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Assisted reproduction in endometriosis

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Endometriosis – a disease causing pain and infertility – is encountered in nearly 50% of infertile women. While medical treatment is effective on pain and recurrence of symptoms after surgical excision, it is of no help for treating infertility for which the only options considered are surgery and ART.

Surgery enhances the chances of conceiving naturally during the 12–18 ensuing months irrespective of the stage of the disease. Surgery however is of no help when ART is considered, as it does not improve outcome and can only harm the ovarian response to stimulation. Today therefore, ART is commonly the primary option to be considered in women whose infertility is associated with endometriosis and whose ovarian reserve is compromised and/or who are over 35 years of age. When, ART is envisioned it is best to opt for a segmented ART approach with agonist trigger, freeze all and deferred embryo transfer.

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Practice Points

- Endometriosis alter fertility by actions taking place in the pelvic cavity, ovaries and the uterus itself.
- Inflammatory reactions in the pelvic cavity primarily interfere with sperm–oocyte interaction, and thus affect natural conception chances.
- Surgery enhances the chances of conceiving naturally in the 12–18 months following surgery. Hence, surgery can be envisioned if there is time to wait for natural conception – ovarian reserve – and natural conception is possible (sperm, tubes).
- In today's practice, lots of patients undergo IVF-first therapy because of their advanced age and therefore diagnostic laparoscopy is not routinely practiced any more. This calls for alternate methods of diagnosing endometriosis using imaging approaches – ultrasound and MRI – notably.
- If IVF is necessary in case of endometriosis, we recommend using an antagonist protocol with GnRH trigger and deferred embryo transfer, which limits the risk of disease flaring and optimizes results.
- If IVF is opted for, there is in principle no surgery performed before IVF as this does not improve outcome and can hamper ovarian reserve. Exception to his rule of no surgery before IVF include the presence of hydrosalpinxes and very large endometrioma.

Research Agenda

- Classically, the treatment of endometriosis includes ovarian suppression using either GnRH agonist or the oral contraceptive (OC) pill. New research should aim at assessing the effects of ant fibrosis molecules on endometriosis, as commonly more than 50% of lesions are constituted of fibrosis.
- Doubts persist as to whether implantation potential of women affected by endometriosis is altered or not in IVF. Adequately designed RCTs ought to assess the exact impact of endometriosis on implantation chances in ART.
- Recent data indicate that endometriomas do not negatively affect pregnancy chances in ART. Properly designed RCTs should address this point in further details.

Introduction

Endometriosis – a disease inflammatory in nature causing pain and infertility – is of unknown origin. It interferes with fecundity by affecting the pelvic cavity, ovaries and the uterus itself [1]. Assisted reproduction technologies (ART) is a valid option – often the primary choice nowadays – for women whose infertility is associated with endometriosis. ART bypasses the pelvic cavity so that inflammation in the pelvic cavity, which interferes with natural conception, is irrelevant there. Endometriosis does affect ovaries – endometriomas – and the uterus, by interfering with the response to ovarian stimulation (OS) and implantation, respectively [1].

Assisted reproduction 40 years after Louise Brown

Nearly since inception, ART has employed OS for increasing the number of oocytes available. OS leading to the retrieval of multiple oocytes was associated with the common practice of multiple embryo transfers for enhancing ART outcome. Today – 40 years into the history of ART – we reckon that OS has been the single most effective measure ever taken for enhancing the efficacy of ART. The consequence of this symbiotic relationship between OS and ART is that the quality of the response to OC and ART outcome are often confused. The distinction between the OC response and ART outcome is, however, important, as we will see, in the setting of endometriosis.

Over the years, the efficacy of ART has markedly increased across the board. Yet, ART efficacy remains a concern for women whose response to OS is insufficient due compromised ovarian reserve, as is too often the case in endometriosis. The equation between the optimal number of oocytes retrieved and the embryos transferred has changed however. By mitigating the risk of ovarian hyperstimulation syndrome (OHSS) – through agonist trigger and deferred embryo transfer (ET) – the number of oocytes retrieved is not limited anymore. Conversely, the improved efficacy of IVF – higher implantation rates – speaks for the option of elective single embryo transfer (eSET), to curb the risk of multiple pregnancies.

