimulation was equal or superior in the affected gonads in 8 women (35%, 95%CI: 16-57%), 7 women (30%, 95%CI: 13-53%) and 2 women (10%, 95%CI: 2-30%) in group 1, 2 and 3, respectively. The median [IQR] number of developed follicles in the affected and intact ovaries was 6 [3-7] and 5 [4-9] in group 1 (p=0.21), 4 [1-6] and 4 [3-7] in group 2 (p=0.08), 5 [3-7] and 7 [4-8] in group 3 (p=0.01), respectively. This result is illustrated in Figure 1.

We also performed intra-patient comparisons according to ovarian responsiveness in the intact gonads. We divided patients of each group in two subgroups of similar magnitude, one with subjects who developed 2 to 6 follicles in the intact gonad and one with subjects who developed more than 6 follicles in the intact gonad. These results are shown in Table 3. A statistically significant difference emerged only in the subgroup of women with larger cysts (40-49 mm) whose intact gonads responded with more than 6 follicles.

Discussion

Based on our results, the size of the endometrioma appears to influence ovarian responsiveness. Specifically, we observed a detrimental effect for cysts with a mean diameter between 40 and 49 mm, suggesting that a threshold of 4 cm could be used to discern between cysts that do and do not affect ovarian responsiveness.

Our study may explain previous inconsistencies of the literature. The observation of an altered response that emerged only in the studies from Coccia *et al.* (2014) and Ferrero *et al.* (2017) is presumably due to the exclusive inclusion of large endometriomas (> 3 cm and > 5 cm, respectively) in these two studies. In the previous available evidences, the mean diameter of the cysts was markedly smaller, varying between 21 and 28 mm (Somigliana *et al.*, 2006; Benaglia *et al.*, 2011; Almog *et al.*, 2011; Esinler *et al.*, 2012; Ashrafi *et al.*, 2014; Filippi *et al.*, 2014). On the other hand, Coccia *et al.* (2014) and Ferrero *et al.* (2017) could not extrapolate a precise threshold to discern between cysts that do and do not influence ovarian response because of the small sample sizes and the dichotomous analyses based on an threshold decided *a priori*. Our study design was more appropriate for this goal and allowed us to disentangle a threshold of 4 cm. Indeed, differences in ovarian response between the two ovaries became statistically significant only in women carrying endometriomas of 40-49 mm. Interestingly, our study also showed that the magnitude of ovarian responsiveness may be important. The detrimental impact may be less relevant for women with reduced ovarian reserve. However, this finding needs to be confirmed in further studies since this emerged from a secondary analysis.

In general, albeit clinically interesting, our data cannot be used to draw therapeutic inferences. In particular, claiming surgery to overcome the detrimental effect on ovarian response of endometriomas larger than 4 cm is not justified. Randomized controlled trials are warranted for reliable recommendations on this point. In this regard, the risk of surgery-mediated damage to ovarian reserve should receive utmost attention. Studies comparing ovarian responsiveness in women operated with the classical stripping technique only on one side showed that ovarian response is halved and, in some cases, ovaries do not display any response (Somigliana *et al.*, 2015). To note, in our study, responsiveness in ovaries carrying endometriomas larger than 4 cm was only modestly reduced (the median number of follicles was 7 compared to 5 in the contralateral gonad). In addition, the total number of oocytes retrieved and the pregnancy rate did not also differ

among the study groups (we even found a statistically significant increase in live birth rate in women carrying the largest endometriomas). In other words, surgery cannot consent a recover of the affected ovary, it can even worsen the situation. There is growing evidence that alternative surgical approaches such as laser vaporization may limit the damage to the ovary but, up to now, definitive conclusions on this issue cannot be drawn (Rehmer *et al*., 2019; Gordts and Campo, 2019). On the other hand, women with endometriomas scheduled for IVF may be operated in certain cases, but this decision should not be taken based on reduced responsiveness. It should be a shared decision with the patient taking into consideration the several pros and cons of surgery and expectant management, highlighting in particular the possible benefits of the intervention in terms of pain relief and prevention of endometrioma infection but, concomitantly, also informing the patient of the general risks of surgery and the possibility of causing a damage to the ovarian reserve (Somigliana *et al*., 2015).

Some limitations of our study should be acknowledged. Firstly, albeit obtained with the concomitant efforts of two independent units, the sample size is relatively small. Unfortunately, the stringent criteria needed to provide valuable information hampered the selection of large series. In fact, we cannot exclude that larger sample sizes could have allowed us to identify a statistically significant difference also for endometriomas with a mean diameter between 30 and 39 mm. In this regard, it has however to be underlined that only marked differences may be of clinical relevance and that the interest of identifying milder differences by extending the sample size is modest. On the other hand, the paired study design and the exclusion of previously operated cases, of poor responders and of women with multiple endometriomas allowed to provide specific information on the pure effect of the endometrioma. To note, this study design also allowed us to overcome possible criticisms related to the inclusion of women from different centres and using different protocols and drugs. Only ovaries of the same woman were indeed compared. They were thus exposed exactly to the same conditions. Secondly, one may argue that a definitive histological

