EXPERT REVIEWS

Ovarian endometrioma: guidelines for selection of cases for surgical treatment or expectant management

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Ovarian endometrioma is a benign, estrogen-dependent cyst found in women of reproductive age. Infertility is associated with ovarian endometriomas; although the exact cause is unknown, oocyte quantity and quality are thought to be affected. The present research aims to analyze current treatment options for women with ovarian endometriomas, discuss the role of fertility preservation before surgical intervention in women with ovarian endometriomas and present guidelines for the selection of cases for surgery or expectant management. This review analyzed the factors of ovarian reserve, cyst laterality, size and location, patient age and prior surgical procedures. Based on these factors, the authors recommend three distinct treatment pathways: reproductive surgery to achieve spontaneous pregnancy following treatment, reproductive surgery to enhance IVF outcomes and expectant management with IVF.

Keywords: endometriosis • expectant management • fertility preservation • *in vitro* fertilization • laparoscopic surgery • ovarian endometrioma • ovarian reserve • stimulation protocols

Endometriosis is a benign, estrogen-dependent gynecological disease characterized by endometrial tissue located outside the uterus. The disease affects approximately 5–10% of women of reproductive age in the USA, and symptoms include chronic pelvic pain, dysmenorrhea, dyspareunia and/or infertility [1].

Approximately 17% of subfertile women have endometriomas, and it is estimated that 20–40% of women who undergo reproductive technology (ART) have endometriosis [2]. ART procedures are not only expensive – an average IVF cycle costs US$12,400 – but emotionally draining for the couple seeking treatment [3]. Therefore, it is important to understand how ovarian endometrioma affects fertility and ART procedures. Currently, there is no general consensus regarding the proper management of women with ovarian endometrioma who wish to conceive. This article aims to review and discuss the effects of ovarian endometriomas on fertility, analyze current treatment options, discuss the role of fertility preservation in women with ovarian endometriomas and present guidelines for the selection of cases for surgery or expectant management.

Cause of ovarian endometrioma

Ovarian endometrioma, a subtype of endometriosis, affects 17–44% of women with endometriosis [4,5]. Ovarian endometriomas, also known as 'chocolate cysts', contain thick, old blood that appears as a brown fluid. The pathogenesis of ovarian endometriomas is a controversial topic, but there are three main theories: invagination of ovarian cortex secondary to bleeding of a superficial implant; invagination of ovarian cortex secondary to metaplasia of coelmic epithelium in cortical inclusion cysts; and endometriotic transformation of functional cysts. The first theory was described by Hughesdon in 1957, in which he suggested that endometrial implants, located on the surface of the ovary, are the cause of endometriomas. According to Hughesdon's theory, menstrual shedding and the endometrial implant bleeding are trapped and cause a gradual invagination of the ovarian cortex, which results in a psuedocyst [6]. Brosens *et al.*, in agreement with Hughesdon, reported menstrual shedding and blood accumulation at the site of the implants through ovariscopy [7]. This theory is important in the treatment of ovarian endometriomas

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Table 1. Expectant management versus surgical techniques and IVF outcomes.

Study (year)	Type of study	Subjects	Treatment	Subjects (n)	Bilateral (%)	Oocytes retrieved (n)
Expectant management						
Kumbak *et al.* 2008)	Retrospective	IVF–ICSI and ovarian cyst	OE, EM	85	Unilateral only	13.9
			Other benign cyst	83	Unilateral only	16.4, p = 0.03
Almog *et al.* (2011)	Retrospective case–control	Infertility and first attempt IVF	OE, EM (group 1)	81	Unilateral only	0.98 A/C, NS p = 0.8, 11.4 ± 0.5 total
			No OE or endometriosis (group 2)	162		11.9 ± 0.8, NS p = 0.3, 1 vs 2
Opøien *et al.* (2012)	Retrospective cohort	Infertile	Stage III–IV endometriosis, no OE (group 1)	164		8.6 ± 5.3
			Stage III–IV endometriosis, OE EM (group 2)	186		7.6 ± 5.5, NS group 1 vs 2
			Tubal factor infertility (group 3)	1171		9.2 ± 5.6, p < 0.01 group 1 + 2 vs 3
Benaglia *et al.* (2012)	Retrospective	OE, no prior surgery	Affected ovary	84	Unilateral only	6(4–8)
			Contralateral ovary			6(4–9), NS p = 0.18
Expectant management versus traditional treatments						
Bongioanni *et al.* (2011)	Retrospective case–control	Infertility and first-attempt IVF	OE, EM, (group 1)	142	14.10%	9.4 ± 4.3
			OE, prior cystectomy (group 2)	112	19.60%	8.2 ± 5.3, NS 1 vs 2
			Tubal factor infertility (group 3)	174		9.6 ± 4, NS 1 vs 3
Barri *et al.* (2010)	Observational	Infertile	OE, surgery†, followed by IVF (group 1b)	483	Not reported	
			OE, EM with IVF (group 2)	173	Not reported	
			Male factor infertility (group 4)	334		
Expectant management versus aspiration with sclerotherapy						
Salem *et al.* (2011)	Prospective controlled	Infertile and OE	Ultrasound-guided aspiration with 95% EST	100	Not reported	8.7 ± 4.1
			OE EM with IVF–ICSI	50	Not reported	6.0 ± 2.7

†Mostly cystectomy, but actual procedures not reported.
A/C: Ratio affected/contralateral ovary; EM: Expectant management; EST: Ethanol sclerotherapy; ET: Embryo transfer; ICSI: Intracytoplasmic sperm injection;

MII oocytes (n)	Fertilization rate (%)	Implantation rate (%)	Pregnancy rate/ cycle (%)	Live birth rate (%)	Cancellation rate (%)	Ref.
10.3	82	19	43.4 per ET			[19]
11.8, NS	79, NS	28, p = 0.02	48.2 per ET, NS			
						[40]
	62.5%	6.90	40.20	30.5 per ongoing pregnancy	2.3; groups 1 + 2	[23]
	61.6; NS, group 1 vs 2	20.9, NS, group 1 vs 2	26.3; p < 0.01, 1 vs 2	18.8 per ongoing pregnancy, p < 0.05, group 1 vs 2		
	63.5; NS, group 1 + 2 vs 3	24.9; NS, group 1 + 2 vs 3	34.7; NS, group 1 + 2 vs 3	25.3; NS, group 1 + 2 vs 3	1.2; NS 1 + 2 vs 3	
						[92]
71.20%	67.7	24.20	48.4 per ET	34.6 per ET	7.50	[20]
68.60%	0.734	24.60	44.1 per ET	25.8 per ET	9.80	
66.9%, NS	70.2, NS	22.1; NS	40.1 per ET, NS	30.8 per ET, NS	2.9; p < 0.02, group 1 vs 3, group 2 vs 3	
7.3 ± 5			30.40			[29]
10.1 ± 2.2; p < 0.03, group 1b vs 2			32.20			
10.3 ± 6 (significance not reported)				33.5 per patient; NS, group 1b + 2 vs 4		
	72 ± 12	18	30	28		[69]
	60.8 ± 10	14	22	18		

NS: Not significant (p < 0.05); OE: Ovarian endometrioma.

because the ovarian cortex is the internal surface of the psuedocyst wall; thus, ovarian cortex is lost during excision of the endometrioma. The second theory in the pathogenesis of ovarian endometriomas was described by Donnez *et al.* in 1996 and suggests that the invagination of ovarian endometriomas is not due to bleeding of the implant, but instead is caused by metaplasia of the coelomic epithelium invaginated into the ovarian cortex [8]. Donnez *et al.* suggest that the potential cause of recurrence after excision of endometriomas or vaporization is due to the invagination of endometriotic tissue into the ovary; thus, Donnez *et al.* recommend vaporization of the cyst wall [9]. The final theory postulates that the endometrioma is formed by endometriotic transformation of functional cysts and was first described by Nezhat *et al.* in 1992 [10].

The gold standard diagnostic technique of an ovarian endometrioma is laparoscopy. However, a transvaginal ultrasound can assist in the initial diagnosis and help differentiate endometriomas from other benign ovarian tumors with the typical endometrioma appearance of homeogenous low-level internal echoes and thick walls [11]. Van Holsbeke *et al.* report that the single best ultrasound variable to differentiate between endometriomas and other adnexal masses in premenopausal women is round glass echogenicity of cyst fluid, with a sensitivity of 73% and a specificity of 94% [12]. Guerriero *et al.* found that transvaginal ultrasounds are able to detect the presence of pelvic adhesions in patients with endometriomas, and identification of pelvic adhesions can help with determining the proper treatment [11]. Color Doppler identifies the vascularization of the mass, and endometriomas typically have peripheral blood flow. 3D ultrasounds are becoming increasingly popular in clinical practice; Alcazar *et al.* report that in premenopausal women, B-mode ultrasound with the use of mean gray value has a sensitivity of 80% and specificity of 91% in differentiating endometriomas from other unilocular cysts [13]. MRI can further assist in the differentiation of ovarian endometriomas and other ovarian cysts. Endometriomas are usually present as T-1 bright lesions and Froehlich *et al.* recommend using 'fat-saturation on precontrast, T1-weighted sequences instead of T2-weighted sequences' to differentiate an endometrioma from a mature teratoma [14].

Endometriomas can occur unilaterally or bilaterally, and approximately 28% of endometrioma patients have bilateral endometriomas [15]. Women with endometriomas have many of the same symptoms as those with endometriosis, including dyspareunia and/or subfertility. One potential issue with ovarian endometrioma treatment is the presence of other pelvic endometriotic lesions. One study reported that only 19 out of 1785 patients (1.06%) had ovarian endometriomas without any other pelvic endometriosis [5]. Furthermore, Fauconnier *et al.* found that ovarian endometriomas did not contribute to chronic pelvic pain, but were highly associated with deep infiltrating endometriosis, which is known to cause chronic pelvic pain [5,16]. Therefore, when creating a treatment plan for women with chronic pelvic pain and endometriomas, the physician may need to consider treating the deep infiltrates as well. Ovarian endometriomas can be further complicated by the formation of adhesions that can fixate the pelvic organs. Fixation of the pelvic organs may distort the anatomical locations and reduce natural fertility [17].

Effect of ovarian endometrioma on fertility

Studies have compared IVF outcomes in women with endometriosis with those of women with tubal factor infertility and the results are conflicting. In a meta-analysis in 2002, Barnhart *et al.* found that endometriosis patients had a decreased pregnancy rate (odds ratio [OR]: 0.56; 95% CI: 0.44–0.60) [2]. However, this finding has been contested, and a group of ten university hospitals in Japan found no significant difference in fertilization, cleavage and pregnancy rates between endometriosis and tubal factor infertility patients (Table 1) [18]. Compared with other benign ovarian cysts, ovarian endometrioma did not significantly affect pregnancy rates per embryo transfer [19]. Furthermore, in a retrospective study of women with ovarian endometriomas and tubal factor infertility, the groups had similar implantation, pregnancy and live birth rates per cycle. However, the endometrioma patients had higher IVF cancellation rates than the tubal factor infertility patients [20].

