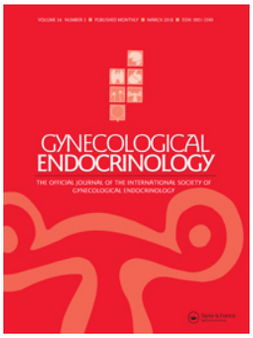

Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: http://www.tandfonline.com/loi/igye20

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To cite this article: Isil Kasapoglu, Göktan Kuspinar, Seda Saribal, Pinar Turk, Berrin Avcı & Gürkan Uncu (2018) Detrimental effects of endometriosis on oocyte morphology in intracytoplasmic sperm injection cycles: a retrospective cohort study, Gynecological Endocrinology, 34:3, 206-211, DOI: 10.1080/09513590.2017.1391203

To link to this article: https://doi.org/10.1080/09513590.2017.1391203

Published online: 23 Oct 2017.

GYNECOLOGICAL ENDOCRINOLOGY, 2018
VOL. 34, NO. 3, 206–211
https://doi.org/10.1080/09513590.2017.1391203

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ENDOMETRIOSIS EFFECTS ON OOCYTE MORPHOLOGY

Detrimental effects of endometriosis on oocyte morphology in intracytoplasmic sperm injection cycles: a retrospective cohort study

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ABSTRACT

While an association can be addressed among endometriosis and subfertility, the causal relationship has not been elucidated yet. Impaired oocyte quality in endometriosis patients has been accused for the unsuccessful outcomes of assisted reproductive techniques. There are limited studies in literature evaluated association between endometriosis and oocyte morphology. We conducted this retrospective study to evaluate whether morphological abnormalities of oocytes are more common in women with endometriosis than women with diagnosis of male factor infertility as a source of healthy oocytes. Totally 1568 oocytes, 775 (49.4%) in endometriosis groups and 793 (50.6%) in control group were evaluated for morphological parameters before ICSI cycles. Abnormal oocyte morphology was detected in 352 (22.4%) of 1568 oocytes. Of the abnormal oocytes, 208 (59.1%) were in endometriosis group and 144 (40.9%) in control group ($p < .001$). The following dysmorphisms were significantly higher in oocytes retrieved from endometriosis group: dark cytoplasm; dark, large or thin zona pellucida; and flat or fragmented polar body ($p < .05$ for all). When morphological parameters for oocytes of endometriosis patients evaluated, the oocyte defects has increased significantly in endometriosis patients. These findings are thought to be useful to clarify the subfertility in endometriosis patient, which needs to be confirmed with further studies.

ARTICLE HISTORY
Received 28 January 2017
Revised 28 August 2017
Accepted 9 October 2017
Published online 18 October 2017

KEYWORDS
Endometriosis; oocyte morphology; infertility; intracytoplasmic sperm injection

Introduction

Endometriosis is characterized by the presence of endometrial tissue outside the uterine cavity. It is encountered in 6–15% of fertile and 35–50% of subfertile women [1]. Additionally, 30–50% of women with endometriosis deal with infertility [2]. Although there is an association between endometriosis and subfertility, the exact causal relationship has not been elucidated yet [3,4]. Distorted pelvic anatomy has been suggested to be the cause of subfertility in cases with severe endometriosis [2]. On the other hand, immunological defects, poor oocyte and embryo quality has been accused for early stages [5,6].

Assisted reproductive techniques (ART) represent most efficient means of overcoming infertility caused by endometriosis [7–9]. However, in many studies, it was suggested that endometriosis-related infertility is associated with lower outcome of ART compared to unexplained or tubal factor infertility [10,11]. Also lower implantation and pregnancy rates have been reported in endometriosis [12,13]. Although these findings have been supported by a meta-analysis [14], more recently meta-analyses on IVF outcomes in endometriosis indicates that live birth rates were not altered in patients with minimal/mild endometriosis, whereas moderate and severe endometriosis patients had poorer outcomes including lower retrieved oocytes, implantation rates and birth rates [15]. When retrieved oocyte number considered as ovarian response to controlled ovarian stimulation (COS) and as a success parameter, data in the literature are more conflicting. While some studies reported similar numbers of oocytes being collected from ovaries containing endometriomas and without endometriomas [16,17], Somigliana et al. reported decreased co-dominant follicles in ovaries with endometriomas [18]. Also, in a recent meta-analysis, it was concluded that endometriosis patients had less retrieved total and mature oocytes than controls [19].

