Risks of conservative management in women with ovarian endometriomas undergoing IVF

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BACKGROUND: Classical surgical management of endometriotic ovarian cysts using the laparoscopic stripping technique has been recently questioned because of the surgical-related injury to the ovarian reserve. Accordingly, available guidelines suggest that endometriomas with a mean diameter below 4 cm should not be systematically removed before IVF procedures. However, conservative management may have some potential drawbacks and risks. The presence of the endometrioma may theoretically interfere with ovarian responsiveness to hyperstimulation and oocyte competence, the retrieval of the oocytes may be more difficult and risky, the disease may progress during the procedure, pregnancy outcome may be affected and there is the risk of missing occult malignancies with cancer development later in life. In the present review, we aimed at assessing whether these risks do exist and, if so, at estimating their clinical relevance.

METHODS: We searched PubMed for articles published in the English language between January 1990 and August 2014 that reported on endometriomas and assisted reproductive techniques. Special care was given to studies reporting data purporting to distinguish the effects of ovarian endometriomas *per sé* from those consequent to surgery for endometriosis or from endometriosis in general.

RESULTS: Based on the evidence reviewed in the present study, it can be concluded that conservative management may actually expose women to four of the following theoretical risks, i.e. infection of the endometriomas, follicular fluid contamination with the endometrioma content, higher risk of pregnancy complications and cancer development later in life. The first three conditions do not justify surgery because these events are uncommon and the number of women needed to be treated would be exceedingly high and would not justify the costs and risks of the intervention. Albeit also very rare, the possibility of developing ovarian cancer later in life is more troublesome because it is a life-threatening condition.

However, this alarmism is supported by only one cohort study and this risk can be effectively prevented by postponing surgery until after the IVF programme is concluded or when women have definitely satisfied their reproductive wishes.

CONCLUSION: The available evidence on the risks of conservative management does not support systematic surgery before IVF in women with small ovarian endometriomas.

Key words: endometriosis / endometrioma / IVF / conservative management / surgery

Introduction

Classical surgical management of endometriotic ovarian cysts using the laparoscopic stripping technique has been recently questioned because of the overwhelming evidence demonstrating that ovarian reserve may be affected by the intervention. The rate of spontaneous ovulation is lower in operated ovaries (Loh et al., 1999; Candiani et al., 2005; Horikawa et al., 2008), serum levels of anti-Mullerian hormone (AMH) decrease after surgery (Raffi et al., 2012; Somigliana et al., 2012) and responsiveness to ovarian hyperstimulation is reduced (Gupta et al., 2006; Somigliana et al., 2011). The magnitude of this damage is relevant. Based on IVF studies, ovarian responsiveness is halved in operated ovaries (Somigliana et al., 2011) and, most important-ly, ovarian reserve is definitely compromised in 13–15% of cases (Busacca et al., 2006; Benaglia et al., 2010). From a clinical perspective, the consequences of surgical mediated damage are mostly unremarkable in unilateral cases since the contralateral intact gonad may properly compensate for the reduced function of the operated one (Demirol et al., 2006; Tsoumpou et al., 2009). In contrast, the damage may become clin-ically relevant in bilateral cases. Accordingly, in women operated on for bilateral endometriomas, there is a low but definite risk of post-surgical premature ovarian insufficiency (Busacca et al., 2006; Di Prospero and Micucci, 2009), menopause occurs earlier (Coccia et al., 2011) and, in IVF cycles, responsiveness to ovarian hyperstimulation is significantly reduced and the chances of pregnancy are lower (Esinler et al., 2006; Somigliana et al., 2008).

Not surprisingly, we have witnessed during the last decade the spread of conservative management and there is now an increasing agreement that endometriomas, in particular those with a mean diameter below 4 cm, should not be systematically removed before IVF (Garcia-Velasco and Arici, 2004; Garcia-Velasco et al., 2004; Garcia-Velasco and Somigli-ana, 2009). This recommendation is clearly stated in both the ASRM (American Society of Reproductive Medicine) and the ESHRE (European Society of Human Reproduction and Embryology) currently available guidelines for the management of endometriosis (Practice Committee of the American Society for Reproductive Medicine, 2012; Dunselman et al., 2014). Surgery prior to IVF is an expensive option and exposes women to low but consistent additional risks such as vascular or intestinal injury, infections and anaesthesia-related complications. According to the results of a systematic literature review, major and minor complications occur in, respectively, 1.4 and 7.5% of laparoscopies (Chapron et al., 2002). In the context of women with ovarian endometriomas these rates may be even higher considering that most of them has already been operated, endometriosis is expected to be more advanced and adhe-sions may be more extended and dense. The conservative approach is also facilitated by the high accuracy of the non-invasive diagnosis of ovarian endometriomas using transvaginal sonography and, in doubtful cases, mag-netic resonance imaging (Guerriero et al., 2009; Savelli, 2009; Exacoustos

et al., 2014). In fact, a balanced and shared approach with the women, taking into consideration all the pros and cons of surgery, is currently recommended. This view is clearly advocated in the recent ASRM and ESHRE guidelines for the management of endometriosis (Practice Committee of the ASRM, 2012; Dunselman et al., 2014). As a matter of fact, more and more infertile women with ovarian endometriomas will enter an IVF programme without surgical treatment for the endometriomas.

However, conservative management is not without potential draw-backs and risks. The presence of the endometrioma may interfere with ovarian responsiveness to hyperstimulation and oocyte competence, the retrieval of the oocytes may be more difficult and risky, the disease may progress during the IVF procedure, pregnancy outcome may be affected and there is the risk of missing occult malignancies or causing cancer development later in life (Somigliana et al., 2006; Garcia-Velasco and Somigliana, 2009; Practice Committee of the ASRM, 2012). The overall magnitude of these risks is considered modest but, to our knowl-edge, a systematic approach to this issue is lacking in the literature. Drawing a clear figure for these risks is crucial in order to properly counsel affected women and to help the physicians in the complex decision-making process. In the present study, we thus performed a sys-tematic review of the literature aimed at assessing whether these risks do exist and, if so, estimating their clinical relevance.

Methods

We searched PubMed for articles published in the English language between January 1990 and August 2014 using the following MeSH search terms: 'endometrioma' OR 'endometriotic ovarian cyst' OR 'ovarian endometri-osis' combined with 'Assisted Reproductive Technology' OR 'ART' OR 'in vitro fertilization' OR 'IVF' OR 'intracytoplasmatic sperm injection' OR 'ICSI' with restriction to the human species. Data were extracted independ-ently by four investigators (L.B., E.S., A.B. and A.P.) who also performed an initial screening of the title and abstract of all articles to exclude citations deemed irrelevant to all observers. A manual search of review articles and cross references completed the search. Data presented exclusively as abstracts in national and international meetings were also excluded. Special care was given to studies reporting data purporting to distinguish the effects of ovarian endometriomas per sé from those consequent to surgery for endometriosis or from endometriosis in general. A binomial dis-tribution model was used to estimate the 95% confidence interval (95% CI) of proportions.