The difference in IVF outcomes between women with endometriosis and endometriomas is also controversial. Two studies found no significant difference in clinical pregnancy rates [21,22]. However, in a recent study looking at Stage III–IV endometriosis with and without endometriomas, Opøien *et al.* found significantly reduced pregnancy rates per cycle and live birth rates per ongoing pregnancy in women with endometriomas (Table 1) [23].

Predictors of IVF success in women with endometrioma

Ovarian reserve is defined as a woman's total ovarian follicle pool, which includes the primordial and growing follicles. In general, ovarian reserve declines with age, and a low ovarian reserve is associated with a decreased chance of pregnancy [24]. However, there is no single biomarker that can accurately estimate a woman's ovarian reserve. In an IVF patient, a woman's response to controlled ovarian hyperstimulation (COH) is thought to be an accurate measure of ovarian reserve since a poor response is associated with fewer embryos available for implantation and reduced pregnancy rates [25,26]. Some authors argue that the current predictors of ovarian response are adequate for predicting the quantity, but not the quality, of oocytes and pregnancy outcomes [27]. Three factors are used to help to predict a woman's response to COH during an IVF cycle: levels of day 3 follicle-stimulating hormone (FSH), the antral follicle count (AFC) and more recently, levels of anti-Müllerian hormone (AMH) [26].

Traditionally, basal FSH is measured on day 3 of a woman's menstrual cycle. It is believed that women with a good ovarian reserve have lower levels of FSH because the ovary produces enough hormones (estrogen) to further inhibit production of FSH. FSH levels above 10 IU/l have a high specificity for predicting a reduced response to COH (80–100%), but the sensitivity for actually identifying these women is low (10–30%) [26]. While there is no general consensus on the predictability of FSH on IVF outcomes, Abdalla *et al.* found that women with higher levels of FSH produced significantly fewer oocytes (and thus embryos) for transfer than women with moderately elevated FSH levels. They also reported that higher FSH levels are a good quantitative, but not qualitative measure of ovarian reserve.

Although pregnancy rates and live birth rates decrease as levels of FSH levels increase, live births are still possible in patients with elevated FSH levels (>20 IU/l), especially in younger women [28]. In one study, women who had *in situ* endometriomas or prior surgery for endometriomas had significantly higher FSH levels than a control group of women undergoing IVF for male factor infertility. However, this study did not compare the FSH levels of women with *in situ* endometriomas from those with prior surgery [29]. As seen in Table 2, Bongioanni *et al.* reported no significant difference in FSH levels between women with *in situ* endometriomas, prior surgery for endometriomas and women with tubal factor infertility [20].

The AFC is calculated via transvaginal ultrasound and is used to predict ovarian response and the number of oocytes that can potentially be retrieved in IVF. In patients with a reduced AFC, specificity was high (73–100%) and sensitivity was low (9–73%) for a poor response to COH. Furthermore, specificity was high (64–100%) and sensitivity low (8–33%) for failure to conceive [26]. As seen in Table 3, a study by Barri *et al.* compared women with ovarian endometriomas and women undergoing IVF for male factor infertility and found that the endometrioma patients had a significantly lower AFC than the control group [29]. Other benign ovarian cysts do not negatively affect AFC, but in women with a unilateral endometrioma, the AFC was significantly lower in the affected ovary than in the contralateral unaffected ovary [30].

A new proposed measurement of ovarian reserve and predictor of ovarian response is AMH. The level of AMH is suggested to predict the primordial follicle pool [31–33]. AMH levels correlate with age, decreasing from pre-pubescent years until menopause [34]. In women with low levels of AMH (0.2–0.7 ng/ml), specificity was high (78–92%) and sensitivity was moderate (40–97%) for a poor response, but no significant correlation for pregnancy was found [26]. Another study found conflicting results and reported that increased serum AMH levels prior to IVF treatment were associated with a higher oocyte yield and higher live birth rates [35]. However,

Table 2. Surgical technique and follicle-stimulating hormone.

Study (year)	Type of study	Group	Treatment	Subjects (n)	Mean diameter (cm)	Bilateral (%)	Basal FSH days 3–5 (IU/l)	Ref.
Cystectomy								
Almog *et al.* (2010)	Retrospective	OE and IVF	Cystectomy	38	3.9 ± 1.9	Unilateral only	7.6 ± 3.3	[111]
Biacchiardi *et al.* (2011)	Prospective cohort	Normo-ovulatory and OE	Cystectomy	43	3.68 ± 1.08	23.30	1.4 (MD); NS	[56]
Cystectomy versus three-stage technique								
Tsolakidis *et al.* (2010)	Prospective, randomized control trial	OE, no prior surgery	Cystectomy (group 1)	10	3.79 ± 0.48	Unilateral only	9.1 (MD); NS baseline vs follow-up	[61]
			Three-stage (group 2)	10	3.68 ± 0.55	Unilateral only	3.4 (MD) NS, baseline vs follow-up; NS group 1 vs 2	
Aspiration with sclerotherapy								
Yazbeck *et al.* (2009)	Prospective	Infertile and recurrent OE	Aspiration with 95% EST (group 1)	31	3.86 ± 1.12	12.90	6 ± 1.5	[68]
			Control – moderate to severe endometriosis, no OE (group 2)	26			9 ± 4.8; $p < 0.01$ group 1 vs 2	
Shawki *et al.* (2012)	Prospective case–control	Infertile and OE	Aspiration with MT	65	6.5 ± 1.53	Unilateral only	7.2 ± 1.5	[71]
Expectant management versus traditional techniques								
Bongioanni *et al.* (2011)	Retrospective case–control	Infertile and first attempt at IVF	OE, no prior surgery (group 1)	142	Not reported but all <6 cm	14.10	7.2 ± 3.9	[20]
			OE, prior cystectomy (group 2)	112	Not reported but all <6 cm	19.60	7.9 ± 4.2	
			Tubal factor infertility (group 3)	174			6.6 ± 3.5, NS	

EST: Ethanol scleropathy; FSH: Follicle-stimulating hormone; MD: Mean difference (baseline vs follow-up); MT: Methotrexate; NS: Not significant ($p > 0.05$); OE: Ovarian endometrioma.

Table 3. Surgical technique and antral follicle count.

Study (year)	Type of study	Group	Treatment	Subjects (n)	Mean diameter (cm)	Bilateral (%)	AFC	Ref.
Cystectomy								
Ercan *et al.* (2011)	Prospective cohort	OE, no prior surgery	Cystectomy (group 1)	36	5.2 ± 1.4	Unilateral only	-0.8 (MD)	[112]
			Contralateral ovary (group 2)				1.2 (MD); p < 0.05, group 1 vs 2	
Almog *et al.* (2010)	Retrospective	OE and IVF	Cystectomy, operated cyst	38	3.9±1.9	Unilateral only	4.5 ± 3.8	[111]
			Nonoperated ovary				7.4 ± 5.2; p = 0.003 group O vs N	
Biacchiardi *et al.* (2011)	Prospective cohort	OE	Cystectomy	43	3.68 ± 1.08	23.30%	1.8 (MD), NS	[56]
Cystectomy versus ablation								
Roman *et al.* (2011)	Retrospective	OE >3 cm, no prior surgery	Plasma ablation (group 1)	16	3.8 ± 1.3	Unilateral only	5.5 ± 3.9, 0.83±0.31 (O/N)	[64]
			Cystectomy (group 2)	15	4.7 ±1.6, p = 0.10 group 1 vs 2	Unilateral only	2.9 ± 2.4; p = 0.03, group 1 vs 2, 0.33 ± 0.25 (O/N); p < 0.001, group 1 vs 2	
Cystectomy versus three-stage technique								
Tsolakidis *et al.* (2010)	Prospective, randomized control trial	OE, no prior surgery	Cystectomy (group 1)	10	3.79 ± 0.48	Unilateral only	0.4 (MD)	[61]
			Three-stage technique (group 2)	10	3.68 ± 0.55	Unilateral only	3.06 (MD); p = 0.02, baseline vs follow-up; p = 0.002, group 1 vs 2	
Combined cystectomy and ablation								
Donnez *et al.* (2010)	Prospective	OE, no prior surgery	Combined cystectomy and ablation (group 1)	52	4.6 ± 1.3	61.50%	6.1 ± 3.2	[65]
			Combined cystectomy and ablation, unilateral (group 1b)	20			0.98 (O/N), NS	
			Male factor infertility, no OE (group 2)	20			6.2 ± 4.8, NS, group 1 vs 2	

†Mostly cystectomy but actual procedures not reported.
A/C: Ratio affected ovary:contralateral ovary; AFC: Antral follicle count; EM: Expectant management; EST: Ethanol sclerotherapy; MD: Mean difference (baseline vs follow-up); MT: Methotrexate; NS: Not significant (p > 0.05); O/N: Ratio operated:nonoperated ovary; OE: Ovarian endometrioma.

Table 3. Surgical technique and antral follicle count (cont.).

Study (year)	Type of study	Group	Treatment	Subjects (n)	Mean diameter (cm)	Bilateral (%)	AFC	Ref.
Aspiration with sclerotherapy								
Yazbeck *et al.* (2009)	Prospective	Infertile and recurrent OE	Aspiration with 95% EST (group 1)	31	3.86 ± 1.12	12.90%	9.6 ± 4.7	[68]
			Control – stage III–IV Endometriosis, no OE (group 2)	26			10.6 ± 6.8, NS	
Shawki *et al.* (2012)	Prospective case–control	Infertile and OE	Aspiration with MT (group 1)	65	6.5 ± 1.53	Unilateral only	9.6 ± 1.7	[71]
			Contralateral ovary (group 2)				11.7 ± 2.3, NS, group 1 vs 2	
Expectant management								
Almog *et al.* (2010)	Retrospective	Ovarian cyst	Endometrioma cyst	53	2.7 ± 0.2	Unilateral only	0.806 (A/C), p = 0.03	[30]
			Functional cyst	198	1.9 ± 0.07	Unilateral only	0.966 (A/C), NS, p = 0.39	
			Dermoid cyst	14	2.1 ± 0.3	Unilateral only	1.29 (A/C), NS, p = 0.16	
			Multioculated cyst	8	2.3 ± 0.3	Unilateral only	0.96 (A/C), NS, p = 0.9	
Expectant management versus traditional treatments								
Bongioanni *et al.* (2011)	Retrospective case–control	Infertility and first attempt at IVF	OE, no prior surgery (group 1)	142	All <6 cm	14.10%	16.9 ± 11.1	[20]
			OE, prior cystectomy (group 2)	112	All <6 cm	19.6%, NS	11.7 ± 9.4; p < 0.001, group 1 vs 2; p < 0.001, group 2 vs 3	
			Tubal factor infertility (group 3)	174			16.6 ± 9.5	
Barri *et al.* (2010)	Observational	Infertile	OE, surgery†, then IVF(group 1b)	483	5.8 ± 2.1	Not reported	5.9 ± 6.1	[29]
			OE, EM with IVF (group 2)	173	5.4 ± 3.2	Not reported	7.8 ± 5.1; p < 0.03, group 1b vs 2	
			Male factor infertility (group 4)	334			10.2 ± 5.1; p < 0.004, group 1b + 2 vs 4	

†Mostly cystectomy but actual procedures not reported.
A/C: Ratio affected ovary:contralateral ovary; AFC: Antral follicle count; EM: Expectant management; EST: Ethanol sclerotherapy; MD: Mean difference (baseline vs follow-up); MT: Methotrexate; NS: Not significant (p > 0.05); O/N: Ratio operated:nonoperated ovary; OE: Ovarian endometrioma.

when oocyte yields were accounted for, AMH was no longer a significant predictor of the live birth rate, indicating that AMH is not a good predictor of oocyte or embryo quality [32].