New perspectives in ART – strong OS and eSET when possible – apply to women with endometriosis, as they do for other women, even if the response to OS is often diminished in endometriosis. We discuss below the impact of OS on the disease – the risk of endometriosis flare – which is adequately controlled today, as reviewed in details below. Flares of the endometriotic disease during OS are rare exceptions.

As discussed in details below, the inflammation-mediated hormonal effects of endometriosis on the eutopic endometrium – increased estrogenization and progesterone resistance – can be adequately controlled by ovarian suppression at the time of ET. Performing ET while the ovaries are suppressed is possible today through the remarkable successes of vitrification, which allows cryopreservation of embryos and deferred ET with minimal loss of embryo developmental capacity [2]. As discussed in the section dedicated to endometrial receptivity, this approach – freeze-all and deferred ET – enables ET while ovarian function is suppressed, thereby neutralizing the effects of endometriosis on endometrial receptivity [3].

Endometriosis and infertility

Impact on fertility

As said above, endometriosis is a disease of unknown origin – inflammatory in nature – that causes pain and infertility. The impact of endometriosis on fertility is verified by the respective incidence of the disease in the general population of women of reproductive age – approximately 10% – and that seen in infertile women – 40–50% [1,4].

The endometriosis related factors involved in infertility are multiple. In Fig. 1, we regrouped these factors according to three primary territories where they apply:

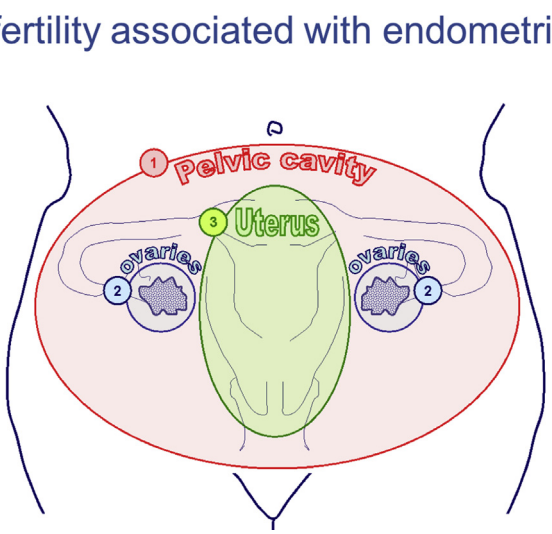

Fig. 1. Infertility associated with endometriosis. Endometriosis is responsible of inflammation related mechanisms exerted in: 1. the Pelvic Cavity; 2. Ovaries; and 3. Uterus. Adapted from de Ziegler, D., B. Borghese, and C. Chapron, *Endometriosis and infertility: pathophysiology and management.* Lancet, 2010. **376**(9742): p. 730–8., with permission.

1. Inflammation in the pelvic cavity increases the levels of inflammation related products – cytokines and other substances – which alter sperm–oocyte interactions and in this way, impede natural conception.
2. Endometriosis affecting the ovaries – and surgery for such endometriotic lesions – alters ovarian reserve and the response to OS in ART.
3. Last but not least, endometriosis is also known to alter endometrial receptivity by inflammation-related phenomena that affect the eutopic endometrium. The impact of endometriosis on the eutopic endometrium is addressed in detail in a later section of this review dedicated to endometrial receptivity.

The practical consequences of endometriosis on ART – the topic of this review – are on (i) ovarian function and in turn responses to OS and, (ii) endometrial receptivity. Conversely, the inflammatory effects prevailing in the pelvic cavity, which hamper natural conception, are bypassed in ART.

Diagnosis of endometriosis

Classically, the diagnosis of endometriosis is surgical with histological confirmation of biopsied lesions [5]. The fact that diagnostic laparoscopies are not routinely done anymore as part of all infertility workups in our ART era [6] presumably leads to under diagnosis of endometriosis. This is notably the case in the ART population if one strictly adheres to diagnosis-by-surgery rule for endometriosis. In a study recounting data from the US registry of ART activity – SART – the incidence of reported endometriosis in women undergoing ART was a low 11% [7]. This number clearly does not coincide with the incidence of endometriosis in infertile women of about 40–50% established in an era when routine laparoscopy was included in the assessment of infertility [1,4]. The majority of ART patients being infertile – except for the spouses of severe male factor infertility – a negative diagnosis bias clearly exists in the SART report [7]. This mainly results from diminished incidence of diagnostic laparoscopy in infertile women undergoing ART and hence, a marked underreporting of endometriosis in ART patients if one solely relies on the surgical diagnosis of endometriosis. We have to face the fact that diagnostic laparoscopy no is warranted when ART imposes itself as the best first-line therapeutic option. Hence, we need to revert toward alternate modes of diagnosing endometriosis in infertile women who are candidate for ART for a right picture of endometriosis in ART.