Despite the failure to demonstrate a causal relationship between endometriosis and infertility, there seems to be an association. Impaired oocyte quality in endometriosis patients also has been accused for the unsuccessful outcomes [20,21]. Assessment of oocyte morphology is obligatory for the evaluation of oocyte quality and it has been known that quality of the oocyte has an impact on the fertilization outcomes [22]. Oocyte quality is determined by its morphological, cellular, and molecular evaluations [23]. However, there are limited studies on the association between endometriosis and oocyte morphology [24]. No comprehensive assessment have so far been performed about the aforementioned issue.

Thus, in this study, we aimed to evaluate the morphological abnormalities and fertilization outcomes of oocytes retrieved from patients with endometriosis in ICSI cycles in comparison to those from women with male factor infertility.

Materials and methods

This was a retrospective cohort study, conducted between August 2015–2016, at a tertiary care hospital.

Endometriosis group consisted of 72 women (mean age, 30.9 ± 3.9 years) with diagnosis of endometriosis, who underwent ICSI cycles. Endometriosis was diagnosed either with laparoscopy or presence of endometriomas in ultrasonographic examination. The partners of women in endometriosis group had normal

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sperm parameters according to the World Health Organization criterias, 2010 [25]. Sixty, age-matched women (mean age, 29.8 ± 3.9 years) who underwent ICSI cycles due to male factors including abnormal sperm parameters constituted the control group.

Recombinant gonadotrophins were administered for controlled ovarian stimulation (COS). When the leading follicle reached to 18 mm diameter, ovulation was triggered by using recombinant human chorionic gonadotropin (hCG) or gonadotropin-releasing hormone (GnRH) agonist. Oocyte retrieval was performed 36 h after hCG or agonist administration. Oocytes were collected transvaginally.

Cumulus–oocyte complexes were exposed to 80 IU/mL hyaluronidase in order to facilitate mechanical removal of the cumulus cells and evaluating of oocyte morphology. Prior to injection, mature oocytes were screened for morphological anomalies.

All oocytes were evaluated morphologically by an inverted microscope with ×200 magnification, by one experienced embriologist. Cytoplasmic morphology was evaluated for the presence or absence of granularity, coloration, inclusion and clustering. Also polar body morphology was assessed for shape, size, surface and integrity. The perivitelline space and zona pellucida was also evaluated for size and texture. Oocyte was considered as abnormal if any of these dysmorphologies were shown. Only metaphase II oocytes were prepared for the ICSI procedure.

Also ovarian response to COS was evaluated between two groups. Ovarian response to COS was assessed by the number of retrieved total oocytes and mature metaphase II (MII) oocytes per patient for both groups.

The study protocol was approved by Local Institutional Ethics Committee. (2016–19/20)

Statistical analysis

Study data were summarized using descriptive statistics (mean ± standard deviation for continuous variables, percentage for categorical variables). For continuous variables, independent sample *t*-test (Student's *t*-test) or Mann–Whitney U-test was used for intergroup comparisons of normally or non-normally distributed variables, respectively. Fisher's exact test was used for the comparisons of categorical variables. For the correlations of non-normally distributed variables analyses, Spearman's Rho test was performed. The chi-squared test was used to compare categorical data. Linear regression analysis (enter method) controlling for identifying factor associated with the rate of abnormal oocyte number and between parameters of ovarian response to COS were also performed. All the analysis was performed by the SPSS software package for Windows (Statistical Package for Social Sciences, version 23.0, SPSS Inc., Chicago, IL). A two-tailed $p < .05$ was considered statistically significant.

Results

Demographic and clinical characteristics were summarized in Table 1. Endometriosis patients had significantly lower body mass index (22.9 kg/m^2 vs. 24.9 kg/m^2) and infertility duration than those in control group ($p = .005$ and $p < .001$, respectively). Additionally, initial luteinizing hormone and estradiol levels were significantly higher when anti-mullerian hormone levels were lower in endometriosis group ($p = .022$, $p = .005$, and $p = .007$). Progesterone levels on hCG-day was also significantly higher in endometriosis group ($p = .046$). In terms of ovulation induction, higher total gonadotropin doses administered to endometirosis patients ($p = .005$) (Table 1).