In one study, AMH levels were not significantly different between patients with and without endometriosis [25]. However, most studies do not agree with this finding. In a retrospective study, Yoo *et al.* found serum AMH levels to be significantly lower in women with endometriosis [36]. This finding is supported by Hwu *et al.* who found that the mean serum AMH level was significantly lower in women with endometriomas than in those without. Furthermore, Hwu *et al.* found significantly decreased levels of AMH in patients with bilateral endometrioma compared with unilateral disease, indicating that bilateral endometrioma inflicts more damage on ovarian reserve [37]. Yoo *et al.* also found that AMH was a better predictor of mature oocytes and reduced ovarian response than FSH and age during COH in women with endometriosis [36].

A potential benefit of using AMH compared with other ovarian reserve measures is that AMH levels do not change throughout a woman's menstrual cycle.

Mechanism & effects of ovarian endometrioma on fertility

The exact mechanism by which ovarian endometrioma causes infertility is unknown. In cases of severe endometriosis, infertility is associated with adhesions, tubal blockage and anatomical distortion. Milingos *et al.* reported that women with ovarian endometriomas might have infertility associated with chronic pelvic pain, and therefore dyspareunia [38]. However, for women without pelvic pain or anatomical distortions, endometrioma infertility is potentially associated with a decreased oocyte retrieval rate, reduced oocyte quality and reduced embryo quality.

In a recent retrospective case–control study, the AFC and number of oocytes retrieved was not significantly different between the affected and contralateral healthy ovary, and the total number of retrieved oocytes did not differ from that of a control group of women undergoing IVF (Table 1) [40]. However, most studies are not in agreement with these findings. In a meta-analysis of two studies by Gupta *et al.,* significantly fewer follicles were found following stimulation in women with endometriomas as compared with a control group (weighted mean difference [WMD]: -0.88; 95% CI: -1.43 to -0.32). Furthermore, in a meta-analysis of five studies, fewer oocytes were retrieved in women with ovarian endometriomas compared with women without endometriomas (WMD: -0.74; 95% CI: -3.16 to -0.23) [40]. The finding that the number of aspirated oocytes is reduced is supported by a recent histological study in women under the age of 35 years, in which ovarian tissue adjacent to the ovarian endometrioma cysts had one- to two-thirds fewer follicles compared with ovarian tissue adjacent to other benign ovarian cysts [41]. Kitajima *et al.* attributed this decrease in follicle count to a mechanism other than mechanical stretching of the ovarian cortex, and suggested that the inflammatory response led to fibrosis in normal ovarian cortex [42]. In support of this finding, Matsuzaki *et al.* found that levels of oxidative stress were higher in women with endometriomas in the surrounding normal ovarian tissue than in women with other benign ovarian cysts [43]. Zhang *et al.* reported that *in vitro* oxidative stress induced apoptosis in oocytes and necrosis in early follicles [44], which supports the theory that endometrioma damage to the follicles is caused by oxidative stress. Oxidative stress is a potential cause of necrosis in an ovary with endometrioma and reduced follicular density [42]. Kuroda *et al.* report that in women over 35 years, the number of follicles in adjacent ovarian tissue is not significantly different between women with ovarian endometrioma cysts and women with benign ovarian cysts. This finding suggests that the reduction in follicles found in women below 35 years of age with ovarian endometriomas, but not in women with other benign ovarian cysts, may be a protective mechanism in ovarian endometriosis for the adjacent tissue or may be a selection of age-resistant follicles [41].

The effect of ovarian endometriomas on oocyte quality is controversial and difficult to assess. Kumbak *et al.* found women with ovarian endometriomas had a significantly fewer number of oocytes retrieved compared with women with simple, basal ovarian cysts, but the number of mature oocytes retrieved and the fertilization rate were not significantly different between the groups [19]. However, other researchers have found decreased oocyte quality with fewer mature oocytes retrieved in women with endometriosis compared with women undergoing IVF for male factor infertility [25]. Kumbak *et al.* reported a significantly reduced implantation rate, which is in agreement with other studies [19].

Oocyte donation studies provide the best evidence for the negative effect of endometriosis on oocyte quality. In one study, oocyte donations from women without endometriosis were not associated with significantly different IVF outcomes in terms of implantation and pregnancy rate when compared with women without endometriosis. However, donated oocytes from women with endometriosis had significantly lower implantation rates, but not pregnancy rates [45]. Furthermore, oxidative stress may occur early in endometrioma patients, and cyst removal does not improve oocyte quality, which may explain why many studies have not shown improvements in IVF outcomes after laparoscopic removal of ovarian endometriomas (see section on 'Expectant management' and Tables 1 & 4) [43].

Embryo quality is another important determinant in IVF success. Bongioanni *et al.* found significantly higher cancellation rates due to a poor response in women with *in situ* endometriomas and prior surgery for ovarian endometriomas compared with women with tubal factor infertility, but there was no significant difference in the live birth rate in those who did not cancel. A poor response is associated with fewer follicles. Reinblatt *et al.* found that women with bilateral endometriomas did not differ from women with tubal or male factor infertility with regard to IVF outcome measures of AFC, number of oocytes retrieved, fertilization rate, cleavage rate, number of embryos transferred and percentage of good embryos transferred – this suggests that embryo quality is not negatively impaired in women with endometriomas [46]. The results from a study by Barri *et al.* agree with this finding in that the number of embryos available for transfer and the number of embryos that were frozen were significantly lower in the women with endometriomas, but the reduction was due to fewer oocytes retrieved. In addition, the live birth rate was not significantly different [29].

Overall, how ovarian endometrioma causes infertility is not well understood, and recent research suggests that ovarian endometrioma infertility is associated with reduced oocyte quantity and quality, but not embryo quality. Understanding how ovarian endometriomas affect fertility can help improve surgical treatments, fertility preservation techniques and IVF protocols.

Traditional treatment techniques: an overview

Treatment for women with ovarian endometriomas is a controversial topic and depends on a variety of factors including ovarian reserve prior to treatment, cyst laterality, location and hindering effects, patient age and prior treatment. Although medical treatment such as oral contraceptives has been shown to reduce

symptoms of ovarian endometrioma, use of such treatment is counterproductive in women who are trying to conceive.

Laparoscopic cystectomy

Cystectomy, a conservative surgical procedure, is a controversial treatment for endometriomas due to the invasive nature of the surgery. The laparoscopic procedure strips the cyst wall – the portion of the cyst containing the endometrial tissue. The benefits of this procedure include decreased recurrence rates, increased chance of spontaneous pregnancy and significant reduction in pelvic pain. After one procedure, recurrence rates range from 9.6 to 45% (Table 5) [47–49]. Another advantage of cystectomy is the increase in spontaneous pregnancy rates following surgery. Studies have reported a wide range in spontaneous pregnancy rates ranging from 14 to 54% (Table 6) [47,49]. Kitajima *et al.*, suggested that the increase in spontaneous pregnancy following cystectomy might be due to decreased ovarian inflammation, which can lower follicular density [42]. Women who are 35 years of age or younger are encouraged to wait 1 year before considering IVF. Women who are older than 35 years of age are encouraged to wait 6 months before attempting IVF [29].

However, the main controversy associated with cystectomy is that it damages or removes healthy ovarian cortex and follicles, leading to a decrease in ovarian reserve following the procedure. The AFC and AMH seem to be most affected by cystectomy (Tables 3 & 7). In a meta-analysis comparing eight studies of ovarian endometrioma treatment, the patients who had either unilateral or bilateral cystectomy had significantly lower AMH levels following the surgery than before surgery (WMD: -1.13; 95% CI: -0.36 to -1.88) (Table 7) [50,51]. Ovarian failure, a serious risk associated with cystectomy, has been reported after bilateral endometrioma cystectomy, with rates ranging from 2.3 to 3.03% [37,52].

In addition to potentially removing healthy cortex, inflammation after surgery could further damage the cortex or decrease vascularization [53,54]. The damage caused by scar tissue may reduce the volume of the healthy ovary, and scar tissue may interfere with oocyte retrieval [52]. A recent study on laparoscopic ovarian cystectomy reported that inexperienced surgeons had significantly diminished outcomes compared with experienced surgeons [55]. However, Biacchiardi *et al.* found reduced ovarian reserve following cystectomy even when the procedure was performed by experienced surgeons [56].

Bongioanni *et al.* performed a retrospective, case–control study to assess the effects of cystectomy on IVF outcomes. This study consisted of women with an endometrioma, women who had a cystectomy for an endometrioma and women with tubal factor infertility. The results showed that IVF pregnancy rates per cycle were not significantly different between any of the groups (Table 1). However, the prior cystectomy group did have a significantly reduced AFC compared with both groups and reduced ovarian sensitivity (Table 3). Ovarian sensitivity is defined as the ovarian response to FSH stimulation independent of administered FSH. Therefore, Bongioanni *et al.* concluded that ovarian endometriomas do not significantly decrease IVF pregnancy rates compared with tubal factor infertility, and surgical treatment for endometriomas does not improve IVF outcome but instead may negatively affect ovarian response [20]. As stated previously, Matsuzaki *et al.* believed that cystectomy does not improve pregnancy outcomes due to the oxidative stress from the endometrioma that remains in healthy tissue following surgery, which continues to negatively affect oocyte quality [43]. Therefore, cystectomy should be avoided in women who do not have time to undergo the surgery and subsequently wait 6 months to 1 year before trying to attempting IVF. It should also be avoided in women with an already reduced ovarian reserve.

