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Treatment of endometrioma for improving fertility

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ABSTRACT

Endometrioma is a frequent clinical manifestation of endometriosis. It is controversial how endometriomas may affect women's fertility. This review addresses: the impact of the endometrioma *per se* and of its surgical treatment on ovarian physiology, on the ovarian reserve, on spontaneous conception and pregnancy outcomes, and on IVF/ICSI outcomes.

Based on current evidence, although there are plausible biological detrimental effects on the ovarian cortex surrounding the endometrioma and an impairment of the normal ovarian physiology, the clinical impact of the endometrioma *per se* is not significantly altered. There is a negligible detrimental effect on ovarian reserve with spontaneous ovulation not being impaired. Conversely, surgical excision of an endometrioma reduces ovarian reserve as measured by AMH levels. Studies investigating the impact of the endometrioma *per se* and of its surgical treatment in women requiring IVF/ICSI show similar implantation rates, clinical pregnancy rates and live birth rates between women with endometrioma and controls.

Introduction

Q3 Ovarian endometriotic cyst is a clinical manifestation of endometriosis that affects 17–44% of women suffering of this disease [1–3]. The pathogenesis of endometrioma is controversial and three main theories have been proposed to explain its origin: invagination of ovarian cortex secondary to bleeding of superficial implants [4,5], invagination of the ovarian cortex secondary to metaplasia of coelomic epithelium in cortical inclusion cysts [6] and endometriotic transformation of functional cysts [7]. The effect of the endometrioma on women's fertility is still debated and controversial.

The aims of this review are: (I) to describe the impact of the endometrioma *per se* on ovarian physiology; (II) to elucidate the impact of the endometrioma *per se* and of its surgical treatment on the ovarian reserve; (III) to determine the impact of the endometrioma *per se* and of its surgical treatment on spontaneous conception and pregnancy outcomes; (IV) to assess the impact of the endometrioma *per se* and of its surgical treatment on IVF/ICSI outcomes.

The impact of endometrioma *per se* on ovarian physiology

There is growing evidence focused on assessing the potential detrimental effect of endometrioma on ovarian physiology. A systematic review by Sanchez and colleagues suggests that the presence of an endometrioma causes ovarian damage independently from its size [8] by mechanical stretching [9]. In fact the detrimental effect induced by the endometrioma is supported by the demonstration of a plethora of morphological and functional features that make the affected ovary different from the healthy one [10].

The first explanation to support the impairment of the normal ovarian function by the endometrioma *per se* derives from the content of the cyst that represents a potential source of 'toxicity' for the surrounding healthy tissue. Firstly, endometriotic cysts contain high levels of cellular damage-mediating factors, proteolytic enzymes, inflammatory molecules, reactive oxygen species (ROS) and iron [11–13]. The fluid content causes critical alterations to the endometriotic surrounding cells, including modifications in the expression of critical genes and genetic changes potentially initiating tumorigenesis [13,14]. Secondly, there are higher levels

Q2 * Corresponding author at: Unit of Obstetrics and Gynaecology, IRCCS AOU San Martino – IST, Largo R. Benzi 10, 16132 Genoa, Italy. Tel.: +39 010 511525; fax: +39 010 511525; mobile: +39 3477211682.
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of oxidative stress in the healthy ovarian cortex surrounding an endometrioma compared to other benign cysts [15]. A higher amount of ROS may promote a fibrogenic response together with transforming growth factor (TGF)-β and plasminogen activator inhibitor (PAI)-1 characterized by the expansion of mesenchymal elements, synthesis of collagen and fibronectin [16–18], and collagen matrix remodelling [19]. Alterations of the oxidative stress metabolism have been associated with a detrimental effect on oocyte and embryo development, and pregnancy outcome [20–22]. Moreover, the oxidative stress imbalance has been also identified as a potential cause of oocyte apoptosis and necrosis in early follicles [23]. The relationship between the ovarian follicle and the endometrioma allows the understanding of the impact of an endometrioma on healthy ovarian tissue. Maneschi et al. investigated the functional morphologic features of the ovarian cortex surrounding benign cysts. It showed that the ovarian cortex is not morphologically impaired in the presence of teratomas or benign cystadenomas, whereas, microscopic stromal implants and decreased follicular number and activity were related to the presence of endometriomas. Other have showed that the follicular density was lower in ovarian biopsies from the healthy ovarian tissue surrounding endometriomas in comparison with non-endometriomas [24] and that the ovarian tissue inadvertently stripped during laparoscopic surgery had different morphologic characteristics in case of endometriotic cysts compared with other benign cysts [25,26]. Indeed, normal ovarian tissue was more frequently present in specimens after endometrioma excision (54%) *versus* non-endometriosis cysts (6%) [25]. Furthermore, regular vascular network was much less frequent in the ovarian tissue surrounding the endometrioma in comparison with other ovarian cysts, as well as the overall follicular maturation up to the antral stage [9]. Inhibition of ovarian angiogenesis and capillary loss are mediated directly by the high levels of ROS and indirectly by the cellular injury that in turn triggers over-expression of factors affecting the vascular system, such as thrombospondin (TSP)-1, a negative angiogenic regulator [10]. Qiu et al. showed that endometriotic cysts are associated with decreased microvessel density and higher levels of TSP-1, which reflected ovarian interstitial microvascular injury and a decrease in blood perfusion [27].