The quality of pelvic imaging has made tremendous progress in the past decade, to the point of now offering an alternate mean of diagnosing endometriosis. This is at least the case for invasive disease, such as endometriomas and the various forms of deep infiltrating endometriosis, which can reliably be diagnosed by magnetic resonance (MR) imaging and trans-vaginal or trans-rectal ultrasound [8]. The latter group of researchers propose an interesting mapping system of reporting endometriosis on pelvic ultrasound [8]. In a recent review article, Bazot and Darai showed that for deep infiltrating endometriosis, MR imaging had a sensitivity and specificity of 92% and 96%, respectively, which fulfills the criteria for qualifying as a replacement test [9]. In a Cochrane systematic review and meta-analysis, Nisenblat et al. conclude that both trans-vaginal ultrasound and MR imaging have high sensitivity and specificity for the diagnosis of deep infiltrating endometriosis, especially recto-sigmoid lesions [10]. Only the superficial forms of endometriosis evade diagnosis by trans-vaginal ultrasound or MR imaging.

Alternate noninvasive methods of diagnosing endometriosis are sought with some promising results such as serum determination of certain non-coding micro-RNAs (mRNA) [11,12]. While interesting results are being reported, none of these novel non-invasive approaches stands yet as a valid alternative(s) to surgery and/or imaging techniques [13].

Medical and surgical treatment of endometriosis

Medical treatment of endometriosis

Several forms of medical treatment for alleviating the symptoms of endometriosis have been offered over the years. Remarkably, all the existing therapeutic regimens, from danazol to GnRH

agonist (GnRH-a) – with and without addback – progestins and the oral contraceptive (OC) pill, appear to have relatively similar efficacy on pain [14] and ability to prevent recurrence after surgery [15]. Needless to say, however, the profile of side effects varies greatly among these regimens, with the OC pill taken continuously being best tolerated as well as most cost effective [15]. While the purported modes of action of these therapies differ, all share the common property of blocking ovulation. It follows, therefore, that all available medical treatments are contraceptive. Recently, reports of efficacy with titratable doses of a novel orally active GnRH antagonist, elagolix (Ferring Pharmaceuticals), provide hope that such treatment might be adjusted to the actual needs without totally blocking ovarian function [16]. It is improbable, however, that a dose can be found that preserves ovulation while retaining therapeutic efficacy.

Other treatment options are being developed, but none are available at present. As reviewed by Vercellini et al., the addition of aromatase inhibitors to ovarian blockage does not improve efficacy, while definitively creating more side effects [14].

Considering the contraceptive properties shared by all medical treatments of endometriosis, for them to be effective on fertility would imply a rebound of fecundity upon stopping. While such rebound has been hoped for, actual data speak otherwise [17]. This indicates that fertility-wise the time spent on medication is simply time lost for fertility, as no fertility rebound occurs upon stopping the medical treatments of endometriosis [17].

Surgical treatment of endometriosis

Surgical treatment of endometriosis has been shown to increase natural fecundity at all stages of the disease [18]. The figure commonly reported are pregnancy chances of approximately 50% in the 12–18 months following surgery, as reported in a meta-analysis [18]. The authors warn that these numbers may be inflated by the two following facts: (i) Not all women who underwent surgery were trying to conceive prior to surgery and, (ii) only the best surgeons tend to report their data.

Surgery for endometriosis carries the risk of altering ovarian reserve [19] and further responses to OS [20]. This is particularly the case for the surgical removal endometriomas [20,21], especially when these are bilateral [22].

The issue of whether surgery improves ART outcome is still being debated with a majority of publications indicating that surgery offers no help and may too often harm ART outcome by diminishing ovarian response to OS [23]. In a prospective analysis of AMH levels in women undergoing surgery, we observed no difference between endometriosis patients – all stages – and controls, but levels were lower in the subgroup of women who previously had surgery [19]. Other reports show lower AMH levels and antral follicle count (AFC) in women who had undergone surgery for endometriomas [24]. The sum of current data suggests that surgery for ovarian endometriosis is more likely to harm fertility than the disease itself. Moreover, the harm of surgery is highest with bilateral and/or large endometriomas [25]. Articles that looked at the different surgical techniques for managing endometriomas – excision or conservative ablation – showed no difference in their effects on ovarian reserve in spite of hopes that ablation might be less traumatic as compared to classical cystectomy [26].