Aspiration

Aspiration is a noninvasive option in which a transvaginal ultrasound identifies the location of a cyst. Needle aspiration is then used to remove the fluid by transvaginal access. There are three common risks associated with the procedure: recurrence, infections and adhesions [57,58]. A study by Zhu *et al.* consisting of infertile patients with ovarian endometriomas (Table 5) reported that cyst recurrence was high after the first procedure (91.5%), but after repeat aspiration (up to six separate procedures) only 5.4% of patients had recurrent cysts. The average number of treatments needed was 3.1 ± 2.3, and repeated aspirations took place on average 33 days after the prior procedure. The cumulative pregnancy rate after 2 years was 43.4%, with 73.2% of the women achieving pregnancy doing so within 7–18 months following surgery. Of the 56 women achieving pregnancy, 44 did so naturally and 12 used intrauterine insemination for either male factor or other cervical factor infertility (Table 6). None of the patients had infections following cyst aspiration or oocyte retrieval [59]. Overall, aspiration alone has traditionally been regarded as an ineffective treatment for endometriomas. However, repeating the procedure in recurrent endometriomas can be a less invasive alternative to surgery.

Laparoscopic endometrial ablation

Laparoscopic endometrial ablation is an invasive surgical procedure in which the cyst is drained and the cyst wall is destroyed by electrosurgical current or laser energy [60].

The CO_2 laser is considered as a tissue-sparing energy source that has a more controlled penetration than electrical energy sources [61]. Reported pregnancy rates and recurrence rates at 60 months are similar between cystectomy and CO_2 laser ablation (Tables 5 & 6) [48]. After CO_2 laser ablation, the number of retrieved follicles and mature oocytes in women undergoing IVF was similar to that of women with tubal factor infertility, suggesting that while CO_2 laser ablation does not negatively affect IVF outcomes, it does not improve them (Table 4) [62].

In a retrospective study of infertile women with ovarian endometriomas, following potassium-titanyl-phosphate (KTP) laser ablation, 48.9% became pregnant spontaneously and 50% of the remaining patients who elected to undergo IVF successfully achieved pregnancy during the first cycle (Tables 4 & 6). Cysts recurred in 24.4% of patients and KTP does not negatively affect ovarian reserve (Table 4) [63].

Table 4. Surgical techniques and IVF outcomes.

Study (year)	Type of study	Subjects	Treatment	Subjects (n)	Bilateral (%)	Oocytes retrieved
Cystectomy						
Somigliana *et al.* (2008)	Prospective case–control	Infertile	OE, prior cystectomy (group 1)	68	All bilateral	5.7 ± 4
			Male or tubal factor (group 2)	136		7.2 ± 3.6; p = 0.023, group 1 vs 2
Almog *et al.* (2010)	Retrospective	OE	Cystectomy, operated cyst	38	Unilateral only	4.3 ± 3.9
			Nonoperated ovary			7.6 ± 4.8; p < 0.001, group C vs N
Ablation						
Donnez *et al.* (2001)	Retrospective	OE	OE, prior CO_2 ablation (group 1)	85	54%	
			Tubal factor infertility (group 2)	289		
Shimizu *et al.*, (2010)	Retrospective	OE	KTP ablation, operate		Unilateral only	7.3 ± 3.6
			Nonoperated ovary			4.6 ± 2.7; NS p = 0.99, group O vs N
Aspiration with sclerotherapy						
Yazbeck *et al.* (2009)	Prospective	Infertile and recurrent OE	Aspiration with 95% EST (group 1)	31	12.90%	11.4 ± 6.1
			Stage III/IV endometriosis, no OE (group 2)	26		7 ± 4.7; p = 0.03, group 1 vs 2
Shawki *et al.* (2012)	Prospective case–control	Infertile and OE	Aspiration with MT (group 1)	65	Unilateral only	8.1 ± 1.5
			Contralateral ovary (group 2)			10.2 ± 0.5; NS

EST: Ethanol sclerotherapy; ICSI: Intracytoplasmic sperm injection; KTP: Potassium-titanyl-phosphate; NS: Not significant (p < 0.05); OE: Ovarian endometrioma.

A plasma laser is similar to a CO_2 laser in that it destroys the tissue without coagulum destruction. Plasma energy laser uses argon gas and is reported to have no risk of accidental intraoperative overshoots and metallic instrument reflection. In a retrospective study of unilateral endometriomas using plasma energy ablation compared with cystectomy, Roman *et al*. reported that plasma laser was a better treatment option because the procedure results in less reduction in ovarian volume and AFC than cystectomy (Table 3). However, spontaneous and IVF pregnancy rates were not reported for this study [64]. Currently, a prospective clinical trial is comparing the effects of plasma laser ablation and cystectomy for ovarian endometriomas on AFC following surgery [201].

According to a Cochrane review, there is insufficient evidence in support of either cystectomy or ablation for IVF success (OR: 1.40; 95% CI: 0.47–4.15) [60]. Therefore, except in cases of extreme pain or ovarian endometriomas that hinder oocyte retrieval, endometriomas can be managed expectantly.

Combined treatment techniques

Three-stage technique

Developed in 1996 by Donnez *et al.*, the three-stage technique consists of laparoscopic cyst drainage followed by gonadotropin-releasing hormone (GnRH) agonist treatment for 3 months to reduce cyst diameter, and then a second laparoscopic procedure for vaporization of the cyst wall by CO_2 [8]. This combination technique is potentially more beneficial than cystectomy because normal ovarian tissue is not removed and it causes less thermal damage. In a prospective randomized control trial comparing cystectomy and the three-stage technique, Tsolakidis *et al.* found cystectomy patients had lower AMH levels after surgery, which suggests that ovarian reserve is less compromised with

MII oocytes	Fertilization rate (%)	Embryos/ cycle	Implantation rate (%)	Pregnancy rate/cycle (%)	Live birth rate (%)	Cancellation rate	Ref.
		2 ± 1.9	7	7	8	17/68 (28%)	[54]
		2.8 ± 2; p = 0.024	16; p = 0.048	19; p = 0.037	24; p = 0.049	8/136 (6%); p < 0.001	
							[111]
10.6 ± 4.2	60.9	2.5 ± 0.1	15	37.4			[62]
8.6 ± 6.3; NS	61.4; NS	2.3 ± 0.9; NS	14.9; NS	34.6; NS			
							[63]
10.4 ± 5.4	60.8 ± 26	6.1 ± 3.1	31.5 ± 38.4	48.3			[68]
6.1 ± 3.8; p = 0.02, group 1 vs 2	80.1 ± 25, NS	4.5 ± 2.8, NS	32.3 ± 43.1, NS	19.2; p = 0.04			
	67.5 ± 1.32	5.8 ± 1.7	30.70	32.3	66.6		[71]
	70 ± 0.55, NS	7.2 ± 0.5, NS					

the three-stage technique (Table 7). The study also found that the AFC was significantly higher in the patients who underwent the three-stage technique (Table 3) [61]. However, as previously outlined, thermal damage is still a risk. A drawback to the three-stage technique is the length of time that is needed before IVF can be started. More research is needed to determine if this procedure increases IVF outcomes as compared with expectant management.

Combined ablation & cystectomy

In 2010, Donnez *et al*. developed a surgical technique that combines cystectomy and CO_2 ablation. A surgeon removes 80–90% of the cyst with the cystectomy technique and uses the laser to ablate the remaining cyst wall. A GnRH agonist is then used for 3 months following surgery. This technique reduces the risk associated with cystectomy and recurrence associated with ablation alone. 6 months after surgery, the ovarian volume and AFC in the operated ovary and contralateral ovary were not significantly different (Table 3). The pregnancy rate was 41% after a mean follow up of 8.3 months (Table 6). Recurrence was noted in one case (2%) (Table 5) [65]. IVF rates were not reported by Donnez *et al*., and more research is needed in order to assess the benefits of combined ablation and cystectomy on infertile women who do not achieve spontaneous pregnancy following surgery. The benefit of this surgery over traditional laparoscopic procedures is that recurrence rates are low, although a longitudinal randomized control trial study is needed to fully assess recurrence rates. For both the three-stage technique and combined ablation and cystectomy, more research is needed on the potential of using the KTP or plasma laser to maximize fertility outcomes. A potential disadvantage to this procedure is that it can remove healthy cortex and cause thermal damage.

Table 5. Surgical technique and recurrence rates.

Study (year)	Type of study	Subjects	Treatment	Subjects (n)	Mean diameter (cm)	Bilateral (%)	Recurrence rates	Average time to recurrence	Ref.
Aspiration									
Zhu *et al.* (2011)	Retrospective	Infertile and OE	Aspiration	129	9.3 ± 6.2	20.90	91.5% after first treatment, 66.7% after second, 46.5% after third, 21.7% after fourth, 9.3% after fifth, 5.4% after sixth	At 24-month follow-up	[59]
Cystectomy									
Porpora *et al.* (2010)	Prospective, observational	OE	Cystectomy	166	4.9 ± 2.4	31.30	15/166 (9.6%)	At 5-year follow-up	[49]
Hayasaka *et al.* (2011)	Retrospective	OE, no prior surgery	Cystectomy	173	5.4 ± 1.8 nonrecurrent, 6.0 ± 2.0 recurrent		78/173 (45%) after first surgery, 10/22 (45.4%) re-recurrence after second surgery		[47]
Barri *et al.* (2010)	Observational	Infertile	OE, surgery†	144	5.8 ± 2.1	Not reported	32/144 (22.2%)		[29]
Ablation									
Shimizu *et al.* (2010)	Retrospective	Subfertile and OE	KTP laser ablation	45	3.3 ± 1.6	71.10	11/45 (24.4%)	4.9 ± 1.6 months	[63]
Ablation versus cystectomy									
Carmona *et al.* (2011)	Prospective, randomized clinical trial	OE, no prior surgery	Cystectomy (group 1)	36	6.28 ± 1.72	22.20	4/36 (11%)	At 12 months	[48]
							8/36 (22%)	At 60 months	
			Laser ablation (group 2)	38	6.25 ± 1.68	31.60	12/38 (31%); p = 0.04, group 1 vs 2	At 12 months	
							14/38 (37%) NS; group 1 vs 2	At 60 months	
Combined cystectomy and ablation									
Donnez *et al.* (2010)	Prospective	OE, no prior surgery	Combined cystectomy and ablation (group 1)	52	4.6 ± 1.3	61.50	1/52 (2%)	At 6-month follow-up	[65]
Aspiration with sclerotherapy									
Yazbeck *et al.* (2009)	Prospective	Infertile and recurrent OE	Aspiration with 95% EST	31	3.86 ± 1.12	12.90	4/31 (12.9%)	10 months	[68]

†Mostly cystectomy but exact number not reported.
EST: Ethanol sclerotherapy; KTP: Potassium-titanyl-phosphate; MT: Methotrexate; NS: Not significant (p > 0.05); OE: Ovarian endometrioma.

Table 5. Surgical technique and recurrence rates (cont.).