The impact of the endometrioma *per se* and of its surgical treatment on the ovarian reserve

There has been a significant research interest on the impact of an endometrioma *per se* and its surgical removal on ovarian reserve.

The impact of the endometrioma per se *on the ovarian reserve*

The antral follicle count (AFC) has been largely used in research studies to estimate the ovarian reserve of women undergoing surgery for endometrioma. Two studies with unilateral endometrioma have studied the preoperative assessment of both the healthy and affected ovary ([28,29]; Table 1). The pooled analysis of preoperative AFC show that the mean AFC for the ovary with the endometrioma was lower than the contralateral one (mean difference −2.79, 95% confidence interval [CI] −7.10 to 1.51), but statistical significance was not reached ($p = 0.20$) [30]. Several studies have reported on serum anti-Müllerian hormone (AMH) in patients with unoperated ovarian endometriomas to assess the impact of the endometrioma on ovarian reserve ([31–34]; Table 2). In a Taiwanese retrospective study 141 women with endometrioma were compared with 1323 infertility patients without endometrioma which showed that the mean AMH concentration in control group was significantly higher than in the endometrioma group [31]. Jim et al. conducted a retrospective case–control study including 102 women with endometrioma *versus* 102 body mass index (BMI)-matched controls. Serum AMH and the multiples of the median for AMH (AMH-MoM) were lower in endometrioma cases than in controls, but this was not statistically significant. In addition, women with stage IV endometriosis had lower serum AMH and AMH-MoM compared with controls [32]. A Turkish prospective study included 30 women with endometrioma >2 cm with 30 age-matched healthy women without ovarian cysts with the primary objective of evaluating the ovarian reserve before (cases *versus* controls) and after surgery (cases at baseline *versus* cases at 1- and 6-month follow-up) showing that, at baseline, women with endometrioma had significantly lower AMH levels compared with controls [33]. Similar findings were reported in another prospective study conducted by Chen et al. who evaluated the impact of the presence of endometrioma and laparoscopic cystectomy on ovarian reserve as assessed by serum AMH levels. Before surgery the endometrioma group had significantly lower AMH levels compared with the other benign ovarian cyst group and the tubal factor infertility group [34]. On the contrary, in a large retrospective French study published in 2012, Streuli et al. demonstrated that both endometriosis and endometriomas *per se* do not decrease AMH levels. AMH levels are decreased in women with previous surgery for endometriotic cysts independently from the presence of current endometriomas [35].

The impact of endometrioma surgical treatment on the ovarian reserve

Menopausal transition occurs earlier in women with previous surgery for endometriotic cysts [36] and, although rare, cases of postsurgical ovarian failure in patients operated for bilateral endometriomas have been described [37,38]. Different techniques (*e.g.* ablation, excision), haemostatic procedures (*e.g.* bipolar coagulation, sutures) and technologies (*e.g.* laser, plasma energy) have been proposed to treat ovarian endometriotic cysts to minimize surgical damage on healthy ovarian tissue and optimizing the preservation of the ovarian reserve and decreasing the risk of recurrence [28,39–45]. In 2014, a systematic review and meta-analysis investigated the impact of surgery for an ovarian endometrioma on the ovarian reserve assessed by AFC. Of the 24 studies considered in detail, 13 were included for data extraction and meta-analysis, including a total of 597 patients. This study demonstrated that the AFC of the operated ovary did not significantly change after surgery (0.10, 95% CI −1.45 to 1.65; $p = 0.90$). Furthermore, the operated ovary showed a significantly

Table 1
Characteristics of the study evaluating the impact of the endometrioma *per se* on the ovarian reserve as evaluated by AFC.

	Country	Study design	Number of included patients	Mean (±SD) endometriotic cyst diameter (cm)	Unilateral/ bilateral	Day of AFC measurement	AFC healthy ovary (mean ± SD)	AFC affected ovary (mean ± SD)
Biacchiardi et al. [28]	Italy	Prospective cohort	43	3.7 ± 1.1	33/10	Early follicular	8.4 ± 6.0	3.3 ± 3.2
Ercan et al. [29]	Turkey	Prospective cohort	36	5.2 ± 1.4	36/0	2	5.2 ± 3.5	4.5 ± 2.0

AFC, antral follicle count; SD, standard deviation.

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