Oocyte quality and quantity in endometriosis

The age-related decrease in ART outcome – plummeting after 37 years of age – appears to parallel the reported age-related decrease in the number of primordial follicles [27], as illustrated in Fig. 2. Conversely, the results of donor egg ART remain stable until the age of 50 years, as reported by SART (https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2015). This indicates that the decrease in ART outcome is due to the decrease in oocyte quality, since donation of oocytes from young to older women abrogates completely the effects of aging on fertility. The parallel decrease in oocyte quality – decrease in ART outcome – and quantity – number of primordial follicles illustrated in Fig. 2 – led to the erroneous belief that oocyte quality and quantity are inherently linked. Endometriosis as well as a number of other conditions showed us that this is not the case however. The appearance of a link between oocyte quality and quantity is only due to a bias, the effects of age, which affects both oocyte quality and quantity.

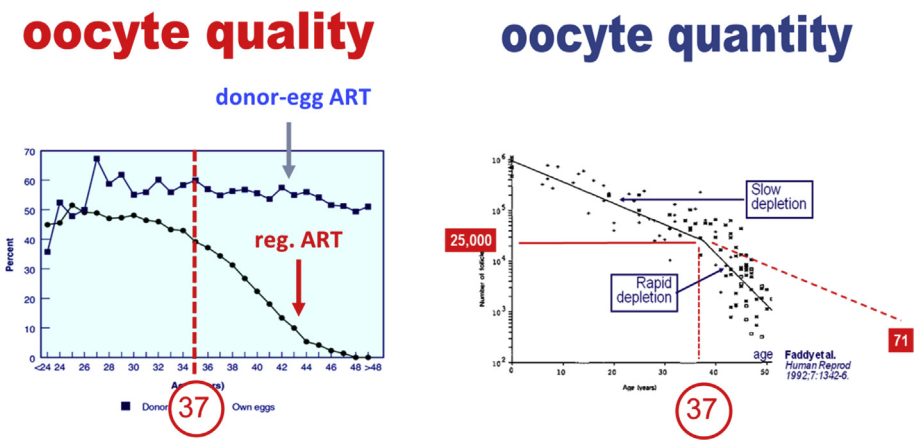

Fig. 2. Decrease of oocyte quality and quantity as a function of age. Adapted from Faddy, M.J., et al., *Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause.* Hum Reprod, 1992. **7**(10): p. 1342–6., with permission.

When oocyte quantity is affected by an age-independent factor, as for example endometriosis, there is not necessarily a decrease in oocyte quality [28]. In a recent study, we showed that the embryo aneuploidy rate was similar in endometriosis and unaffected controls, as illustrated in Fig. 3, despite poorer responses to OS [29]. Reports of similar pregnancy rates in endometriosis and unaffected controls, despite weaker responses to OS in endometriosis [30], are in agreement with this concept that oocyte quality in maintained in endometriosis. These observations, therefore, should lead to different management guidelines for patients whose poor response to OS is due to endometriosis compared to those with age-related infertility.

OS responses are often – but not always – diminished in endometriosis thus, commonly mandating energetic OS regimens. No OS regimen has been proven superior to others, so the antagonist OS protocol now is preferred, as it allows access to GnRH-a triggering, which is key for a segmented ART approach. This is indeed well tolerated in endometriosis [31]. It prevents OHSS while providing equal [32], or increased outcome [33] depending on the ovulatory status, in the general non-endometriosis population.