Study (year)	Type of study	Subjects	Treatment	Subjects (n)	Mean diameter (cm)	Bilateral (%)	Recurrence rates	Average time to recurrence	Ref.
Shawki *et al.* (2011)	Randomized control trial	OE, no prior aspiration	Aspiration with saline (group 1)	95	6.59 ± 1.85	Unilateral only	70/95 (73.6%) after first treatment, 56/95 (58.9%) after second treatment, 43/95 (45.3%) after third treatment	At 12-month follow-up	[71]
			Aspiration with MT (group 2)	93			31/93 (33.3%) after first treatment; $p < 0.05$, group 1 vs 2, 20/93 (21.5%) after second treatment; $p < 0.05$, group 1 vs. 2, 13/93 (14%) after third treatment; $p < 0.05$, group 1 vs 2	At 12-month follow-up	

†Mostly cystectomy but exact number not reported.
EST: Ethanol sclerotherapy; KTP: Potassium-titanyl-phosphate; MT: Methotrexate; NS: Not significant ($p > 0.05$); OE: Ovarian endometrioma.

Cystectomy with vasopressin

In a technique proposed by Saeki *et al.,* vasopressin was injected into the cyst to reduce the amount of bipolar coagulation needed for hemostasis and the amount of healthy tissue that is accidentally removed, since the injection of vasopressin improves the view of the plane of cleavage between the cyst and the ovary. Saeki *et al*. reported a significant reduction in the number of procedures requiring coagulation to achieve hemostasis. Saline was injected to help reduce the risk of brachacardia and also to assist in hydrodissection. Saeki *et al*. recommended vasopressin as a beneficial technique in treating endometriomas to reduce the potential loss of ovarian reserve [53]. The study, published in 2010, is the only known study to assess vasopressin, and more research is needed to determine if the vasopressin technique could help improve pregnancy rates, both spontaneous and after IVF.

Cystectomy with gelantine-thrombin matrix seal

In 2009, two research groups evaluated the use of a gelantine-thrombin matrix seal (FloSeal®, Baxter Inc., IL, USA) for hemostasis as a replacement for coagulation. Both research groups found FloSeal to be useful following cystectomy. However, longitudinal studies and studies including IVF outcomes following the procedure are needed in order to assess the benefits of FloSeal in endometrioma patients [66,67]. A clinical trial recently examined AMH levels following cystectomy with a hemostatic matrix versus bipolar coagulation, but the results have yet to be reported [202].

Aspiration with sclerotherapy

Ovarian sclerotherapy uses ultrasound-guided aspiration with a sclerosing agent such as 95% ethanol (EST) or methotrexate. The purpose of the sclerosing agent is to prevent cyst regrowth by chemically destroying the wall of the cyst. This treatment option is less invasive than laparoscopic surgery and takes approximately 20–30 min to perform. Sclerotherapy, unlike other treatment options, is less likely to damage healthy ovarian tissue and, thus, is less likely to reduce ovarian reserve. Risks associated with sclerotherapy include infection, internal bleeding, and irritation from the sclerosing agent. To reduce irritation, the agent is removed after 10 min, and the pelvic area is rinsed with saline.

Endometrioma patients treated with EST had significantly higher ongoing pregnancy rates after one IVF cycle than patients with moderate to severe endometriosis but no ovarian endometrioma (Table 4). The endometriosis-only group also had a significantly reduced ovarian reserve, as measured by FSH and AMH levels, compared with the EST group (Tables 2 & 7) [68]. In a prospective controlled clinical trial, patients were divided into an aspiration with 95% EST followed by IVF–intracytoplasmic sperm injection (ICSI) group or a control group of only IVF–ICSI. Although significance levels were not reported, the number of oocytes retrieved, fertilization rate, embryos available, implantation rate, pregnancy rate and continued pregnancy rate were all higher in the aspiration with ethanol group (Table 1) [69]. This study suggests that ethanol sclerotherapy may improve ART outcomes, but more research is needed to determine if these differences are significant.

Table 6. Surgical technique and spontaneous pregnancy rates.

Reference	Type of study	Subjects	Treatment	Subjects (n)	Mean diameter (cm)	Bilateral (%)	Spontaneous pregnancy rate	Average time to pregnancy post-operation	Ref.
Aspiration									
Zhu *et al.* (2011)	Retrospective	Infertile and OE	Aspiration	129	9.3 ± 6.2	20.90	44/129 (34.1%)	7–18 months	[59]
Cystectomy									
Porpora *et al.* (2010)	Prospective, observational	OE	Cystectomy	166	4.9 ± 2.4	31.30	28/52 (53.8%)	Within 24 months	[49]
Hayasaka *et al.* (2011)	Retrospective	OE, no prior surgery	Cystectomy	173	5.4 ± 1.8 nonrecurrent, 6.0 ± 2.0 recurrent		24/173 (13.8%) after first surgery, 3/22 (13.6%) after second surgery		[47]
Barri *et al.* (2010)	Observational	Infertile	OE, surgery† (group 1a)	483	5.8 ± 2.1	Not reported	262/483 (54.2%)	11.2 months	[28]
			OE, no treatment (group 3)	169	Not reported	Not reported	20/169 (11.8%); $p < 0.0001$, group 1 vs 3	Within 8-year period	
Ablation									
Shimizu *et al.* (2010)	Retrospective	Subfertile and OE	KTP ablation	45	3.3 ± 1.6	71.10	22/45 (48.9%)	10.4 ± 12.6 months	[63]
Ablation versus cystectomy									
Carmona *et al.* (2011)	Prospective, randomized clinical trial	OE, no prior surgery	Cystectomy (group 1)	36 (26 desired pregnancy)	6.28 ± 1.72	22.20	8/26 (30.8%)	At 60-month follow-up	[48]
			Laser ablation (group 2)	38 (24 desired pregnancy)	6.25 ± 1.68	31.60	8/24 (33.3%)	At 60-month follow-up	
Combined ablation and cystectomy									
Donnez *et al.* (2010)	Prospective	OE, no prior surgery	Combined cystectomy and ablation	52 (37 desire pregnancy)	4.6 ± 1.3	61.50	15/37 (41%)	8.3 months	[66]

†Mostly cystectomy but actual numbers not reported.
KTP: Potassium-titanyl-phosphate; OE: Ovarian endometrioma.

Methotrexate is a folate antagonist that prevents DNA synthesis and is believed to suppress cells in the endometrioma cyst wall. A randomized control trial by Shawki *et al.* compared cyst recurrence rates in women with endometriomas treated with aspiration or aspiration with methotrexate. A significant difference was noticed in the persistence of the cysts – only 14% of women had a cyst remaining after three treatments in the methotrexate group, compared with 45.3% of women in the aspiration-only group (Table 5) [70]. Methotrexate is used in ectopic pregnancies and, therefore, potential risks such as increased oocyte damage, spontaneous abortion and congenital abnormalities may be associated with its use in women trying to achieve pregnancy. However, in a case–control study of unilateral endometriomas, the AFC, number of oocytes retrieved, fertilization rate and embryo quality were not different between the ovary treated with methotrexate and the unaffected contralateral ovary (Tables 3 & 4). The researchers used methotrexate 30 mg diluted with 3 ml of saline, which is one-third of the dose normally used with ectopic pregnancies. The researchers suggested that the low dose was less toxic, and the results demonstrated that methotrexate did not negatively affect oocyte quality and future pregnancy outcomes. Twenty-one out of the 65 women using ART became pregnant, and 14 of these pregnancies resulted in a live birth – none of the neonates had post delivery congenital abnormalities (Table 4) [71]. These results further demonstrate that a low dose is a plausible treatment option. One potential downside to aspiration with methotrexate is the amount of waiting time needed until an IVF cycle can be started. In this particular study, the authors waited for a minimum of 3 months to begin COH [71]. More research is needed to determine if this treatment is plausible in women with bilateral endometriomas and if methotrexate improves IVF outcomes compared with expectant management.

Overall, newer combined techniques seem to not be as damaging to the ovary as traditional surgical techniques, but recurrence rates are high and more research is needed on IVF outcomes.

Role of fertility preservation with surgical interventions

Fertility preservation is an important consideration for women undergoing surgery for ovarian endometriomas, especially for those with existing low ovarian reserve, those at high risk for ovarian dysfunction after surgical intervention, and those who are likely to experience a recurrence of ovarian endometriomas or premature ovarian failure [72].

There are several reasons as to why fertility preservation should be a priority for patients undergoing surgical intervention for ovarian endometriomas. Surgery is often associated with a loss of ovarian reserve. Somigliana *et al.* reported a mean reduction in follicular reserve of 53% following laparoscopic cystectomy [73]. This may be the result of the excision of healthy ovarian tissue along with the endometriotic cyst [74]. In fact, follicles were found in 69% of the ovarian tissue close to the ovarian hilus that was inadvertently removed from along the wall of the endometrioma [74].

Premature ovarian failure is an additional complication associated with invasive surgery. Premature ovarian failure is associated with abnormal amounts of estrogen production and irregular release of oocytes, which can result in infertility. Too much surgery may deplete the ovarian reserve or reduce ovarian function, and too little or incomplete surgery may lead to cyst recurrence. The recurrent cysts may form spontaneously or may develop from the lesions resulting from the surgery [75]. Patients with recurrent endometriomas, especially those experiencing severe pain, may opt for additional surgical procedures to remove the new cysts, which may have a further impact on their fertility [76]. Because surgery for ovarian endometrioma is often associated with postoperative reductions in fertility, preservation and improvement of fertility should be considered before surgical intervention.

Current methods of fertility preservation in patients with ovarian endometriomas include combined surgical techniques; autotransplantation of cryopreserved or fresh, healthy ovarian tissue; and cryopreservation of oocytes or embryos. As previously outlined, Donnez *et al.* recently developed a new surgical method combining both excisional and ablative techniques [72]. This procedure allows for complete excision of the cyst without removing or damaging healthy ovarian tissue in the process, in order to avoid recurrence of the endometrioma and protect the ovarian reserve [72]. This option is likely best for women with a high chance of spontaneous conception after surgery or those patients who wish to avoid the use of ART to achieve a pregnancy.

Autotransplantation of cryopreserved or fresh ovarian tissue is another potential option for patients undergoing surgical intervention for endometriomas. Donnez *et al.* reported a case study of two women with severe endometriosis who underwent oophorectomy immediately followed by heterolateral orthotopic transplantation of fresh ovarian cortex tissue [77]. Viable primordial follicles were found in both cases, and revascularization of the transplanted tissue was demonstrated by the presence of a network of many small vessels. This procedure helps increase the follicular reserve of the remaining or unaffected ovary.

In 2010, Oktay *et al.* conducted a follow-up with 59 female cancer patients who had undergone ovarian tissue cryopreservation between May 1997 and March 2008 [78]. Of these women, 5.1% had chosen to reimplant the harvested tissue, and one woman was able to spontaneously achieve a pregnancy. The study concluded that ovarian tissue cryopreservation and transplantation appear to be a safe and relatively effective procedure, but evidence is limited due to the low clinical utilization of the technique. Ovarian tissue autotransplantation is the best option for women undergoing radical oophorectomy, with a high likelihood of recurrence after conservative surgery or when the remaining healthy ovarian tissue may be compromised [72].