The number of total oocytes retrieved per patient was significantly lower in endometriosis group (median 10.5 vs. 12.5, p=.035). Also number of metaphase-II oocytes retrieved per patient was significantly lower in endometriosis group (median 10 vs. 6, p=.001) (Table 2).

A total of 775 (49.4%) in endometriosis and 793 (50.6%) in control group, totally 1568 oocytes were morphologically evaluated. (Table 2). Abnormal oocyte morphology was detected in 352 (22.4%) of 1568 oocytes. Of the abnormal oocytes, 208 were in endometriosis group and 144 in control group, which was

Table 1. Baseline clinical characteristics of patients before ICSI cycles in control and endometriosis groups.

		Control group (male factor infertility)	Endometriosis group	Total	*p*
Number of patients		60	72	132	
Age (years)		29.8 ± 3.9 (23–41)	30.9 ± 3.9 (20–39)	30.4 ± 3.9 (20–41)	.114[a]
Body mass index (kg/m^2)		24.9 ± 4.5 (16.8-40.2)	22.9 ± 3.7 (16.3–32.5)	23.8 ± 4.2 (16.3–40.2)	.005[a]
Duration of infertility (years)		7.5 (2–19)	4 (1–22)	5 (1–22)	<.001[b]
Initial hormones	FSH (mIU/mL)	5.6 (2.1–16.0)	6.0 (3–19.6)	5.8 (2.1–19.6)	.078[a]
	LH (mIU/mL)	4.1 (1.2–19.0)	4.6 (0.7–9.7)	4.3 (0.7–19.0)	.022[a]
	E_2 (pg/mL)	34.05 (14.0–286.0)	50.0 (3.0–396.0)	42.0 (3.0–396.0)	.005[a]
	AMH (ng/ml)	3.09 (0.13–8.03)	2.10 (0.01–10.10)	2.86 (0.01–10.10)	.007[a]
E_2 and P on hCG-day	E_2 (pg/ml)	1377.0 (161–3350), ($n = 51$)	1543.0 (90–9720), ($n = 51$)	1423.5 (90–9720)	.563[a]
	P (ng/ml)	0.40 (0.10–2.20), ($n = 45$)	0.70 (0.10–2.60), ($n = 49$)	0.50 (0.10–2.60)	.046[a]
Regimen of ovulation induction	Long agonist protocol	2 (3.3%)	10 (14.1%)	12 (9.2%)	
	Flexible antagonist	0 (0.0%)	3 (4.2%)	3 (2.3%)	
	Fixed antagonist	57 (95.0%)	28 (39.4%)	85 (64.9%)	
	Ultralong protocol	0 (0.0%)	29 (40.8%)	29 (22.1%)	
	Aramotase Inhibitor/ antagonist	1 (1.7%)	1 (1.4%)	2 (1.5%)	
Ovulation induction drug	rhCG	56 (93.3%)	71 (100%)	127 (96.9%)	.042[b]
	GnRH agonist + rhCG	4 (6.7%)	0 (0.0%)	4 (3.1%)	
Total gonadotropin dose (U)		2250 (1000–6750)	2475 (1050–4875)	2400 (1000–6750)	.005[a]
Cycle length (days)		10.5 (5–16)	10.0 (6–14)	10.0 (5–16)	.301[a]

[a]Mann–Whitney U-test.
[b]Fisher's exact test.
AMH: anti-mullerian hormone; E_2: estradiol; FSH: follicle-stimulating hormone; LH: luteinizing hormone; P: progesterone; rhCG: recombinant human chorionic gonadotropin.
Data are given as mean ± standard deviation (min–max), median (min–max), or *n* (%).

significantly higher in endometriosis group (59.1% vs. 40.9%, $p < .001$; Table 2). Meiotic maturation rates were comparable for both groups ($p = .708$; Table 2). In a multiple linear regression analyses, number of abnormal oocytes was not associated with patient age ($\beta = -0.082$, $p = .948$), BMI ($\beta = -0.066$, $p = .482$) or the total gonadotrophin dose ($\beta = -0.006$, $p = .065$) for all patients. However, abnormality of the oocytes was positively associated with increasing ovarian response to COS overall ($\beta = 0.454$, $p < .001$). Association between progesterone levels on the hCG day and number of abnormal oocytes were also positively correlated ($r = 0.334$, $p = .004$).