The issue has been raised as to whether extended ovarian suppression between the oocyte retrieval and deferred embryo transfer using GnRH agonist offers any advantage. It is possible that temporary

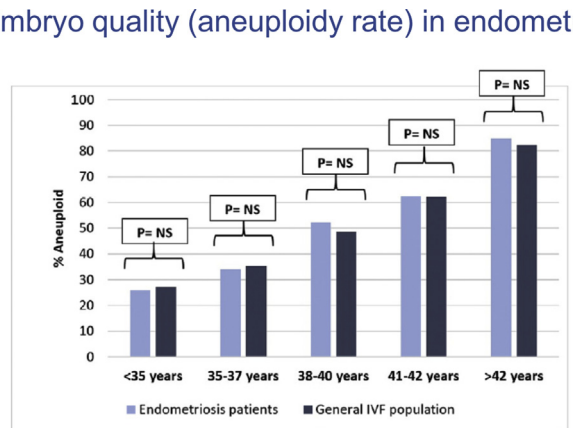

Fig. 3. Embryo quality expressed as aneuploidy rate in women suffreing from endometriosis and unaffected controls as a function of age. Adapted from Juneau, C., et al., *Patients with endometriosis have aneuploidy rates equivalent to their age-matched peers in the in vitro fertilization population.* Fertil Steril, 2017. **108**(2): p. 284–288., with permission.

ovarian suppression using a GnRH agonist or OC pill might be helpful in case of adenomyosis, but this awaits experimental verification.

Endometrial receptivity and endometriosis

A slew of publications indicates that the eutopic endometrium is altered in endometriosis [34]. The alterations encountered in the eutopic endometrium amount to two categories of disorders:

1. Increased estrogen exposure – notably through local inflammation-dependent activation of CYP-19, the gene coding for aromatase activity [35,36]. This leads to increased local production of estrogen.
2. A certain degree of inflammation-dependent resistance to the effects of progesterone, first reported by Giudice's team [37] and now widely recognized [38].

Converging evidence indicates that the functionality of the eutopic endometrium reverts to normal after ovarian function is blocked, using either GnRH agonist [39], the OC pill [40], or levonorgestrel-releasing IUDs [41].

In ART, reports have indicated that outcome improves after 3–6-month of treatment with GnRH agonist [42,43] or 6–9 weeks on the OC pill [28]. Today however, in era of embryo vitrification, the best option to consider in cases of endometriosis is to revert to segmented ART and deferred ET [3]. This allows dissociation of oocyte retrieval from ET, the latter being performed while ovarian function is suppressed using exogenous E2 and progesterone. Furthermore, the segmented ART option fosters antagonist OS protocol with GnRH agonist trigger. This approach provides milder stimulation of the ovaries compared to the classical hCG trigger. We showed this approach is less likely to cause cysts, pain and discomfort [31]. In a retrospective analysis of prospectively recorded data, we showed that OS did not trigger increased pain or other side effects compared to unaffected controls [31]. While flares of the disease can sporadically and seldomly occur, they mandate OS discontinuation. However, this is far from being the rule, contrary to earlier beliefs [31].

Endometriosis and comorbidities

Chronic endometritis

In a recent report, we provided evidence that another inflammatory process taking place in the endometrium – chronic endometritis (CE) – is frequently encountered in endometriosis [44]. In this study, the incidence of CE diagnosed by hysteroscopy, histology and CD138 immunostaining was of 42.3%, 38.5% and 38.5%, respectively in women affected by endometriosis. In unaffected controls, CE was diagnosed by the same modes in 15.4%, 14.1% and 14.1%, respectively [44]. Furthermore, treatment of CE by antibiotics was shown to enhance ART outcome when it effectively corrected CE [45].

The association of CE and endometriosis leads to hypothesis that at least certain cases of endometriosis could be candidates for novel forms of treatment targeted toward CE [46]. Of interest in these authors' observation was the fact that GnRH agonist treatment increased – not decreased – the bacterial contamination of the endometrium [46].

Access to the gene' signatures of bacteria has truly upended our views on the bacteriologic environment of the uterus. This organ that we believed to be sterile outside of pathological infections is actually inhabited by its own microorganisms, or microbiota [47]. In a seminal study, Carlos Simon's team showed that in cases when the endometrial microbiota was lactobacillus dominant pregnancy rates in ART were favorable [48]. Conversely, when the uterine microbiota was non-lactobacillus dominant [48] less favorable ART outcomes were observed. In a recent article, we reported that the diagnosis of CE through histology, microbial cultures and hysteroscopy concorded with molecular biology [49]. This latter finding is important, as it paves the way for the possibility of easily singling out women who are carriers of CE, a diagnosis that was up to now notoriously difficult and highly observer dependent. Identifying CE by its molecular biology signature thus opens the door to new approaches for diagnosing CE, a condition found in nearly half of the women suffering from endometriosis.