Oocyte and embryo cryopreservation are effective methods of fertility preservation for patients with ovarian endometriomas. Recent improvements in oocyte freezing thawing using both slow freezing and vitrification techniques, and a growing body of evidence that these techniques are successful, have expanded the potential use of this process as a method of fertility preservation [79]. Embryo cryopreservation is currently the only established method of fertility preservation in women, as oocyte and ovarian tissue cryopreservation remain experimental techniques [80]. However,

Table 7. Surgical technique and anti-Müllerian hormone.

Study (year)	Type of study	group	Treatment	Subjects (n)	Mean diameter (cm)	Bilateral (%)	AMH (ng/ml)	Ref.
Cystectomy								
Kitajima *et al.* (2011)	Prospective cohort	Ovarian cyst	OE, cystectomy† (group 1)	19	6.7 ± 1.9	Unilateral only	-1.25 (MD), -24.6%D	[113]
			Non-OE cyst, cystectomy (group 2)	13	6.8 ± 2.1, NS, group 1 vs 2	Unilateral only	3.3%D; p = 0.02, group 1 vs 2	
Ercan *et al.* (2010)	Prospective cohort	OE, no prior surgery	Cystectomy†, unilateral OE (group 1)	33	0.59 ± 0.08	Unilateral only	-0.79 (MD)	[98]
			Cystectomy†, bilateral OE (group 2)	14	0.86 ± 0.11	Bilateral only	-0.27 (MD); NS, group 1 vs 2	
			Control – fertile, no OE (group 3)	12			2.06 ± 0.51; NS, group 2 vs 3 (baseline and follow-up)	
Biacchiardi *et al.* (2011)	Prospective cohort	Normo-ovulatory and OE	Cystectomy†	43	3.68 ± 1.08	23.30%	-1.7 (MD); p < 0.001	[56]
Ercan *et al.* (2011)	Prospective cohort	OE, no prior surgery	Cystectomy†	36	5.2 ± 1.4	Unilateral only	-0.08 (MD), NS	[112]
Lee *et al.* (2011)	Prospective cohort	OE, no prior surgery	Cystectomy†	13	4.0 ± 1.8	Unilateral only	-1.4 (MD); p < 0.002, baseline vs follow-up	[114]
Hirokawa *et al.* (2011)	Prospective cohort	OE, no prior surgery	Cystectomy†, unilateral (group 1)	20	6.1 ± 2.5	Unilateral only	-1.2 (MD)	[99]
			Cystectomy†, bilateral (group 2)	18	6.7 ± 1.8, p = 0.125, group 1 vs 2	Bilateral only	-2.4 (MD); p < 0.001, group 1 vs 2	
Cystectomy versus three-stage technique								
Tsolakidis *et al.* (2010)	Prospective, randomized controlled trial	OE, no prior surgery	Cystectomy † (group 1)	10	3.79 ± 0.48	Unilateral only	-1 (MD); p = 0.026, baseline vs follow-up	[61]
			Three-step (group 2)	10	3.68 ± 0.55	Unilateral only	-0.51' NS, baseline vs follow-up, p = 0.026, group 1 vs 2	

†Study included in Raffi *et al.* (2012) meta-analysis [50].
%D: Percent difference baseline versus follow-up; AMH: Anti-Müllerian hormone; EST: Ethanol sclerotherapy; MD: Mean difference (baseline vs follow-up); MT: Methotrexate; NS: Not significant (p > 0.05); OE: Ovarian endometrioma.

Table 7. Surgical technique and anti-Müllerian hormone (cont.).

Study (year)	Type of study	group	Treatment	Number of subjects	Mean diameter (cm)	% Bilateral	AMH (ng/ml)	Ref.
Aspiration with sclerotherapy								
Yazbeck *et al.* (2009)	Prospective	Infertile and recurrent OE	Aspiration with 95% EST (group 1)	31	3.86 ± 1.12	12.90	3.1 ± 2	[68]
			Contro – Stage III/IV endometriosis, no OE (group 2)	26			2.2 ± 2.9; p = 0.03, group 1 vs 2	
Shawki *et al.* (2012)	Prospective case–control	Infertile and OE	Aspiration with MT	65	6.5 ± 1.53	Unilateral only	3.3 ± 0.4	[71]
Expectant management versus traditional treatments								
Hwu *et al.* (2011)	Retrospective	Tubal or male infertility (group 1)	No treatment	1323			3.94 (≤30 years old), 3.31 (31–35 years), 1.98 (≥36 years)	[37]
		In situ OE, no prior surgery (group 2)	No treatment	141	≥3 cm (mean not reported)	22.60	2.97 (≤30 years old); p < 0.05, group 1 vs 2; 2.34 (31–35 years); p < 0.001, group 1 vs 2; 1.35 (≥36 years); p < 0.05, group 1 vs 2	
		Unilateral (group 2a)		109			2.45 ± 0.17	
		Bilateral (group 2b)		32			1.56 ± 0.24; p < 0.05, group 2a vs 2b	
		Prior cystectomy OE (group 3)	Prior cystectomy	147	≥3 cm (mean not reported)	44.90	1.74 (≤30 years old); p < 0.001, group 1 vs 3; p < 0.05, group 2 vs 3; 1.53 (31–35 years); p < 0.001, group 1 vs 3, p < 0.05, group 2 vs 3; 0.53 (≥36 years); p < 0.001, group 1 vs 3; p < 0.05, group 2 vs 3	
		Unilateral (group 3a)		81			1.48 ± 0.14	
		Bilateral (group 3b)		66			1.01 ± 0.11; p < 0.05, group 3a vs 3b	
		In situ OE cystectomy (group 4)	Cystectomy†	31	≥3 cm (mean not reported)	Unilateral only	-1.94 (MD); p < 0.01	

†Study included in Raffi *et al.* (2012) meta-analysis [50].
%D: Percent difference baseline versus follow-up; AMH: Anti-Müllerian hormone; EST: Ethanol sclerotherapy; MD: Mean difference (baseline vs follow-up); MT: Methotrexate; NS: Not significant (p > 0.05); OE: Ovarian endometrioma.

embryo cryopreservation requires the patient to have a partner. Oocyte cryopreservation offers more flexibility, as IVF can be used with either donor or a partner's sperm when a woman desires to become pregnant in the future. As outlined previously, ovarian endometriomas are associated with reductions in oocyte quality, and further research is needed to determine the potential effectiveness of oocyte cryopreservation as a fertility preservation measure in women with endometriomas. Oocyte and embryo cryopreservation are especially useful methods for women with low ovarian reserve, and should be considered the first line of treatment for patients with a high risk of premature ovarian failure following surgical intervention for ovarian endometriomas [72].

Fertility preservation is recommended as a part of pre-operative counseling for young patients with endometriosis [81]. Along with the guidance of their surgeons, women should carefully consider each method of fertility preservation before undergoing surgery for ovarian endometrioma, and decide which option fits best with their plans for fertility in the future.

Nonintervention for ovarian endometrioma (expectant management)

As previously noted, the risks associated with surgical procedures for ovarian endometriomas are high, and the proper treatment protocol is a matter of debate, especially in women trying to conceive. There are no well-designed randomized control trials using nonintervention as a potential treatment option for endometriomas due to ethical reasons [82]. The European Society of Human Reproduction and Embryology recommends laparoscopic surgery in the treatment of endometriomas that are more than 4 cm in diameter [83]. However, several recent studies (see Table 1), including a meta-analysis by Tsoumpou *et al.*, are promoting a change in the protocol as surgical management does not seem to significantly improve IVF clinical pregnancy rates per cycle compared with no treatment (OR: 1.34; 95% CI: 0.61–1.38). In addition, there is no significant difference in the number of embryos available (WMD: 0.57; 95% CI: -0.27–1.41), oocytes retrieved (WMD: -1.53; 95% CI: -3.23–0.17) and gonadotropin required for stimulation between expectant management and surgical intervention (WMD: 1.55, 95% CI: -9.21–12.31) [82].

Risks

One risk that endometrioma patients should be concerned with is cyst puncture during oocyte retrieval. Benaglia *et al.* reported that 2.8% of patients had a cyst punctured during oocyte retrieval. All patients were given a propholactic antibiotic [84]. Although none of the women developed infections, case studies have reported infection following oocyte aspiration. The women who developed infection required intravenous antibiotics and in one case, bilateral oophorectomy [85,86]. Suwajamkorn *et al.* found no significant difference between patients with a punctured endometrioma during oocyte retrieval, nonpunctured endometrioma and control patients regarding oocyte and embryo quality. However, the fertilization and pregnancy rates were lower in the patients with punctured cysts [87]. Contamination could potentially affect embryo development and implantation, but more research is needed.

Similarly, spontaneous rupture of the endometrioma is a risk associated with expectant management. As with puncture during oocyte retrieval, infection may occur. In a small case study follow-up 3 years after rupture, three out of 11 women achieved pregnancy, which suggests that rupture does not negatively affect future fertility [88]. In response to COH, Benaglia *et al.* reported that none of the 58 women who underwent IVF with an *in situ* cyst experienced spontaneous rupture or pelvic inflammatory disease [89]. A concern among critics of expectant management is the increase in size of an untreated endometrioma during COH. Benaglia *et al.* found no significant difference in cyst volume before and after IVF–ICSI. However, only ten out of 70 (14.3%) cysts examined were greater than 3 cm, so the conclusion is that IVF–ICSI is safe in endometrioma patients, but should not be overgeneralized to all cases [89].

If a woman becomes pregnant following IVF–ICSI, some researchers argue that the endometrioma can cause pregnancy complications such as preterm birth, antepartum hemorrhage, placenta complications or pre-eclampsia [90,91]. Other researchers disagree, and have found that pregnant women with endometriosis are not at a greater risk for complications during pregnancy [29]. A recent multicenter retrospective cohort study looking at pregnancy outcomes in women with ovarian endometriomas and women undergoing IVF for other infertility issues found that ovarian endometriomas did not increase obstetrical complications in pregnant women and the live birth rate was not significantly different between the two groups [92].

Another risk associated with expectant management is the potential to miss a diagnosis of early-stage malignancy. However, only 0.7% of women develop malignancy from endometriosis [93,94]. Van Holsbeke *et al.* found that CA-125 levels were not useful in distinguishing ovarian endometriomas from other benign ovarian tumors and malignancies, but that color Doppler ultrasound observation of the flow in papillations was useful in premenopausal women. With continued monitoring, malignancies can be detected by an experienced sonologist without surgical removal, with a 0.9% risk of misclassification of malignancies as endometriomas [12]. Tanaka *et al.* found that the mean diameter of malignant tumors was significantly larger than that of benign tumors (11.2 vs 7.8 cm, respectively) [95]. In another study by Tanaka *et al.*, unilateral cysts were more likely to be malignant than bilateral cysts, and in cases of the latter, when one cyst was significantly larger than the contralateral cyst, the woman was at an increased risk of malignancy [96].