Ovarian responsiveness to hyperstimulation

IVF outcome in women with ovarian endometriosis has been extensively studied (Gupta et al., 2006; Tsoumpou et al., 2009; Harb et al., 2013). All the available studies and meta-analyses are however exposed to sig-nificant confounders. Most of the available contributions included both

previously operated and non-operated women, do not distinguish women with unilateral and bilateral endometriomas and used as controls infertile women with non-endometriosis indications for IVF. These inaccuracies significantly affect the results and, to date, definite conclusions from the available meta-analyses are difficult to draw.

However, the literature offers some wise, even if less considered, contributions that are more enlightening in the context of this review. In particular, studying never operated women with unilateral endometriomas undergoing IVF is a valuable model to reliably investigate the detrimental effects of these cysts on the responsiveness to ovarian hyperstimulation. Comparing ovarian responsiveness in the affected ovary and in the contralateral intact gonad protects the findings from several confounders, such as age, regimen of stimulation and drug dosage, since each eligible woman provides both a case (the affected ovary) and a control (the contralateral intact gonad). Moreover, this study design also offers the possibility to use paired statistical analyses that are more efficient.

We identified seven studies in the literature evaluating ovarian responsiveness to hyperstimulation in never operated women with unilateral endometriomas (Somigliana *et al.*, 2006; Almog *et al.*, 2011; Benaglia *et al.*, 2011; Esinler *et al.*, 2012; Ashrafi *et al.*, 2014; Coccia *et al.*, 2014; Filippi *et al.*, 2014) (Table I). Three studies were prospective (Ashrafi *et al.*, 2014; Coccia *et al.*, 2014; Filippi *et al.*, 2014). None of them documented significant differences in terms of ovarian responsiveness (Table I). Some differences however emerged when including more than one cycle per woman (Somigliana *et al.*, 2006), when exclusively focussing on the larger follicles (Coccia *et al.*, 2014) or the oocytes retrieved (Coccia *et al.*, 2014).

A possible limitation of the available evidence is that most studies included women with relatively small endometriomas. Evidence from women with larger lesions is thus required. On the other hand, it has to be underlined that, in four of these studies, some sub-analyses were drawn to evaluate the impact of the size of the endometriomas. A potential detrimental effect of the dimension of the cyst emerged in two of them (Somigliana *et al.*, 2006; Coccia *et al.*, 2014) but could not be found in the other two (Almog *et al.*, 2011; Benaglia *et al.*, 2011).

Evidence from non-IVF contexts (and thus including larger lesions) is more conflicting but also generally tends to rule out a marked effect of the presence of ovarian endometriomas. On one hand, two studies observed a 1:2 ratio of ovulation between the affected and contralateral

intact gonads in unoperated women with unilateral endometriomas, thus suggesting a possible detrimental effect (Horikawa *et al.*, 2008; Benaglia *et al.*, 2009). On the other hand, five studies reported on preoperative serum AMH in women with endometriomas and four of them did not observe any difference with controls (Kitajima *et al.*, 2011; Streuli *et al.*, 2012; Kim *et al.*, 2013; Somigliana *et al.*, 2014). Only one small study documented lower serum AMH in women with endometriomas (Uncu *et al.*, 2013).

Oocyte competence

Even if data on ovarian reserve and ovarian responsiveness are reassuring overall, at least in women with endometriomas smaller than 30 mm, there is the need for evidence on the quality of the oocytes that can be retrieved from affected ovaries. Of relevance here is that the ovarian endometriomas have been shown to contain a plethora of factors that can be potentially toxic to the oocytes (Sanchez *et al.*, 2014a). Some of these factors, such as free iron in particular, can actually easily diffuse through the cyst wall and can thus display their toxic effects to the adjacent growing follicles (Sanchez *et al.*, 2014b).

Again, data from women with unilateral endometriomas undergoing IVF may be very informative. Unfortunately, most of the contributions using this study design are retrospective and thus meaningless on this point because oocytes retrieved from affected and unaffected ovaries are typically handled together during the laboratory phase and there is no way to retrospectively obtain independent data. In fact, only two of these studies provide valuable information (Ashrafi *et al.*, 2014; Filippi *et al.*, 2014). Based on data from 37 women, Ashrafi *et al.* (2014) reported a similar number of oocytes retrieved (2.8 ± 2.4 and 3.4 ± 2.7), mature oocytes (2.0 ± 2.1 and 2.3 ± 2.2), formed embryos (1.5 ± 1.5 and 2.0 ± 1.4) and top quality embryos (0.5 ± 0.5 and 0.8 ± 0.8) from the affected and contralateral intact ovaries, respectively. The rate of maturation was however lower in oocytes from affected gonads (75 versus 87%, $P = 0.04$) but the fertilization rate was similar (72 versus 70%). Filippi *et al.* compared the embryological development of the oocytes retrieved from the affected ($n = 91$) and contralateral intact ($n = 103$) gonads, respectively, of 29 women and observed that the fertilization rate (64 and 64%), the cleavage rate (58 and 51%) and

Table I Ovarian responsiveness to hyperstimulation in unoperated women with unilateral endometriomas.

Studies	No. of cases	Diameter of the cysts (mm)	Outcome*	Affected ovary	Intact ovary	P
Somigliana *et al.* (2006)	36	21 ± 7	foll. ≥ 16 mm	3.2 ± 2.0	4.1 ± 2.2	n.s.
Benaglia *et al.* (2011)	84	21 ± 8	foll. ≥ 11 mm	5 (3–7)	5 (3–8)	n.s.
Almog *et al.* (2011)	81	28 ± 4	Oocytes	6.0 ± 0.4	6.1 ± 0.5	n.s.
Esinler *et al.* (2012)	19	22 ± 5	Oocytes	5.9 ± 4.3	5.4 ± 3.8	n.s.
Ashrafi *et al.* (2014)	37	<30 mm	foll. ≥ 11 mm	7.0 ± 6.9	6.6 ± 5.8	n.s.
Filippi *et al.* (2014)	29	25 ± 9	foll. ≥ 11 mm	3.7 ± 2.4	4.1 ± 1.7	n.s.
Coccia *et al.* (2014)	64	12 (19%) ≥ 30 mm	foll. ≥ 11 mm	5.1 ± 3.2	5.7 ± 3.3	n.s.

Data are mean $\pm$ SD or median (interquartile range).
*The preferred outcome was the total number of developing follicles (foll.) (≥ 11 mm). If this outcome was not reported alternative outcomes in order of preference were the number of co-dominant follicles (≥ 16 mm) or the number of oocytes retrieved.
Benaglia *et al.* (2011) and Almog *et al.* (2011) tested statistical significance using the paired Wilcoxon test and the Mann–Whitney *U*-test, respectively. All the other contributions applied the paired *t*-test.

the rate of high quality embryos (31 and 21%) did not significantly differ (Filippi *et al.*, 2014).