diagnosis of endometriosis is lacking. In our opinion, however, this limitation is of scant relevance. The accuracy of a diagnosis of endometriomas based on ultrasounds is excellent, with sensitivity and specificity being 93% (95%CI: 87-99%) and 96% (95%CI: 92-99%), respectively (Nisenbalt *et al*., 2016). In addition, one has to take into consideration the clinical perspective. This study was designed to provide clinical information to be used in real life situation. Physicians have to take decisions (such as whether or not to operate) based on ultrasound findings, not on histology. Thirdly, studied groups differed in some characteristics. In particular, significant differences emerged for the protocol of hyper-stimulation and for the cumulative chances of live birth. However, given the design of the study (intra-patient comparison of ovarian response), we do not deem this imbalance of high relevance. Fourthly, our study was retrospective and provided information on ovarian responsiveness but we lack data on oocytes quality. Unfortunately, to properly address this concern, one would require a prospective recruitment to allow an independent evaluation of the embryological phases separately for the oocytes obtained from the two ovaries (Ragni *et al*., 2005; Filippi *et al*., 2014; Takashima *et al*., 2017). Given difficulties in selecting women (a collaborative effort was here necessary to achieve a sufficient number of cases), this would require a recruitment phase of several years.

In conclusion, the size of ovarian endometriomas may influence ovarian responsiveness to hyper-stimulation. The threshold to be used to distinguish between cysts that could and could not interfere is 4 cm in diameter. Future research is required to determine whether this information deserves consideration in the decision-making process.

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Table 1. Baseline characteristics of the study groups.

Characteristics	Diameter 20-29 mm	Diameter 30-39 mm	Diameter 40-49 mm	p
Number of cases	23	23	21	-
Age (years)	35.7 ± 4.0	36.3 ± 4.1	35.3 ± 4.3	0.74
BMI (kg/m2)	22.0 ± 2.2	21.1 ± 2.3	21.4 ± 2.0	0.40
Smoking	5 (22%)	3 (13%)	1 (5%)	0.30
Previous deliveries	2 (9%)	2 (9%)	3 (14%)	0.78
Duration of infertility (years)	2 [2-3]	2 [2-4]	3 [1-4]	0.70
Male factor	4 (17%)	5 (22%)	6 (29%)	0.71
Previous surgery for endometriosis [a]	5 (22%)	4 (17%)	3 (14%)	0.85
Previous IVF cycles	7 (31%)	7 (31%)	7 (29%)	1.00
Mean cycle lenght (days)	28 [27-29]	28 [25-28]	28 [27-28]	0.32
Day 3 serum FSH (IU/L)	6.4 [5.5-10.1]	6.9 [5.7-8]	7.4 [5.4-8.2]	0.99
AMH (ng/ml)	1.5 [1.2-2.7]	1.9 [1.0-3.8]	2.6 [1.6-3.5]	0.40
Total AFC	10 [5-16]	8 [5-13]	9 [6-12]	0.76

[a] Only women who were previously operated for non-ovarian endometriosis could be included. Surgery for endometriomas was an exclusion criterion.

Data is presented as Mean ± SD or Median [interquartile range] or number (%) and compared using ANOVA, non-parametric Kruskal-Wallis test or Fisher Exact test, respectively.

Table 2. Characteristics of the IVF cycles in the study groups.

Characteristics	Diameter 20-29 mm	Diameter 30-39 mm	Diameter 40-49 mm	p
Number of cases	23	23	21	-
Protocol of hyper-stimulation				0.05
GnRH agonists	2 (9%)	9 (39%)	4 (19%)	
GnRH antagonist	21 (91%)	14 (61%)	17 (81%)	
Duration of stimulation (days)	10.7 ± 2.5	9.8 ± 1.7	10.5 ± 2.1	0.35
Total dose of gonadotropins (IU)	1650 [1400-2475]	1800 [1462-2362]	1800 [1425-2012]	0.85
Serum estrogens at trigger (pg/ml)	2064 [1536-3038]	1680 [1172-3654]	1771 [1080-2760]	0.72
N. oocytes retrieved	8 [4-11]	6 [4-9]	8 [6-12]	0.22
N. suitable oocytes [a]	6 [4-10]	6 [2-7]	7 [5-10]	0.09
Fertilization rate (%)	75 [65-100]	75 [65-100]	67 [53-78]	0.15
Cumulative pregnancy rate [b]	12 (52%)	8 (35%)	13 (62%)	0.21
Cumulative live birth rate [b]	11 (48%)	5 (22%)	12 (57%)	0.03

Data is presented as Mean ± SD or Median [interquartile range] or number (%) and compared using ANOVA, non-parametric Kruskal-Wallis test or Fisher Exact test, respectively.

[a] Suitable oocytes refer to metaphase II oocytes and type 1 cumulus-oocyte complex according to the European Society for Human Reproduction and Embryology Istanbul Consensus Conference (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011).