Guidelines for selection of cases for surgical treatment or expectant management

Reduced ovarian reserve prior to treatment

As previously mentioned, surgical treatment potentially impairs ovarian reserve (Tables 2, 3 & 7). In a recent meta-analysis, Raffi *et al.* found a significant decrease in AMH following cystectomy (Table 7) [50]. One study in the meta-analysis reported a 40% decrease following surgery [56]. In a recent retrospective analysis, Hwu *et al.* reported that women with ovarian endometriomas and low AMH levels prior to surgery had an increased risk of ovarian failure following cystectomy [37]. Therefore, in women with already reduced ovarian reserve (AMH <0.5 ng/ml) prior to treatment, expectant

management should be considered as an optimal treatment plan or fertility preservation techniques should be discussed prior to surgical treatment.

A recent retrospective study in women with prior cystectomy of unilateral endometriomas reported that women with a higher intact ovarian reserve had a higher risk of recurrence [97]. Therefore, asymptomatic women with a high ovarian reserve should be advised on the risk of recurrence and, thus, future fertility issues.

Laterality

Ercan *et al.* found no significant difference in AMH levels between unilateral and bilateral ovarian endometrioma patients pre- or post-cystectomy, and both groups were not significantly different from the control normo-ovulatory group. However, the sample size was small, and the cyst diameters were also very small [98]. More recently, Hwu *et al.* reported that women with bilateral endometriomas already have a reduced ovarian reserve, measured by AMH levels, compared with women with unilateral endometriomas in both nonoperated and cystectomy populations [37]. As previously mentioned, ovarian reserve significantly decreases after cystectomy, and significantly more so in bilateral procedures (Table 7) [50,99]. This leaves women with bilateral endometriomas who already have a reduced ovarian reserve prior to surgery with an increased risk of ovarian failure. In a study by Busacca *et al.*, two out of the 126 (2.4%) bilateral endometrioma patients undergoing cystectomy had ovarian failure [52]. This finding was supported in a recent retrospective study in which two out of 66 (3.03%) bilateral endometrioma patients had ovarian failure following cystectomy. No unilateral patients (n = 81) had ovarian failure. Furthermore, seven of the 66 bilateral (10.6%) cystectomy patients had severely reduced ovarian reserve (AMH <0.5 ng/ml) compared with only one (1.2%) unilateral patient with severely reduced AMH levels [37]. It has been postulated that in unilateral cases, the unaffected ovary compensates for the reduced ovarian reserve in the ovary with endometriosis, and thus, IVF rates are not different following surgery. This is supported by a prospective study of women with unilateral ovarian endometriomas who underwent cystectomy. No oocytes were retrieved from the operated ovary in 29% of cases compared with only 3% of cases with contralateral unaffected ovaries [100]. In a retrospective case–control study, women with prior cystectomy for bilateral endometriomas had a significantly reduced clinical pregnancy rate per cycle, live birth rate per cycle and implantation rate compared with controls (male factor, tubal factor or unexplained infertility) [54]. Therefore, in women with bilateral endometriomas, surgery should be avoided due to the already reduced ovarian reserve and potential for ovarian failure following surgery.

Size, location & hindering effects of cyst

The revised American Society of Reproductive Medicine (rASRM) staging is used to help identify the severity of endometriosis. Adhesions and larger cysts are considered a more severe form of the disease. Hayasaka *et al.* found that a high rASRM score is a risk factor for recurrence in women undergoing ovarian cystectomy [47]. Therefore, women with a high rASRM score should be aware of the chance of recurrence following surgery. A potential problem is that an accurate categorization of rASRM can only be made during a laparoscopic procedure. A cut-off value for the diameter of the cyst is a controversial subject. In a histological assessment after cystectomy, a significant negative correlation between cyst size and the number of follicles removed during cystectomy suggest a potential cut-off value could not be determined. Rather, the authors suggest that younger women with small endometriomas should be advised that healthy follicles could be removed during surgery [101]. In a retrospective study on women with unilateral endometriomas without prior surgery, there was no significant difference between the affected and unaffected ovary in the number of oocytes retrieved, regardless of size (Table 1). There was also no significant correlation between the size of the endometrioma and the number of oocytes retrieved. The number of cysts on the affected ovary did not influence the number of oocytes retrieved [39]. These results indicate that the presence of endometriomas, regardless of size, does not negatively affect IVF outcomes.

Although there is no consensus regarding the exact size of a cyst recommended for surgery, most research supports the removal of cysts that hinder oocyte retrieval. Nakagawa *et al.* suggest surgical treatment in larger endometriomas to establish the pelvic anatomy for oocyte retrieval [102]. As previously stated, the risk associated with oocyte contamination from a punctured cyst is thought to be minimal. Several authors report the location of cysts blocking healthy follicles as a reason for surgery prior to IVF [39,103,104]. However, more research is needed to determine if surgical removal of hindering cysts has better outcomes compared with the risk of accidental puncture during oocyte retrieval. A combined technique such as sclerotherapy with methotrexate or 95% ethanol, or the three-stage technique, could potentially reduce the size of the endometrioma with minimal damage to the healthy follicles located behind the cyst.

Age of woman

A woman's fertility potential decreases with age and the rate of decline of primordial follicles increases around the age of 37.5 years [105]. In women younger than 35 years, infertility is defined as failure to conceive after at least 1 year of trying without protection. However, women over the age of 35 are considered infertile after only 6 months of failure to conceive. Therefore, in older women with ovarian endometriomas, time is a factor that needs to be considered when deciding on a treatment option. Age and AMH levels in women with ovarian endometriomas are negatively correlated, regardless of endometrioma treatment. AMH levels in cystectomy patients who were older than 35 years were found to be significantly lower than levels in both the control (tubal factor, male factor or unexplained infertility) and the nontreatment endometrioma group (Table 7) [37]. As mentioned previously, a reduced ovarian reserve prior to surgical treatment has an increased potential for ovarian failure.

However, women younger than 32 years have a higher risk of losing follicles during cystectomy than older women. In general, age and follicles removed during surgery were inversely related. However, when the women were divided into groups based on

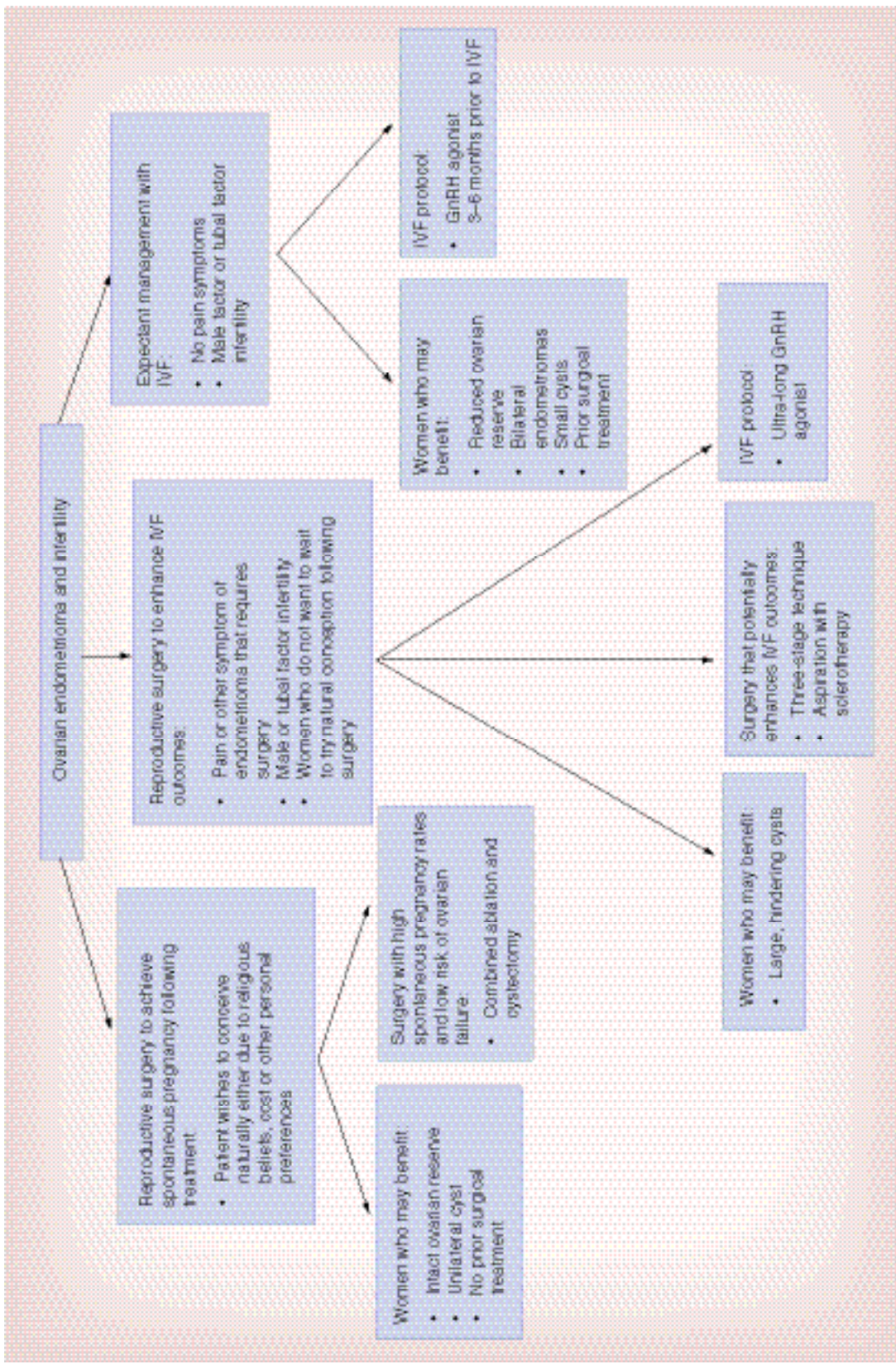

Figure 1. Treatment paths for women with ovarian endometriomas who wish to conceive.
GnRH: Gonadotropin-releasing hormone.

the median age of 32 years, the correlation was only significant in the older group of women. This relationship could be due to the physiological involution of the ovaries in aging women or the decreasing follicle pool found in older women [101]. After histological examination, a significant correlation was found between age and capsule composition with younger women having fibroblastic tissue and older women having fibrocytic tissue. The fibroblastic tissue was associated with higher follicular loss after cystectomy, and Romualdi *et al.* suggested that the cyst wall composition is a predictor of ovarian damage following surgery. However, there are currently no diagnostic tests for endometrioma capsule composition. As previously discussed, younger women with smaller endometriomas should be advised on the increased potential of follicular depletion following cystectomy [101].