A further potentially revealing study design is represented by the study of women with bilateral endometriomas because all the retrieved oocytes are potentially exposed to the detrimental effects of the cysts. Also retrospective studies can be informative here. In fact, two contributions reported on this population and they both referred to women with intact gonads as controls (Reinblatt *et al.*, 2011; Benaglia *et al.*, 2013a). Specifically, Reinblatt *et al.* compared 13 cases and 39 controls retrieving 11.2 ± 1.6 and 12.3 ± 1.0 oocytes, respectively, and showed a similar fertilization rate (66 and 73%), cleavage rate (90 and 98%) and rate of high quality embryos (66 and 75%) (Reinblatt *et al.*, 2011). Benaglia *et al* (2013a) compared 39 cases and 78 age-matched controls and the number of oocytes retrieved, respectively, differed (6.2 ± 2.6 versus 9.6 ± 4.8, $P < 0.001$) but fertilization rate (77 and 71%) and the rate of high quality embryos (33 and 33%) were similar. Interestingly, even if underpowered to draw definitive conclusions, both studies failed to document any detrimental effects associated with ovarian endometriomas on the chances of pregnancy.

Technical difficulties during oocyte retrieval

The presence of ovarian endometriomas is thought to increase difficulties during oocytes retrieval. We argue against this common simplistic assumption or, at least, against this semantic assertion. Indeed, the presence of an endometrioma does not hamper oocytes retrieval *per se*. These cysts can be easily traversed if necessary and the follicles behind the endometrioma effectively aspirated. Technical difficulties during oocytes retrieval in women with endometriomas are mainly related to two important and independent aspects. Firstly, the pelvic anatomy is commonly distorted in women with endometriosis. Ovaries are frequently displaced in less accessible locations (such as behind the uterus) and do not slide due to adhesions. In fact, the ovaries cannot always be effectively mobilized and reached. In other words, endometriosis-associated adhesions, and not endometriomas *per se*, hamper accessibility to the ovaries. Secondly, it is commonly believed that all efforts should be made to avoid traversing the endometriomas because of the risk of cyst rupture, contamination of the follicular fluid with the cyst content and endometriomas infection (see below). Aspiration of follicles that developed behind the endometrioma without traversing it may be, in some circumstances, very demanding, if not impossible.

As a matter of fact, traversing the endometrioma is in some cases necessary. This may cause some complications. A first concern here is the risk of *rupture of the endometrioma*. This event can cause sudden severe pain and possibly chemical peritonitis (Huang *et al.*, 2011, 2014). Differential diagnosis is sometimes challenging and, in some cases, women may require emergent surgery. In addition, it cannot be excluded that pelvic adhesions may be worsened following such events as a consequence of the severe inflammatory insult (Fujiwara *et al.*, 2003; Uharcek *et al.*, 2007; Huang *et al.*, 2014). Surprisingly, despite a clear rationale for concern, we failed to identify case reports linking oocyte retrieval to endometrioma rupture in the literature. We have two possible explanations. Firstly, the iatrogenic fissure caused by oocyte retrieval may be more limited than that occurring spontaneously. The hole mainly corresponds to

the diameter of the needle (16–18 gauge) whereas in spontaneous rupture the cyst wall is actually lacerated rather than only punctured. The amount of endometrioma content that can spill into the pelvis is presumably much more limited. It is also likely that, given its small diameter and the density of the endometrioma content, the hole may rapidly close spontaneously through the healing process without causing any significant spillage. Secondly, the iatrogenic perforation that can occur during oocyte retrieval may correspond to an area of dense adhesions between the ovary and the broad ligament or the pouch of Douglas. With the transvaginal approach, the surface of the ovaries that is punctured is indeed more likely to be adherent to the broad ligament, the Douglas pouch or the uterus. Furthermore, the iatrogenic puncture is more likely to cause the spread within the ovarian stroma rather than in the pelvic cavity. As a matter of fact, this spread may self-limit. Overall, it can be speculated that significant spillage within the peritoneal cavity following iatrogenic puncture is unlikely to occur.

A second possible concern is the *injury to adjacent organs* such as, in particular, the intestine. Less likely but other possible sites of injury include the local blood vessels and the ureter. Efforts aimed at reaching a displaced and non-sliding ovary and at avoiding traversing the endometrioma may actually expose women to higher risks. However, as for the rupture of the endometrioma, we failed to detect case reports in the literature. It is however unlikely that this event never occurred. Underreporting complications in the scientific literature is common and this is even more likely here considering that accidental injury to pelvic organs during oocyte retrieval may be, *prima facie* (but unreasonably), related to unskilfulness. Nonetheless, the lack of evidence in the literature suggests that this risk is, if present, very limited. In this regard, it has also to be noted that injuries determined by needles are generally not severe and may mostly self-resolve. Last, but not least, it is noteworthy that there are no data suggesting that surgery may ameliorate this scenario. Surgery may effectively excise ovarian endometriomas but has not been proved to effectively prevent adhesion reformation or facilitate oocyte retrieval (Somigliana *et al.*, 2011, 2012). Indeed, adhesions may be worsened by surgery. The idea that an operation may facilitate subsequent oocyte retrieval by normalizing the pelvic anatomy lacks supporting evidence and it is likely to be biased.

Infection of the endometrioma

Infection of ovarian endometriomas following oocyte retrieval has become a main concern for physicians engaged in IVF and endometriosis. In fact, this is currently one of the most claimed motivations in favour of surgery prior to IVF. The bloody content of ovarian endometriomas may indeed serve as an excellent culture medium and may facilitate the spread of infections (Chen *et al.*, 2004). Noteworthy, this can occur also spontaneously, i.e. in the absence of an iatrogenic cause such as oocyte retrieval (Kubota *et al.*, 1997; Chen *et al.*, 2004; Phupong *et al.*, 2004).

The development of endometrioma infection following oocyte retrieval in women with ovarian endometriomas was reported by nine independent authors (Table II) (Padilla, 1993; Yaron *et al.*, 1994; Younis *et al.*, 1997; Den Boon *et al.*, 1999; Matsunaga *et al.*, 2003; Moini *et al.*, 2005; Sharpe *et al.*, 2006; Romero *et al.*, 2013). Overall, 14 cases were described. This complication occurred despite the use of prophylactic antibiotics in at least 11 cases. The endometrioma was reported to be punctured or aspirated at the time of oocyte retrieval in seven cases. The vast majority had pelvic abscesses and required surgery. No

Table II Case reports on pelvic infections following oocyte retrieval in women with endometriomas.