On the other hand, fertilization rate was significantly higher in endometriosis group compared to male factor infertility group (71% vs. 61%, $p = .030$; Table 2). Subgroup analysis of fertilization rates in endometriosis patients did not differ when patients evaluated respectively with abnormal oocytes or without (75.5% vs. %70, $p = .149$) . Also there were no correlation between abnormal oocyte rates and fertilization rates of the patients with abnormal oocyte in endometriosis group ($r = 0.042$, $p = .968$).

The following particular morphologic abnormalities of oocytes, were more common in endometriosis group oocytes: dark cytoplasm, dark, large or thin zona pellucida and flat or fragmented polar body ($p < .05$ for all). However, granules or rough endoplasmic reticulum in cytoplasm and granules in perivitelline space were more commonly recorded in control group ($p < .05$ for all) (Table 3).

Discussion

Although the exact mechanism of endometriosis-associated infertility remains largely unknown, increasing evidence shows that decreased oocyte quality is a key factor [26,27]. Clinically we realized that oocytes of endometriosis patients mostly had morphological abnormalities. With this study, we aimed to contribute to the literature, on morphological abnormalities of oocytes for endometriosis in comparison to those from women with male factor infertility as considered healthy oocytes source. Our findings indicated that abnormal oocyte morphology is more prevalent in patients with endometriosis group, indicating detrimental effect of endometriosis on oocyte quality.

Although recent publications do not clearly indicate predictive value of morphological features for ART outcomes [21], it is a common practice to evaluate the morphology of oocytes before ART procedures and select those with no abnormalities. In a systematic review of 92 studies of different morphological parameters, 57 showed a significant correlation between oocyte morphology and outcome of ART, whereas in 35 no predictive value of the microscopic feature was found [21]. For the assessment, the common sites of investigation include meiotic spindle, zona pellucida, vacuoles or refractile bodies, polar body shape, oocyte shape, cytoplasm and perivitelline space [21]. Therefore, in our study, we included the oocytes evaluated for the cytoplasm, polar body, perivitelline space and zona pellucida of all oocytes. It is important to note that in contrary to previous

Table 2. The numbers of total and abnormal oocytes and fertilization rate in control and endometriosis groups.

	Control group (male infertility)	Endometriosis group	Total	*p* value
Number of retrieved oocytes	793 (50.6%)	775 (49.4%)	1568	
Number of oocytes per patient	12.5 (1–30)	10.5 (2–29)	11.0 (1–30)	.035[b]
Number of MII oocytes per patient	10 (1–18)	6 (1–26)		.001[b]
Abnormal oocyte/total abnormal oocyte	144/352 (40.9%)	208/352 (59.1%)		<.001[a]
Number of MII oocytes /Total retrieved oocytes (Meiotic maturation rates)	605 (76.3%)	585 (75.5%)		.708[c]
Fertilization Rates	61 (0.0–100)	71 (0.0–100)		.030[b]

[a]Fisher's Exact test.
[b]Mann–Whitney U-test.
[c]Chi-square tests.
Data are given as median (min–max) or *n* (%).

Table 3. Dysmorphic characteristics of cytoplasm, zona pellucida, perivitelline space and polar body of oocytes retrieved from women in control versus endometriosis groups.