Irritable bowel syndrome

Vigano et al. underscore the common pathophysiological mechanisms shared by irritable bowel syndrome and endometriosis [50]. These include activation of mast cells, neuronal inflammation, dysbiosis and impaired intestinal permeability [50]. The covariance of these two disorders questions their relationship in the generation and maintenance of chronic inflammation [51].

Surgery or ART?

Basis of the problem

Medical treatments – at least the currently available options – all are contraceptive, leaving surgery or ART as the only viable options for women with endometriosis who are trying to conceive. In a not so distant past, routine diagnostic laparoscopy was the standard initial evaluation for all women with infertility. The improved successes of ART and, as discussed below, and accumulating evidence that surgery for endometriosis does not appreciably improve ART outcome have totally upended this classical approach. The new dilemma has become surgery or ART rather than surgery followed by ART.

The surgery-first option in young patients

Early in their workup young women should be counseled about the respective advantages of surgery and ART in case of infertility associated with endometriosis. As outlined above, surgery enhances the chances of natural conception [18]. Surgery thus should be considered in women who have ample time to attempt conception (young age, brief duration of infertility, adequate ovarian reserve, good quality sperm, spontaneous ovulation and patent tubes, see practical management below). If surgery is attempted, the couple should be allowed to conceive naturally for 12–18 months post operatively. Post-surgical medical therapies – such as ovarian blockade by GnRH agonist, progestins or OC pill – provide no value and should be avoided. Women should be advised to attempt conception immediately after surgery. In the end, ART will be offered if spontaneous pregnancy does not occur within the time frame agreed upon beforehand. The age- and ovarian reserve-dependent indications for ART are illustrated in Fig. 4. Patients should understand and agree with the bases of this strategy.

Surgery for pelvic pain

Pelvic pain and other symptoms of endometriosis may reach a point where they are intolerable and resistant to classical medical treatments. Women suffering from severe pelvic pain should be offered the option of surgery for pain. Women facing this scenario should be clearly advised to choose between two priorities – treating pain or attempting conception. Before opting for surgery women must understand that, while surgery is most often highly effective, symptoms may recur after surgery, and also ovarian reserve may be reduced by the surgery.

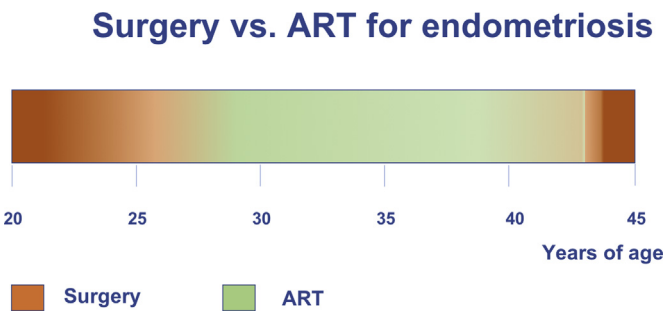

Fig. 4. Infertility associated with endometriosis: Choice between surgery vs. ART as a function of age and ovarian reserve.

In women undertaking surgery for pelvic pain and not wishing to immediately conceive, the possibility of fertility preservation must be discussed [52,53]. Possible access to dual – or duplex – stimulation should be discussed [54].

No surgery before ART

Garcia Velasco et al. were first to reveal that surgery for endometriosis does not improve ART outcome [55,56]. This finding was subsequently confirmed by others, as assessed in a systematic review and meta-analysis [20]. These latter authors reviewed the risks of removing endometriomas before IVF, as well as those that may be encountered when performing ART while endometriomas still are present, as discussed below [20].

Today there is an overwhelming recognition that endometriosis surgery lowers ovarian reserve, and in turn impairs the response to OS. Moreover, surgery does not improve ART outcome [57]. This has generated a widening opinion that surgery to remove endometriosis before ART should be avoided. This emerging view leads to a question of central importance, how should we diagnose endometriosis if routine diagnostic laparoscopy is abandoned as part of the routine infertility workup? As discussed in an earlier section of this review, we now must rely on pelvic imaging – transvaginal ultrasound and MR imaging performed by expert hands – for diagnosing endometriosis in the setting of symptoms associated with the disease. This is important as it carries practical implications for opting for segmented ART – freeze all and defer ET – in cases of endometriosis.