Study	Women age (years)	Prophylaxis with antibiotics	Laterality	Endometrioma diameter (cm)	Puncture/ aspiration	IVF outcome	Time from oocytes retrieval[a]	Diagnosis	Treatment
Padilla (1993)	34	Yes	Unilateral	2.5	Aspirated	Ongoing pregnancy	22 days	Pelvic abscess	Surgical drainage
Yaron et al. (1994)	38	Yes	n.r.	n.r.	Aspirated	Not pregnant	2 weeks	Pelvic abscess	Unilateral adnexectomy and contralateral drainage
Younis et al. (1997)	34	Yes	Bilateral	4 (the one aspirated)	One aspirated	Not pregnant	40 days	Pelvic abscess	Drainage at 1st surgery, bilateral adenexectomy at 2nd surgery
	36	Yes	Bilateral	5 and 6	n.r.	Not pregnant	24 days	Pelvic abscess	Antibiotics and 4 weeks later bilateral adnexectomy
	29	Yes	Bilateral	1 and 1.5	n.r.	Normal delivery of a healthy newborn at term	22 days	Pelvic abscess	Antibiotics
Den Boon et al. (1999)	36	Yes	Unilateral	2.2	No	Twin pregnancy delivered vaginally at 26 weeks: 1 newborn died, one with multiple health problems at 8 months of age.	25 weeks	Pelvic abscess	Surgical drainage at 25 weeks gestation
Matsunaga et al. (2003)	35	n.r.	Unilateral	n.r.	n.r.	Singleton pregnancy ended into spontaneous delivery at 22 weeks (newborn died after birth)	14 weeks	Pelvic abscess	Unilateral adnexectomy
Moini et al. (2005)	n.r.	Yes	Unilateral	3–4	n.r.	Not pregnant	n.r.	PID	n.r.
Tsai et al. (2005)	n.r.	No	n.r.	n.r.	Aspirated	n.r.	n.r.	Pelvic abscess	Unilateral adnexectomy
	n.r.	No	n.r.	n.r.	Aspirated	n.r.	n.r.	Pelvic abscess	Surgical drainage
Sharpe et al. (2006)	35	Yes	Unilateral	4	Aspirated	Twin pregnancy delivered by CS at 31 weeks	11 weeks	Pelvic abscess	Surgical drainage at the time of CS
Romero et al. (2013)	29	Yes	Bilateral	n.r.	No	Not pregnant	1 month	Pelvic abscess	Surgical drainage
	32	Yes	Unilateral	3	Punctured	Not pregnant	2 months	Pelvic abscess	Surgical drainage
	37	Yes	Unilateral	4	No	Not pregnant	3 weeks	Pelvic abscess	Unilateral adnexectomy

PID, pelvic inflammatory disease; CS, Caesarean section.
[a]Refers to the time from oocyte retrieval to development of remarkable symptoms.

woman died, but two dramatic pregnancy complications were documented (Table II). Overall, these data indicate that endometrioma infection following oocyte retrieval can indisputably occur and that prophylactic antibiotics may reduce this risk but cannot abolish it. Moreover, it seems reasonable that puncture of the endometrioma is necessary for infection to occur, but this might not be so. In this regard, it has however to be pointed out that all reports were retrospective and it cannot be excluded that in some of them accidental puncture occurred but was not recorded.

The clinical course of endometrioma infection is problematic. Antibiotics may be ineffective because they cannot reach sufficient concentrations within the cysts. These lesions are indeed devoid of blood vessels and the cyst wall may be an effective barrier to the passage of antibiotics in sufficient amount. The oral or intravenous route may not be enough to reach this very fibrotic tissue. As a matter of fact, most cases develop into pelvic abscess and require surgery (Table II). The intervention may be demanding because of the history of previous surgery (most women have already been operated for endometriosis), the presence of endometriosis-related adhesions and the emergency setting. The affected gonads may need to be removed or, if preserved, their reserve of primordial follicles may be severely damaged. An alternative possibility would be to perform transvaginal ultrasound-guided drainage of the ovarian abscess, an option that has been shown to be effective (Gjelland et al., 2005, 2012). However, data on this approach are currently lacking since none of the described cases were treated in this manner (Table II).

From a clinical perspective, it is important to estimate the magnitude of this complication. This may play a crucial role in the balance of pros and cons of surgery when facing affected women requiring IVF. The literature is poorly informative on this point. Noteworthy, the publication of an overall scanty number of cases ($n = 14$) does not allow us to definitely conclude that this event is rare. Indeed, it is unlikely that papers reporting this complication can systematically be published in the scientific literature due to insufficient originality. This may explain why only one study reporting on three cases has been published since 2006 (Romero et al., 2013) despite the fact that the non-surgical approach is gaining consensus. To our knowledge, there are only two studies aimed at estimating the frequency of endometrioma infection following oocyte retrieval (Tsai et al., 2005; Benaglia et al., 2008). Tsai et al (2005) retrospectively reviewed 108 oocyte retrievals performed during a 5-year period and documented two cases, corresponding to 1.9% (95% CI: 0.3–5.8%). The authors speculated that pre-surgical vaginal disinfection with povidone iodine could reduce this risk since both pelvic abscesses were observed in the first study period when this measure was not performed (2 out of 56 cases, corresponding to 3.6%, 95% CI: 0.6–10.8%) and none after its implementation (none out of 52 cases, corresponding to 0.0%, 95% CI: 0.0–5.5%). This difference however did not reach statistical significance. Noteworthy, all women in this study underwent concomitant aspiration of the endometriomas at the time of oocyte retrieval. The second available study aimed at estimating the frequency of pelvic infections in women with endometriomas is a case series from our group (Benaglia et al., 2008). Women with endometriomas undergoing IVF were identified retrospectively and an active follow-up through telephone calls was performed to rule out complications that could be managed in other institutions. Overall, we failed to identify any case of infection out of 214 oocyte retrievals, including cases in which affected ovaries were punctured (189 women). The frequency of this complication in the whole cohort was thus 0.0% (95% CI: 0.0–1.7%). Unfortunately, the study was not informative on the risk in the subgroup of women with clinically evident endometrioma puncture since this event was recorded in only six women (Benaglia et al., 2008). Prophylactic antibiotics were given in both studies. Taken together, the available evidence suggests that the risk of infection in women with ovarian endometrioma undergoing IVF is very low and should not justify prophylactic surgery. Women should however be informed of this risk, they should receive large spectrum antibiotic prophylaxis and they may be monitored after the oocyte retrieval more carefully. Moreover, the endometriomas should be punctured only if deemed necessary to ensure an appropriate retrieval.