	Control group (male factor infertility) ($n = 144$ oocytes)	Endometriosis group ($n = 208$ oocytes)	Total ($n = 352$ oocytes)	p^a
Central granularization	19 (13.2%)	39 (18.8%)	58 (16.5%)	.190
Granular cytoplasm	19 (13.2%)	5 (3.0%)	24 (7.7%	.001
Refractile bodies in cytoplasm	10 (6.9%)	8 (3.8%)	18 (5.1%)	.147
RER clusters in cytoplasm	11 (7.6%)	5 (2.4%)	16 (4.5%)	.021
Dark cytoplasm	0 (0.0%)	15 (7.2%)	15 (4.3%)	<.001
Vacuolar cytoplasm	4 (2.8%)	1 (0.5%)	5 (1.4%)	.093
Large zona pellucida	3 (2.1%)	27 (13.0%)	30 (8.5%)	<.001
Dark zona pellucida	4 (2.8%)	29 (13.9%)	33 (9.4%)	<.001
Birefringent zona pellucida	2 (1.4%)	10 (4.8%)	12 (3.4%)	.071
Irregular zona pellucida	1 (0.7%)	4 (1.9%)	5 (1.4%)	.320
Thin zona pellucida	0 (0.0%)	8 (3.8%)	8 (2.3%)	.014
Large perivitelline space	15 (10.4%)	18 (8.7%)	33 (9.4%)	.352
Granular perivitelline space	18 (12.5%)	14 (6.7%)	32 (9.1%)	.049
Small polar body	22 (15.3%)	33 (15.9%)	55 (15.6%)	.503
Large polar body	2 (1.4%)	6 (2.9%)	8 (2.3%)	.294
Flat polar body	0 (0.0%)	8 (3.8%)	8 (2.3%)	.014
Fragmented polar body	36 (25.0%)	71 (34.1%)	107 (30.4%)	.043
Irregular polar body	5 (3.5%)	17 (8.2%)	22 (6.3%)	.055
Dark polar body	3 (2.1%)	1 (0.5%)	4 (1.1%)	.189

[a]Fisher's Exact test.
RER: rough endoplasmic reticulum.

studies in which control group consisted of women with reduced ovarian reserve, tubal factor infertility or obesity that may also affect the oocyte morphology [26,28–31], we chose the women with male factor infertility as a control group for the absence of any known factors affecting the oocyte.

The common abnormalities of oocytes from women with endometriosis include brownish oocytes, dark and granular cytoplasm, presence of refractile bodies, impaired mitochondrial structure, incomplete extrusion or division of the first polar body, cortical granule loss, spindle disruption and higher zona pellucida dissolution timing [26,28–31]. Similarly, we particularly detected dark cytoplasm; dark, large or thin zona pellucida; and flat or fragmented polar body in cases with endometriosis.

The main finding of our study was that percentage of abnormal oocytes was significantly higher in endometriosis group. This finding was in line with the previous studies [30] recently reported lower mature and morphologically normal ooctyes in patients with endometriosis. They also reported that worsening of oocyte quality is proportional to the severity of endometriosis [31]. Borges et al. [24] evaluated oocyte morphology in 431 ICSI cycles in women with endometriosis in comparison to 2510 ICSI cycles for other infertilities. They retrieved lower number of oocytes from patients with endometriosis with increased incidence of extra-cytoplasmic, but not intra-cytoplasmic oocyte defects. Similarly, we retrieved less number of total oocytes and MII oocytes per patient as parameters of ovarian response to COS in endometriosis group compared to control group (respectively, median 10.5 vs. 12.5, $p = .035$ and median 10 vs. 6 $p = .001$). In a recent review that evaluated endometriosis and ART outcomes, concluded that patients with endometriosis have a lower mean number of oocyte retrieved per cycle [32].

Our results also showed that anti-Mullerian hormone levels, as universally accepted an indicator of ovarian reserve, was lower in endometriosis group than controls parallelly to our previous prospective study that indicates endometriosis related reduced ovarian reserve [33]. However, ovarian stimulation protocol cycle durations between two groups has no significant differences ($p = .301$), total gonadotrophin dose were higher in endometriosis group than controls ($p = .005$). This may explain with differences of ovarian response and reserve between endometriosis and control groups.

Although some studies suggested that ovarian endometriomas does not affect the treatment outcomes, some reported adverse ART outcomes by oocyte quality in women with endometriosis independent of the location of endometriosis. We recorded higher fertilization rate in endometriosis compared to control group (71% vs. 61%, $p = .022$). This finding was in contrary to the previous studies reporting no significant difference in pregnancy rate between endometriosis-related fertility and other fertilities after ART cycles [30,31]. However, our control group was male factor related infertility patient so poor sperm quality has obviously negative affected fertilization rate. Considering to endometriosis caused alteration of endometrial milieu, comparison of the clinical outcome between groups was not convenient with regard to evaluation of oocyte morphology. On the other side, fertilization rate was affected from oocyte morphology and infertility etiology, but determination of exact affect could be only demonstrated with molecular studies.