Contrary to popular belief, certain – by all means a minority – still claim that surgery improves ART outcome. Among them, Bendifallah et al. proclaim that first-line surgery may be a good option for women with colorectal endometriosis-associated infertility [58]. This team recounts that pregnancy rates are good, even in women who had experienced severe complications from colorectal surgery [59]. Likewise, Opoien et al. reported that time to pregnancy is improved by surgery for minimal endometriosis [60]. The team of Darai et al. also proposes first line surgery before ART, although this latter group suggests that further studies are needed [61]. One must conclude, however, that the recommendation to proceed to surgery before ART is the exception rather than the rule [62]. Divergent opinions still exist about the value of surgery for endometriosis before ART, but a consensus exists that purely diagnostic surgery is not indicated and should be avoided.

When performing surgery, Adamson and Pasta have championed the fertility index concept, a set of surgical findings that predict women who have the best chances of conceiving naturally [63]. This approach – clinically based – has merit once one proceeds to surgery – and has been positively assessed by others [64]. The fertility index concept becomes less important, after we agree that the chances of conceiving ought to be determined before doing surgery, not during surgery. The fertility index is therefore less handy if we resolve to operate only on women who have serious chances of conceiving naturally, orienting the others toward ART without surgery.

ART-first when time and ovarian reserve are lacking

If the prerequisites for surgery are not met – notably young (age and adequate ovarian reserve – patients should be offered direct access for ART. An overwhelming consensus exists – with few exceptions –that surgery does not help and may harm ART outcome. Not doing surgery, as in women over 35 years of age and whose ovarian reserve is low, should not equate to ignoring the possibility that endometriosis exists. The patients' medical histories should indeed be carefully reviewed, looking for symptoms of endometriosis such as dysmenorrhea – including during adolescence – and dyskesia and/or dyspareunia. In case of positive symptoms for endometriosis, an imaging workup – ultrasound and MR imaging – should be ordered to make a definitive diagnosis. This allows prescription of the recommended antagonist OS regimen followed by segmented ART with GnRH-a trigger and deferred ET [3].

ART with endometriomas present

Avoiding surgery in a large fraction of women over 35 years of age, when ovarian reserve is suboptimal, and/or the Fallopian tubes and sperm status are altered, should lead to RT. The presence of

endometriomas raises concerns for decreased ART outcome, but recent ART outcome data do not support these concerns [24]. Conversely, surgery for endometrioma greatly compromises ovarian reserve [65–67], particularly if endometriomas are bilateral [22].

Leaving the endometriomas in place can lead to technically difficult oocyte retrieval and possibly infectious complications. Because of this, some authors recommend aspirating the endometrioma before proceeding to ART, with some claiming improved results [68]. This view is far from gaining a consensus however, as many papers report rapid recurrence of the endometrioma. For this reason, others have advocated sclerosing the endometrioma with alcohol injection [69], but that too has not gotten much credence.

During oocyte retrieval, efforts should be taken to avoid perforating the endometrioma during the procedure. The endometriotic liquid is toxic for the oocyte without directly impacting fertilization rates, but compromises blastulation and embryo implantation rates [70]. If follicular fluid is contaminated by endometriotic fluid, the laboratory ought to be advised in order to avoid contaminating the whole cohort of oocytes retrieved.

The true risk of infectious complication stemming from transvaginal oocyte retrieval in the setting of ovarian endometriomas is poorly understood [20]. In a recent publication, we report that the risk of infectious complication from ART performed while endometriomas are present is both under- and over-reported [71]. We conducted a retrospective analysis of all acute pelvic infections – tubo-ovarian abscesses and salpingitis – treated at our institution over a 4-year period in women who also suffered from endometriosis. We observed a total of 10 such cases, with only three women having had an ART procedure [71]. This therefore indicates that acute infectious complication of ovarian endometriosis can occur spontaneously in the absence of ART [71]. Late occurring cases reported in ART patients may therefore represent spontaneously occurring infections not directly related to ART, and thus lead to over reporting of complications. On the contrary, one of our cases was observed more than 90 days after ART and therefore was not reported to our surveillance system that mandates communicating complications occurring within 60 days of ART. This constituted an underreporting [71]. It was long known that tubo ovarian abscesses in general tend to be more severe in women with endometriosis [72]. Hence, late complications of endometriosis and ART, such as tubo-ovarian abscesses, occurring during pregnancy [73] are not necessarily related to the actual procedure of oocyte retrieval.