Follicular fluid contamination with the endometrioma content

Accidental contamination of the follicular fluid with ovarian endometrioma content is a possible complication of oocyte retrieval. In two retrospective separate studies of our group reporting on IVF in the presence of ovarian endometriomas, this event was recorded in 6 out of 214 (2.8%, 95% CI: 1.1–5.6%) and 19 out of 314 (6.1%; 95% CI: 3.8–9.1%) procedures, respectively (Benaglia et al., 2008, 2014). If we combine data from both contributions (corresponding to 25 events out of 528 oocyte retrievals), the frequency would be 4.7% (95% CI: 3.1–6.8%). Independent and, if possible, prospective confirmations of our estimates are however warranted. Retrospective studies are indeed likely to underestimate this complication since this event may not be systematically recorded.

Contamination of the follicular fluid with endometrioma content may affect oocyte competence and embryo development. There is a strong biological rationale to support this assumption. The endometriomas contain a plethora of factors and some of them are expected to be toxic for the oocytes (Sanchez et al., 2014a). They include growing factors such as corticotropin-releasing hormone (CRH) and urocortin (Florio et al., 2007), metalloproteinases (Mizumoto et al., 2002), cytokines such as interleukin (IL)-6, IL-8, vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-beta and tumour necrosis factor (TNF)-alpha (Badawy et al., 1998; Fasciani et al., 2000; Darai et al., 2003) and elevated concentration of free iron (Yamaguchi et al., 2008; Sanchez et al., 2014b). This elevated iron is of particular concern since high concentrations of free iron could mediate the production of reactive oxygen species via the Fenton reaction and could thus induce oxidative stress (Yamaguchi et al., 2008). This latter mechanism may be particularly relevant given the extreme vulnerability of human oocytes to this kind of insult (Devine et al., 2012).

On the other hand, direct evidence on the detrimental effects of follicular fluid contamination is scanty and controversial. In an in vivo study in mice, Piromlertamorn et al. (2013) observed that the brief exposure of the oocytes to the endometrioma content did not influence embryo development up to the stage of blastocyst but lowered the chances to reach the stage of hatched blastocyst. Evidence from the three available human studies is contradictory. Khamsi et al. (2001) compared oocytes that were and were not accidentally exposed to endometrioma content from 14 women and did not show any difference in terms of embryo development. The study did not report on pregnancy rate. Suwajanakorn et al. (2001) described 38 women with accidental contamination and

did not show significant differences in terms of quality of oocytes and embryos but a reduced fertilization rate and a lower pregnancy rate was observed. Finally, in a recent study of our group, we compared 19 cases with follicular contamination and 38 matched controls with endometriomas but without contamination and showed that *in vitro* embryo development was improved (fertilization rate and rate of top quality embryos were significantly higher) but pregnancy rate was significantly reduced in cases with follicular contamination (Benaglia *et al.*, 2014). To explain this conflicting information, we speculated that the sublethal stress associated with endometriotic content exposure might apparently improve earlier phases of embryo development while being ultimately detrimental. Noteworthy, it has been shown in animal models that transient exposure of oocytes to moderate conditions of hydrostatic pressure, hyperosmotic milieu, hydrogen peroxide (H_2O_2) or heat stress may paradoxically improve embryo development (Pribenszky *et al.*, 2010). This phenomenon was explained by the development of compensatory mechanisms (Pribenszky *et al.*, 2010). This interpretation is however speculative. However, the available conflicting evidence on this issue emerged from very small studies that are inevitably subjected to type II error. In other words, the controversial findings may be simply explained by random fluctuations.

Overall, albeit the evidence is weak and inconsistent, follicular fluid contamination with endometriomas content is uncommon but possible and may be detrimental to the chances of pregnancy. This further strengthens the importance of avoiding inadvertent puncture of ovarian endometriomas. In addition, we advocate some clinical and biological measures to cope with this complication. As soon as the dedicated team becomes aware of follicular fluid contamination, aspiration should be interrupted and the needle should be flushed with oocyte culture media or replaced. Moreover, biologists should promptly separate oocyte-cumulus complexes from the follicular fluid and rinse them (Benaglia *et al.*, 2014).

Finally, despite recognizing the potential detrimental impact of follicular fluid contamination with endometriomas content, it is mandatory to underline that surgery cannot be advocated for this reason. Based on our above-mentioned data showing a 40% relative reduction in live birth rate (from 21 to 12.6%) due to a complication occurring in 6.1% of cases, it can be calculated that the number of women needing to be treated to have one additional live birth would be 195 (Benaglia *et al.*, 2014).

Progression of endometriosis

An intuitive but poorly investigated concern in women with endometriosis undergoing IVF is the risk of disease progression. Since endometriosis is an estrogen-dependent disease and its development is fuelled by hormonal fluctuations (Burney and Giudice, 2012), one may reasonably speculate that ovarian hyperstimulation during IVF may increase the recurrence or the progression of the disease. Of further and utmost relevance here is that there is growing evidence supporting the view that endometriomas originate from ovulatory events (Vercellini *et al.*, 2010). There are at least three main lines of evidence supporting this pathogenic mechanism. Firstly, two independent authors directly demonstrated the transition from a growing follicle/corpus luteum to an endometrioma using serial transvaginal ultrasounds (Jain and Dalton, 1999; Vercellini *et al.*, 2009a). Secondly, follicular fluid is an excellent culture medium for endometrium growth (Bahtiyar *et al.*, 1998; Somigliana *et al.*, 2001). Thirdly, oral contraceptives have been shown

to almost annul the risk of ovarian endometrioma recurrence after surgery (Seracchioli *et al.*, 2010; Vercellini *et al.*, 2013a). Based on a recent meta-analysis the odds ratio (OR) of endometriomas recurrence is 0.12 (95% CI 0.05–0.29) in oral contraceptive users compared with no-users (Vercellini *et al.*, 2013a).

The available literature actually tends to support a possible detrimental effect of IVF on deep infiltrative peritoneal endometriosis. In fact, nine cases of progression of this type of lesion during IVF treatments have been reported (Renier *et al.*, 1995; Govaerts *et al.*, 1998; Anaf *et al.*, 2000; Van der Houwen *et al.*, 2014a). Obstruction of the intestine, ureter or both occurred in eight, one and one cases, respectively. However, there is no reliable estimate on the magnitude of this risk since the denominator, i.e. the number of women with deep invasive endometriosis undergoing IVF is unknown. On the other hand, the available large case series or cohort studies investigating the impact of IVF on endometriosis progression or recurrences were reassuring (D'Hooghe *et al.*, 2006; Benaglia *et al.*, 2009, 2010, 2011; Coccia *et al.*, 2010; Van der Houwen *et al.*, 2014a). In the context of the present review, one study from our group was particularly enlightening since it specifically reported data on ovarian endometriomas (Benaglia *et al.*, 2009). We prospectively evaluated 48 women with endometriomas who underwent unsuccessful IVF and compared ultrasound findings before and 3–6 months after the procedure. The median (interquartile range) diameter of the 70 studied endometriomas before and after IVF was 20 (18–25) and 21 (17–27) mm, respectively (NS). Formation of new endometriomas was observed in one case (2%, 95% CI: 0–11%) (Benaglia *et al.*, 2009).