Although surgery may not remove as many healthy follicles in older women, there are currently no studies demonstrating that cyst removal improves outcomes. The reduction in follicles in histological samples may be due to the decline in ovarian reserve. In an observational study, women who underwent surgery for ovarian endometriomas and were over the age of 35 years had significantly lower spontaneous pregnancy rates than women younger than 35 years. Women over the age of 35 years also had significantly reduced clinical pregnancy rates per retrieval compared with younger women in both the surgical with IVF group and the expectant management with IVF group [29]. Therefore, women should consider the recovery time from treatment to IVF cycle.

Prior surgical treatment

In a retrospective study by Hayasaka *et al.*, 45.1% of women had recurrent endometriomas after laparoscopic excisional surgery (Table 5) [47]. These women had the option either to undergo another surgical procedure or to use IVF. In a study comparing the pregnancy rates of infertile women with endometriosis, in women who underwent one surgery, a cumulative pregnancy rate of 25% was achieved after 12 months and 30% after 24 months. This was significantly higher than the pregnancy rates in the women who underwent a second surgery for recurrent endometriosis within the same 12- and 24-month follow-up time (13 and 22%, respectively; adjusted incidence rate ratio: 0.55; 95% CI: 0.30–0.99) (Table 6) [106]. This study suggests that IVF is a plausible solution in women with recurrent endometriomas in lieu of another surgical procedure. Hayasaka *et al.* assessed women who underwent a second procedure for recurrent endometriomas and found that 45.5% of them had recurrent endometriomas within an average of 20.1 ± 21.6 months (Table 5) [47]. As stated previously, ovarian damage may occur during surgical procedures, and the additive effect of multiple surgeries may be detrimental to a woman's fertility. Therefore, in asymptomatic women with prior surgical treatment, IVF is a reasonable treatment to achieve pregnancy versus an additional surgical procedure.

Treatment paths & desire for fertility

A patient with ovarian endometrioma-associated infertility may not want IVF because of a desire to conceive naturally due to either cost, religion or other personal preferences. Some women, such as those with hindering cysts or pain, may require surgery before IVF. Based on cost and potential risks associated with surgical treatment, some patients may choose to not undergo surgical treatment prior to IVF. Therefore, we propose three treatment paths for infertile women with ovarian endometriomas:

- Reproductive surgery to achieve spontaneous pregnancy following treatment;
- Reproductive surgery to enhance IVF outcomes;
- Expectant management with IVF.

A recent, large, observational study assessed the fertility outcomes of 825 infertile women with ovarian endometriomas, who either chose to undergo surgery (group 1) and if pregnancy was not achieved then IVF (group 1b); women who chose IVF only (group 2); and women who chose not to have surgery or IVF (group 3). Group 1 mostly underwent cystectomy (exact number not reported) and had a significantly higher spontaneous pregnancy rate than the expectant management without IVF group (Table 6) [29]. Therefore, in women who choose to undergo the first treatment path and try to conceive naturally, combined cystectomy with ablation is potentially the optimal treatment option to maximize natural conception without ovarian damage. Of the women in group 1 who did not spontaneously achieve pregnancy, 144 chose to undergo IVF and the clinical pregnancy rate per cycle was not significantly different from group 2, who did not undergo surgical treatment. Barri *et al.* pointed out that the pregnancy rate was higher among group 1 when spontaneous and IVF pregnancy rates were combined (65.8 vs 32.2%) [29].

As seen in the study by Barri *et al.* and others (Tables 1 & 4), cystectomy does not improve IVF outcomes, so for a woman requiring IVF after surgery because of male factor infertility or for those who do not want to wait to conceive naturally, cystectomy should not be the first-line treatment. Although the results were not statistically significant, Salem *et al.* found improved IVF outcomes following aspiration with 95% EST [69]. More research is needed on treatment techniques that enhance IVF–ICSI.

IVF protocols to use with endometriomas

In women with *in situ* unilateral endometriomas, Benaglia *et al.* found no significant difference in the ovarian responsiveness to COH or the number of follicles retrieved between the affected and unaffected ovary (Table 1) [39,107], which is in accordance with results from previous studies. Therefore, the presence of ovarian endometriomas does not negatively affect IVF outcomes.

The goal of research on ovarian endometriomas is to determine how to improve fertility outcomes in infertile women. Two different approaches need to be analyzed: reproductive surgery to improve IVF outcomes and IVF-only protocols.

Pabuccu *et al.* compared COH protocols with a GnRH antagonist and agonist in a prospective randomized trial for women with mild-to-moderate endometriosis, prior surgery for ovarian endometriomas and *in situ* ovarian endometriomas. The mild-to-moderate endometriosis group did not differ on any outcome measures. However, in women with prior endometriomas and

in situ endometriomas, the GnRH analog resulted in significantly more mature oocytes retrieved and embryos available for transfer. In women needing to cryopreserve oocytes or embryos, the GnRH agonist was better than the GnRH antagonist. However, the implantation and pregnancy rates did not differ between the antagonist and agonist for both prior endometrioma and *in situ* endometrioma patients. Pabuccu *et al.* suggested that endometriosis negatively affects endometrial receptivity. More research is needed to explain their findings and to improve IVF protocols in women with endometriosis [108].

As previously noted, some women require surgery for ovarian endometriomas and subsequent IVF. Several recent studies reported longer stimulation times and higher doses of gonadotropins in women who previously underwent surgery for ovarian endometriomas compared with controls and women with *in situ* endometriomas [20,109]. Similarly, Yazbeck *et al.* used an 'ultra-long' GnRH agonist protocol following aspiration with EST, which resulted in a higher cumulative pregnancy rate compared with the control group, which consisted of women with mild-to-moderate endometriosis – this included a woman with prior cystectomy for an ovarian endometrioma [68]. This study demonstrates the need for individualized IVF protocols for each type of surgical procedure. More research is needed on these individualized protocols.

In a systematic review by Sallam *et al.*, three randomized trials were examined to assess the effectiveness of a GnRH agonist for 3–6 months prior to IVF in women with endometriosis compared with no treatment prior to IVF. The GnRH agonist group had a significantly increased live birth rate (OR: 9.19; 95% CI: 1.08–78.22) [110]. A clinical trial is currently being conducted to assess a different drug – triptorelin acetate, which is a GnRH analog – 3 months prior to COH in women with endometriosis and ovarian endometriomas [203].

Conclusion

This review has outlined the current treatment techniques and factors that need to be taken into consideration prior to selection of patients for treatment. As outlined in Figure 1, based on these factors, we propose three treatment paths for women with ovarian endometriomas who wish to conceive: reproductive surgery to achieve spontaneous pregnancy following treatment, reproductive surgery to enhance IVF outcomes, or expectant management with IVF. Reproductive surgery to achieve spontaneous pregnancy following treatment is advised for patients who wish to conceive naturally due to either religious beliefs, costs or other personal preferences. Women with an intact ovarian reserve, unilateral cyst and/or no prior surgical treatment may benefit from this treatment path. We recommend combined ablation and cystectomy due to the high rates of spontaneous pregnancy with reduced risk of ovarian failure. Reproductive surgery to enhance IVF outcomes is advised for women with pain, male factor infertility or women who do not want to wait to try natural conception following surgery. Women with large, hindering cysts may benefit from this treatment path. The authors recommend the three-stage technique or aspiration with sclerotherapy as less invasive procedures to enhance IVF outcomes. An ultra-long GnRH agonist is the recommended IVF protocol. In women with no pain and male or tubal factor infertility, the authors advise the treatment path of expectant management with IVF. Women with reduced ovarian reserve, bilateral endometriomas, small cysts and prior surgical treatment may benefit from this treatment path. The authors recommend a GnRH agonist for 3–6 months prior to IVF for this treatment plan.

Furthermore, this current review emphasizes the need for research and new treatment techniques based on the three individual treatment paths and factors (ovarian reserve, age, laterality, size/location and prior surgery) to achieve the best fertility outcomes. In women undergoing IVF, different IVF protocols are needed based on prior surgical treatment, patient age and ovarian reserve. Women choosing a treatment path with surgery need to be counseled on the potential for ovarian failure. More research is needed on fertility preservation techniques in women with ovarian endometriomas and how IVF protocols may need to be adapted in these cases. Understanding the different treatment paths for reproductive success can help in the selection of cases based on current research, and promotes future research for the development of specific surgical and IVF protocols based on a patient's ovarian endometrioma factors.

Expert commentary

Following an extensive search for recent studies on ovarian endometrioma treatment (Tables 1–7), we found that the factors of ovarian reserve, laterality, size and hindering effects, and prior surgical treatment were used to help select patients for surgical treatment or expectant management to improve fertility outcomes. New and improved treatment options are being created, but more research reporting IVF and pregnancy rates is crucial to determine the most effective treatment in women with ovarian endometriomas.

Five-year view

Today, there is little consensus on the proper treatment of women with ovarian endometriomas, as new research suggests that ART outcomes are not significantly different between those who undergo laparoscopic cystectomy and those who are treated with expectant management. In the future, new treatments will be developed based on how ovarian endometriomas affect fertility, in order to improve natural conception and/or enhance ART. In women with ovarian endometriomas who have an increased risk of premature ovarian failure, fertility preservation techniques will be developed for ovarian tissue and oocyte cryopreservation.

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Key issues

- Ovarian endometriomas are associated with infertility in women of reproductive age.
- Ovarian endometrioma infertility is associated with a decreased oocyte retrieval rate and reduced oocyte quality, but is not associated with reduced embryo quality.
- Traditional treatment options, such as cystectomy and ablation, are associated with lower recurrence and higher spontaneous pregnancy rates, but can potentially cause ovarian damage.
- Traditional treatments such as ablation and cystectomy do not improve IVF outcomes.
- Newer, combined techniques are being developed that are less invasive and reduce ovarian damage, but more research is needed to determine how these procedures affect IVF outcomes.
- Because invasive surgery is often associated with postoperative reductions in fertility, including diminished ovarian reserve and premature ovarian failure, fertility preservation is an important consideration for women undergoing surgical intervention for ovarian endometriomas.
- Potential methods for fertility preservation are combined surgical techniques, autotransplantation of cryopreserved or fresh healthy ovarian tissue and oocyte or embryo cryopreservation for future IVF.
- Expectant management is a potential treatment plan, as recent literature reports suggest that ovarian endometriomas do not negatively affect IVF outcomes.
- Treatment depends on a number of factors, including ovarian reserve prior to treatment, laterality, size and hindering effects of a cyst, patient age, prior surgical treatment and the patient's desire for fertility.
- In women who have undergone prior surgery for endometriomas and in those with *in situ* endometriomas, gonadotropin-releasing hormone agonists increase the number of mature oocytes and embryos available for transfer, but do not improve implantation or clinical pregnancy rates. More research is needed on optimizing IVF protocols for specific treatment plans.
- Understanding the treatment paths and ovarian endometrioma factors that affect fertility outcomes can help fertility specialists create individualized treatment plans.

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