Exceptions to the rule of no-surgery-before-ART

The rule of no surgery before ART knows certain exceptions. Hydrosalpinges visible on ultrasounds are known to alter ART outcome with the chance of pregnancy nearly halved [74]. When present, hydrosalpinges need to be surgically removed – or clipped if salpingectomy is technically challenging or impossible [74]. In certain cases, notably when ovarian reserve is seriously compromised, one may consider a conservative surgical approach where solely the hydrosalpinges are removed (or clipped), while endometriomas are left in place for fear of further deteriorating an already compromised ovarian reserve.

In certain circumstances, one may be forced to remove endometriomas that are too large and possibly prone to impede follicular aspiration. The situations are extremely rare however. Finally, in certain cases with increasing pain one may be forced to intervene even after stopping the OS process and attempted to handle the situation with medical treatment.

Surgery after failed ART

While at first glance the concept may seem paradoxical, one can indeed consider surgery after successive failed ART cycles [75], as illustrated in Fig. 4. In older women whose ovarian reserve is seriously compromised and who failed ART, the chances of conceiving naturally may be better than those emanating from another round of ART. Furthermore, radical – excision – surgery may make sense in symptomatic women before contemplating donor-egg ART.

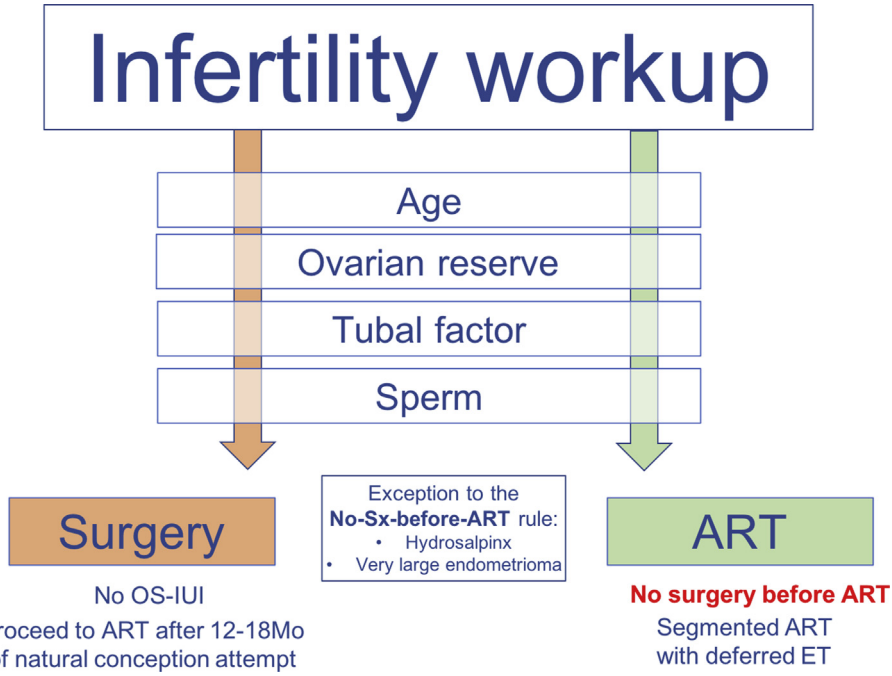

Fig. 5. Therapeutic choice between surgery and ART in women whose infertility is associated with endometriosis.

Practical management

The practical clinical management of infertile women suffering from endometriosis is illustrated in Fig. 5. At the time of the initial infertility workup, it is necessary to assess age, duration of in fertility, ovarian reserve, tubal and sperm status in other to weigh the relative value of surgery-first or ART-first approach. If surgery is pursued, ovarian stimulation and/or intra uterine insemination (IUI) is not warranted. Women should be counseled to attempt conception naturally immediately after surgery with a time frame of 12–18 months. If unsuccessful, patients next should undergo ART. If the ART-first option has been chosen, women should in principle not undergo surgery and a segmented ART strategy should be pursued. There are certain exceptions to the new no-surgery-before-ART rule, notably in case of hydrosalpinxes and uncontrolled pain.

Conclusion

ART has proven efficacy in infertility cases that are associated with endometriosis. Results – if proper measures are taken – are no different from those seen in unaffected controls, even if responses to OS are subpar. This has therefore drastically changed the way we manage infertility associated with endometriosis. For many women ART-first is the preferred option. Contrary to prevailing fears ART and the OS needed for ART does not commonly induce flares of endometriotic lesions and generally are well supported [31].

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