Overall, the available data tend to exclude a relevant effect of IVF on endometriosis recurrences in general and ovarian endometriomas in particular. This is somehow surprising given the above-mentioned fundamental role of ovulation in endometriomas formation. One would logically expect the risk to be proportionally related to the number of corpora lutea formed and thus multiple ovulations should significantly enhance the rate of endometrioma formation. Noteworthy, there is evidence that, in contrast to IVF, ovarian hyperstimulation and intrauterine insemination may actually increase the risk of endometrioma recurrence (D'Hooghe *et al.*, 2006; Van der Houwen *et al.*, 2014a,b). On the other hand, it has to be pointed out that ovulation actually does not occur in IVF cycles, since follicular puncture precedes ovulation thus presumably preventing the complex and still unknown mechanisms causing the formation of the endometriomas.

Pregnancy complications

The relationship between endometriosis and pregnancy outcome is yet debated (Brosens *et al.*, 2007, 2012; Fernando *et al.*, 2009; Hadfield *et al.*, 2009; Stephansson *et al.*, 2009; Benaglia *et al.*, 2012; Vercellini *et al.*, 2012; Conti *et al.*, 2014; Mekaru *et al.*, 2014). Pre-eclampsia or pregnancy-induced hypertension were reported to be increased (Stephansson *et al.*, 2009), decreased (Brosens *et al.*, 2007) or unchanged (Hadfield *et al.*, 2009; Benaglia *et al.*, 2012; Mekaru *et al.*, 2014). The risk of preterm delivery was also controversial, being reported to be either increased (Fernando *et al.*, 2009; Stephansson *et al.*, 2009; Mekaru *et al.*, 2014) or unchanged (Benaglia *et al.*, 2012; Mekaru *et al.*, 2014). Small for gestational age (SGA) was reported to be more frequent (Fernando *et al.*, 2009; Mekaru *et al.*, 2014) or unaffected (Stephansson *et al.*, 2009; Benaglia *et al.*, 2012; Mekaru *et al.*, 2014).

Finally, there is some evidence suggesting an increase in antenatal bleeding/placental complications but this risk would be mainly limited to women with deep infiltrative lesions (Stephansson et al., 2009; Vercellini et al., 2012).

However, we are herein interested in the impact of the presence of ovarian endometriomas rather than endometriosis in general. Specific data on ovarian endometriomas were reported in two studies (Fernando et al., 2009; Benaglia et al., 2012). Fernando et al. used the Australian National registries to investigate the impact of endometriosis at the time of using assisted reproductive techniques (ART) on the risk of preterm birth and SGA (Fernando et al., 2009). They documented that women with ovarian endometriomas ($n = 95$) had a statistically significant increased risk of preterm birth when compared with fertile controls ($n = 1140$) (adjusted OR = 2.0, 95% CI: 1.1–3.6) and a statistically significant increased risk of SGA when compared with women without endometriosis undergoing ART ($n = 1201$) (adjusted OR = 2.0, 95% CI: 1.1–3.6). However, estimates in women with or without endometriomas undergoing ART ($n = 535$) were not significantly different (Fernando et al., 2009). Benaglia et al. (2012) compared pregnancy outcome between 78 women with endometriomas achieving pregnancy using IVF and 156 age-matched controls without endometriosis also achieving pregnancy through IVF. No statistically significant differences emerged for the live birth rate (adjusted OR = 0.8, 95% CI: 0.4–1.7), preterm birth (adjusted OR = 0.5, 95% CI: 0.1–1.5), SGA (adjusted OR = 0.6, 95% CI: 0.1–2.6) and other obstetrical complications (adjusted OR = 1.9, 95% CI: 0.6–5.7) (Benaglia et al., 2012). Overall, evidence is reassuring but further studies are warranted. The most suitable study design would be to compare IVF pregnancy outcome between women with endometriomas and women with endometriosis but without endometriomas at the time of the procedure.

A rare but serious complication in women with endometriomas achieving pregnancy is the risk of rupture of the cyst during pregnancy. This situation may cause chemical peritonitis and may require immediate surgery. Case reports on this subject are summarized in Table III. This event is undoubtedly rare and this may explain why it was reported in only one case in the two available case series on pregnancy outcome in women with ovarian endometriomas (Ueda et al., 2010; Benaglia et al., 2013b) and was not mentioned in the two controlled studies on women with endometriomas discussed above (Fernando et al., 2009; Benaglia et al., 2012). Importantly, pregnancy outcome was not substantially affected in the reported cases and all women recovered (Table III). The unique demanding case requiring prompt pregnancy termination despite early gestational age was reported by Reif et al. (2011). However, in this case, the main reason for delivery was diffuse haemorrhage from the adnexal mass rather than rupture. Discriminating between rupture and haemorrhage is important because surgery may prevent rupture of endometriomas but is presumably less effective for haemorrhage. Of relevance here is that spontaneous haemorrhage during pregnancy is a rare but well-known complication of pregnancy in women with a history of endometriosis and can occur regardless of the presence of endometriomas (Brosens et al., 2012). In fact, the most plausible pathogenic mechanisms of this complication are the progression and local invasion of infiltrative lesions causing blood vessel erosion or tear of vascularized adhesions. Furthermore, also in non-pregnant women, endometrioma rupture is generally associated with severe pain and chemical peritonitis but not haemorrhage (Evangelinakis et al., 2009).

Table III Case reports reporting on endometrioma rupture during pregnancy.

Study	Women age (years)	Pregnancy achievement	Singleton-twins	Gestational age	Cyst diameter (mm)	Symptoms	Concomitant bleeding	Procedure	Pregnancy course
Vercellini et al. (1992)	29	Natural	Singleton	35 weeks	80	Acute peritonitis	Absent	Cystectomy	Immediate CS (newborn fine)
Loh et al. (1998)	25	Natural	Singleton	6 weeks	40	Acute peritonitis	Absent	Cystectomy	Unaffected
Gregora and Higgs (1998)	40	Natural	Singleton	18 weeks	60	Acute peritonitis	Absent	Cystectomy	Unaffected
Garcia-Velasco et al. (1998)	25	Natural	Singleton	9 weeks	70	Acute peritonitis	Absent	Adnexectomy	Unaffected
Ueda et al. (2010)	35	ART	n.r.	2nd trimester	61	n.r.	Absent	Drainage	Unaffected
Reif et al. (2011)	25	IVF	Twins	27 weeks	n.r.	Acute peritonitis	Present	Adnexectomy	Immediate CS (both twins fine)

n.r., not reported; CS, Caesarean section.