Also cumulative effect of multiple abnormal criteria all together on fertility outcomes has been investigated only with restricted numbers of studies. When fertilization rates taken into consideration, the commonly used morphological parameters seems to be failed for the prediction of the fertilization [21]. There has been no concurrence for the effects of the parameters that defined as abnormal on fertilization outcomes. We also found comparable fertilization rates between endometriosis patients that had totally evaluated as normal oocytes per cycle and patients who had abnormal oocytes. Also, in the endometriosis patients, we did not found a correlation between abnormal oocyte rate and fertilization rates.

Besides the exact predictive value of morphological features of the oocytes for ART outcome steps, also altered spindle cell complex of the oocytes retrieved from patients with endometriosis which have been shown [34,35] has being questioned for poor outcomes. These spindle cell complex alterations have been accused for meiotic errors and chromosomal instability [36] which could be related with subsequent aneuploidy risk. In an illustrated murine animal model it has been observed that peritoneal fluid obtained from patients with endometriosis caused microtubule damage in the animal oocytes. Subsequent oocyte anomalies and apoptosis of embryos were followed up also [20]. Also, in another animal study, similar findings were reported with bovine oocytes underwent *in vitro* maturation in the follicular fluid of patients with endometriosis [37]. Recently, a study relevantly evaluated the risk of aneuploidy in patients with endometriosis, found out contrary to the previous animal studies, women with endometriosis undergoing IVF have equivalent aneuploidy rates to their age-matched control group. In this study, oocytes retrieved per patient as an ovarian response criteria to COS, was significantly lower in the endometriosis group, as similar to our findings. Although the fertilization rates were also significantly lower in the endometriosis group in this study, it was concluded that as the end point, usable embryos were equivalent for both groups [38]. Our maturation rates of the oocytes were not significantly different between groups. Also fertilization rates were not altered negatively from the abnormality of the oocytes within endometriosis patients. Abnormality of the oocytes do not directly measure a clinical outcome, and these findings indicates that it is likely that patients with endometriosis could include multiple pathologic mechanisms to explain poor treatment outcomes as an important gap in knowledge.

Elevated progesterone levels on the day of hCG, also accused for negative treatment outcomes. Despite effect of elevated progesterone on the endometrium, knowledge for the relationship for progesterone and oocyte quality is restricted. Different ranges from 0.8 to 2.0 ng/ml have been used as the cutoff value for progesterone levels. Novel studies suggests that 1.5 ng/ml is the threshold value for endometrial influence [39]. In a meta-analysis, it is claimed that higher progesterone levels are correlated with lower clinical pregnancy rates [40]. Some studies evaluated early progesterone increases, suggest a deleterious effect on the endometrium but not on oocyte or embriyo quality [41,42]. On the contrary, we found a significant correlation between increased progesterone levels on the hCG day and number of abnormal oocytes ($p = .004$). Significantly higher progesterone levels on hCG day in endometriosis group may have contributed adversely to the oocyte morphology.

Ovarian response to COS and COS are also known as the most significant factors that impacts oocyte quality [43,44]. Using higher doses including ovarian stimulation protocols to increase number of retrieved oocytes, may cause dysmorphism of the oocytes [45]. Our results also showed significant association between parameters of ovarian response to COS and abnormality of the retrieved oocytes, independent from the gonadotrophin doses used for both groups. Although retrieval of lower oocytes per patient in the endometriosis group, abnormal oocytes were

more prevalent in the endometriosis group, indicating endometriosis related deterioration as well as linked to COS.

The main limitation of our study was its retrospective design, which precludes us from reaching a more definitive conclusion on the relation between oocyte morphology of endometriosis and fertility outcomes. Additionally, we could not evaluate outcomes such as implantation and pregnancy rates, which may be affected by many clinical variables including sperm-related factors in control group. However, there are limited studies in literature on oocyte morphology in endometriosis, and our findings are thought to contribute to these studies.

In conclusion, the abnormal oocyte morphology is more common in endometriosis patients than those with male factor infertility. Thus, endometriosis may cause subfertility, and adversely affect outcomes of ART by its detrimental effects on oocyte morphology which needs to be confirmed with further large-scale studies.

Disclosure of interest

Authors declared no conflicts of interests.

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