[b] Refers to the cumulative chances of pregnancy using all the oocytes obtained in the index cycle (thus considering both fresh and frozen transfers).

Table 3. Intrapatient comparisons according to ovarian responsiveness

Endometriomas' diameter	Developed follicles 2-6				Developed follicles >6			
	N	Affected	Intact	p	N	Affected	Intact	p
20-29 mm	12	4 [3-6]	4 [3-4]	0.59	11	7 [5-8]	9 [7-11]	0.06
30-39 mm	14	2 [1-4]	4 [3-4]	0.19	9	6 [3-9]	9 [7-10]	0.26
40-49 mm	8	3 [2-5]	4 [3-4]	0.49	13	6 [3-7]	8 [7-10]	0.01

Subjects were divided according to ovarian responsiveness in the intact gonad (2-6 vs >6 follicles)
Data is presented as Median [interquartile range] and compared using the paired Wilcoxon test.

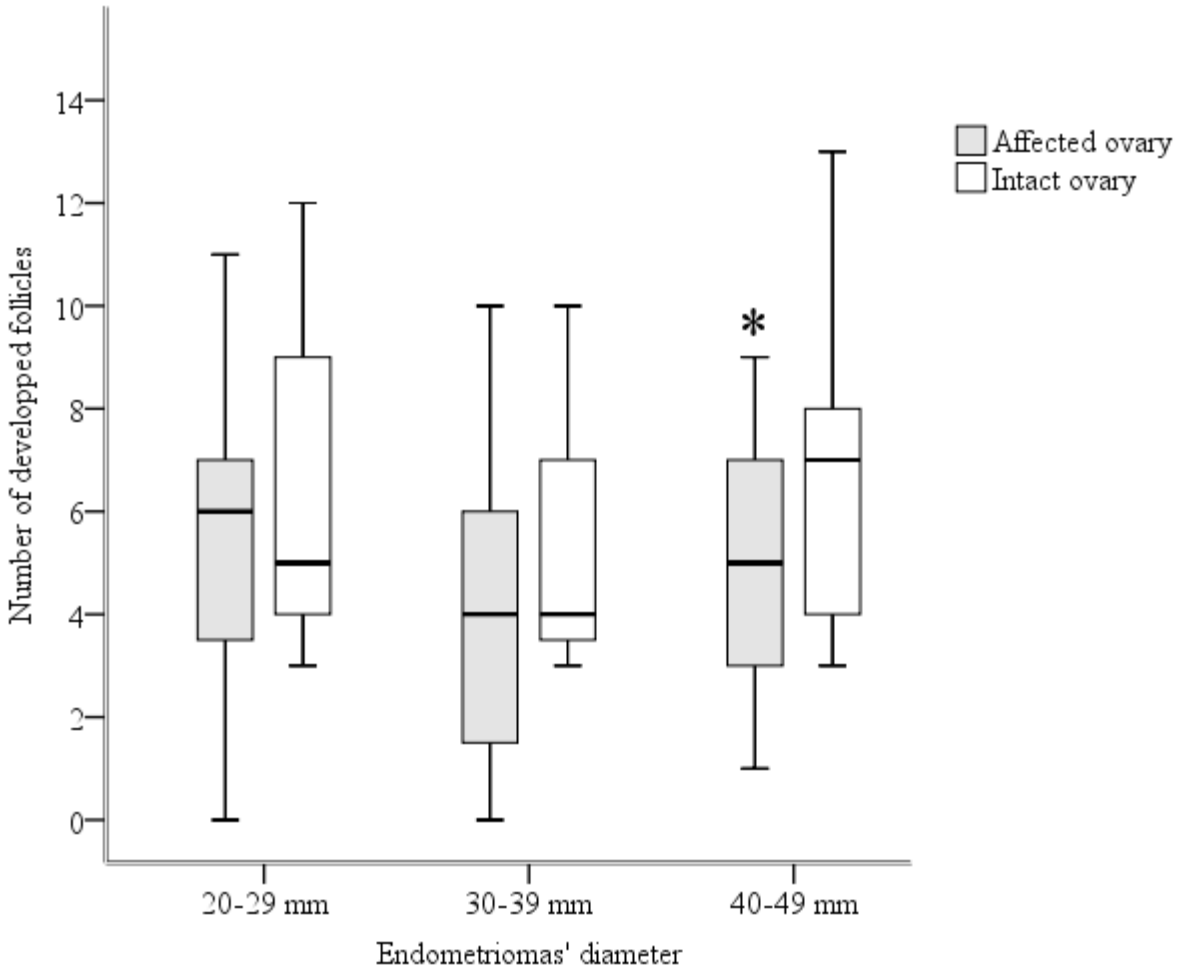

Figure 1: Ovarian responsiveness in the affected and contralateral intact gonads according to the size of the endometrioma. A statistically significant difference (*) emerged only for endometriomas with a mean diameter between 40 and 49 mm