Managing endometriomas in pregnancy may be in some cases clinically demanding for diagnostic reasons. Indeed, endometriomas may rarely undergo decidualization during pregnancy and this may present as rapidly growing cysts with abundantly vascularized intraluminal vegetations (Barbieri *et al.*, 2009; Ueda *et al.*, 2010; Mascilini *et al.*, 2014). Since this is a classical feature of malignancy, surgery may in some cases be necessary to rule out cancer. Differential diagnosis is however possible (Barbieri *et al.*, 2009; Mascilini *et al.*, 2014) and can significantly reduce the number of interventions.

Finally, endometriomas may shrink or disappear after pregnancy. In a recent study of our group on 30 women with 40 endometriomas before IVF and who were scanned after delivery, 16 cysts could not be detected (40%) and we failed to observe any lesion in 11 women (37%) (Benaglia *et al.*, 2013b). Similarly, in a retrospective study conducted on 24 pregnant women with endometriomas, and whose dimensions were recorded during and after pregnancy, Ueda *et al.* (2010) observed size increase in 4 cases (17%), no changes in 6 cases (25%), size reduction in 12 cases (50%) and disappearance in 2 cases (8%).

Endometriomas and cancer

Diagnosing an ovarian malignancy in women who recently underwent IVF is dramatic for the patient and her family, and extremely frustrating for the physician. This situation however can occur (Saylam *et al.*, 2006; Woodard *et al.*, 2012). Nonetheless, we believe that this possibility should be considered rationally and should not lead to a blind and potentially harmful clinical attitude consisting of systematic surgery (Vercellini *et al.*, 2009b, 2014). Within the context of the present review, we believe that the discussion should consider two points separately: (i) the risk of missing an occult malignancy at the time of IVF and (ii) the risk of long-term ovarian cancer development from unoperated endometriomas.

Missing an occult malignancy at the time of IVF

Histology is the only means to rule out malignancies. Unfortunately, biopsy of ovarian endometrioma without its surgical removal is practically unfeasible. Laparoscopy remains the gold standard for a definite diagnosis of endometrioma. On the other hand, transvaginal ultrasound is considered a reliable mean for endometrioma diagnosis (Guerriero *et al.*, 2009; Savelli, 2009). The sensitivity and specificity of transvaginal ultrasound have been reported to be 84–100 and 90–100%, respectively (Savelli, 2009). In inconclusive cases, magnetic resonance effectively discerns between endometriomas and other diagnoses due to its high specificity (98%) (Hottat *et al.*, 2009). Serum CA-125 may be of help but may also complicate the decision-making process. In fact, albeit frequently indicated, the validity of serum CA-125 values has not been proved to reliably discriminate between cysts with and without occult malignancies. First of all, the baseline risk of occult malignancy in ovarian endometriomas should be defined. Two commonly cited large case series suggested that this rate is low but not unremarkable. Mostou-fizadeh and Scully (1980) reported eight malignancies out of 950 operated endometriomas (0.8%, 95% CI: 0.4–1.6%) and Stern *et al.* (2001) identified nine cases out of 1000 specimens (0.9%; 95% CI: 0.4–1.6%). These rates are however an overestimate of the risk of cancer in women with ovarian endometriomas who undergo IVF. Of utmost relevance here is that these two studies were performed on histological

findings. No clinical and sonographic information was provided and it can be reasonably inferred that some of these cases could be suspected before the intervention. In other words, the presumptive preoperative diagnosis sometimes was ovarian malignancy, not endometrioma. Within the focus of the present review, we are indeed interested in the rate of malignancy among women with unremarkable endometriomas detected at ultrasound, not in the rate of malignancy among women with endometriomas in general. Only data on the rate of malignancy in women with unremarkable ovarian endometriomas at ultrasound are clinically important here. This study design was used in a recent contribution of our group in a relatively large sample size of 516 women who were operated on for 874 endometriomas that were unremarkable at preoperative ultrasound (Vercellini *et al.*, 2013b). Specifically, we observed nine specimens with atypical endometriosis and none with occult malignancy. This resulted in a prevalence rate of atypical endometriosis of 1.7% (95% CI: 0.9–3.3%) based on the number of women and 1.0% (95% CI: 0.5–1.9%) based on the number of cysts. The corresponding estimated rates of malignancies were 0% (95% CI: 0.0–0.6%) and 0% (95% CI: 0.0–0.3%), respectively (Vercellini *et al.*, 2013b), thus suggesting that this rate is at least lower than the 0.8–0.9% previously reported. On the other hand, it is mandatory to point out that atypical endometriosis is a potentially relevant condition since this may represent the initial step of the oncogenic process ultimately leading to the development of ovarian cancer later in life (Bedaiwy *et al.*, 2009; Vercellini *et al.*, 2013b). Interestingly, in a study focusing on the rate of atypia in endometriosis in general (i.e. including both ovarian and non-ovarian endometriosis), Bedaiwy *et al.* (2009) observed six cases out of 2000 studied women, corresponding to a rate of 0.3% (95% CI: 0.1–0.6%). Overall, it can be concluded that the risk of missing an occult malignancy is extremely low and with doubtful clinical implications (the number needed to treat (NNT) would be >300 based on our findings) while missing occult atypia may occur and might be of clinical relevance. Conservative management prior to IVF may indeed actually expose a subgroup of women to an increased risk of developing ovarian cancer later in life.

Cancer development after IVF

Endometriosis is associated with invasive epithelial ovarian cancer and, in particular, with endometrioid and clear cell histotypes (Somigliana *et al.*, 2006; Munksgaard and Blaakaer, 2011; Vercellini *et al.*, 2011; Pearce *et al.*, 2012; Heidemann *et al.*, 2014). Even if a causal relationship is likely (Viganò *et al.*, 2007), the strength of the overall association is however generally modest being below 2 in the vast majority of the available contributions (Somigliana *et al.*, 2006; Munksgaard and Blaakaer, 2011; Pearce *et al.*, 2012; Heidemann *et al.*, 2014). Moreover, confounding is likely in most studies. Data are generally not controlled for parity and oral contraceptives use, two variables that are well known to markedly influence the risk of ovarian cancer and to be differently distributed between women with and without endometriosis. In addition, it is noteworthy that most evidence is obtained in women operated for endometriosis and it can be plausibly expected that active endometriosis is absent following surgery in most of the cases.

The potential causal relationship between endometriosis and ovarian cancer is of particular relevance in the context of the present review considering that IVF may also increase *per se* the risk of ovarian cancer (van Leeuwen *et al.*, 2011; Rizzuto *et al.*, 2013; Stewart *et al.*,

2013). Unfortunately, there is no cohort study on the risk of ovarian cancer in women with unoperated ovarian endometriomas undergoing IVF. Considering the relative rarity of ovarian cancer (lifetime risk of ~1%), the latency period between exposure and malignancy (most ovarian cancers develop after 50 years of age) and the expected modest magnitude of the association, conclusive contributions on this point are unlikely to be available in the near future. Of further relevance here is that conservative management in women with endometriomas requiring IVF is a relatively new clinical approach. On the other hand, important information can be obtained from studies reporting on unoperated endometriomas, regardless of IVF. To our knowledge, this population was studied in only one prospective cohort study in Japan (Kobayashi et al., 2007) in which the authors detected 46 incident ovarian cancers out of a cohort of 6398 women with unoperated ovarian endometriomas followed-up for up to 17 years. Based on an expected rate of 5.1 cases, the authors calculated a standardized incidence ratio (SIR) of ovarian cancer of 8.9 (95% CI: 4.1–15.3). The risk was higher in the first 8 years after inclusion and in women who were older (>40 years) at recruitment (Kobayashi et al., 2007). This figure is worrying and, if confirmed, would foster the need for surgical removal of ovarian endometriomas once the IVF programme is terminated. On the other hand, as pointed out by Munksgaard and Blaakaer (2011), some of the included cases of this cohort were presumably originally misdiagnosed as endometriomas and not as ovarian cancer. This is supported by the study period and by the lack of a gradient effect with the time of follow-up. The cohort was indeed recruited between 1985 and 1995, a period of time when the currently available accurate diagnostic tools, such as transvaginal sonography in particular, were not systematically available. Moreover, the highest risk was documented soon after diagnosis rather than increasing with time as one would expect. The SIR was indeed 19.3 (95% CI: 6.9–30.6) when considering a period of follow-up <8 years and then subsequently decreased, thus supporting the possibility of misdiagnoses (Kobayashi et al., 2007).

Conclusions

The potential drawbacks associated with conservative management of ovarian endometriomas prior to IVF and the potential beneficial effects of prophylactic surgery are summarized in Table IV. Overall, two aspects deserve utmost consideration since they may be of practical clinical importance and surgery may prevent them: (i) the risk of endometrioma infection, (ii) the risk of development of ovarian cancer later in life. However, we do not deem these two points sufficiently relevant to claim systematic surgery prior to IVF for the following reasons.

Endometrioma infection up to ovarian abscess development is a demanding situation that requires surgery in most cases. Nevertheless, even if the ovarian reserve of affected ovaries is definitely compromised following this complication, all women facing this complication recovered. Two severe obstetrical complications at advanced gestational age actually occurred (Table II) but an earlier diagnosis might have prevented them. Moreover, the frequency of endometriomas infection is low. As mentioned above, Tsai et al. (2005) overall reported two cases out of 108 oocyte retrievals (1.9%, 95% CI: 0.3–5.8%) and in our study (Benaglia et al., 2008) we failed to document any case in 214 oocyte retrievals (0.0%, 95% CI: 0.0–1.7%). Combining data from both sets of evidence turns into two cases out of 322 oocyte retrievals, corresponding to 0.6% (95% CI: 0.1–2.0%). This translates into a NNT of 167. This compares unfavourably with the reported 13–15% rate of definitive damage to the ovarian reserve following surgery (Busacca et al., 2006; Benaglia et al., 2010). In other words, to prevent ovarian infection and subsequent definitive damage to the ovarian reserve in one case, we would cause iatrogenic definitive injury in >22 cases (13/0.6). It has finally to be underlined that this number is likely to be an overestimate since in one of the two studies used to define the risk (Tsai et al., 2005) systematic aspiration of the endometriomas was performed.

The risk of not treating a potential ovarian cancer that could occur later in life because of conservative management is worrying. However, the reported 9-fold increased risk of ovarian cancer documented in

Table IV Summary of the evidence on the risks of conservative management of ovarian endometriomas prior to IVF.

Item	Theoretical relevance	Demonstrated clinical relevance	Effect of prophylactic surgery
Ovarian responsiveness	+ +	−	Detrimental
Oocytes competence	+ +	−	Ineffective
Technical difficulties	+	−	Doubtful
Endometrioma rupture	+	−	Effective
Injury to adjacent organs	+ +	−	Doubtful
Infection of the endometrioma	+ +	+	Effective
Follicular fluid contamination with the endometrioma content	+	+/−	Effective
Progression of endometriosis	+ +	−	Effective
Pregnancy complications	+ +	+/−	Doubtful
Occult malignancy missed	+ + +	−	Effective
Cancer development after IVF	+ + +	+	Effective

A judgment is given for the theoretical relevance and for the evidence-based relevance ('demonstrated clinical relevance') for the different points separately. The different issues are judged in a semi-quantitative manner.
A judgement is also given for the potential preventive effects of surgery (effective, doubtful, ineffective or even detrimental).

women with unoperated endometriomas is based on a single study with questionable study design (Kobayashi *et al.*, 2007), and more evidence is warranted to definitely create alarm (Munksgaard and Blaakaer, 2011). Moreover, independently of the risk of ovarian cancer development in unoperated ovarian endometriomas in general, we herein exclusively focus on the need for surgery before IVF. From this perspective, we believe that the risk of malignant transformation of endometriomas is not high enough to justify systematic surgery. Cancerogenesis is a long-standing process and delaying surgery for some months or a few years is unlikely to expose women to a significantly increased risk. Surgery could be considered once the IVF programme is concluded or after delivery. Interestingly, surgery has been shown to be of some benefit in terms of enhancing the chances of natural pregnancy, also in women for whom IVF was unsuccessful (Littman *et al.*, 2005; Vercellini *et al.*, 2014). Moreover, as discussed above, some ovarian endometriomas may disappear following pregnancy (Ueda *et al.*, 2010; Benaglia *et al.*, 2013b).

In conclusion, the available evidence on the risks of conservative management does not support systematic surgery before IVF in women with small ovarian endometriomas. Women should be informed on the potential benefits and harms of surgery and a shared decision should be taken. Within this process, it has to be highlighted to women that, based on the currently available evidence, the risks associated with conservative management are overall modest and do not surmount the risks of surgery-related damage to ovarian reserve and, more in general, the risks and costs of surgery. On the other hand, surgery remains appropriate if pain is a significant concern or if the sonographic aspect of the cyst is not reassuring. Alternative surgical approaches may be more sparing in terms of loss of ovarian reserve. Some recent evidence is encouraging (Donnez *et al.*, 2010; Coric *et al.*, 2011; Var *et al.*, 2011; Ferrero *et al.*, 2012; Zaitoun *et al.*, 2013; Song *et al.*, 2014) but more robust studies and independent confirmations are warranted.

Authors' roles

E.S., L.B. and P.V. conceived and designed the study. E.S. drafted the first version of the manuscript. A.P. and P.V. systematically retrieved and interpreted the data on the biological aspects. A.B. and L.B. systematically retrieved and interpreted the data on the clinical aspects. P.V. supervised the study. All the authors revised the manuscript.

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Conflict of interest

None of the authors have any conflict of interest related to the discussed topic to declare.

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