Rethinking mechanisms, diagnosis and management of endometriosis

Charles Chapron[1,2,3], Louis Marcellin[1,2,3], Bruno Borghese[1,2,3] and Pietro Santulli[1,2,3]*

Abstract | Endometriosis is a chronic inflammatory disease defined as the presence of endometrial tissue outside the uterus, which causes pelvic pain and infertility. This disease should be viewed as a public health problem with a major effect on the quality of life of women as well as being a substantial economic burden. In light of the considerable progress with diagnostic imaging (for example, transvaginal ultrasound and MRI), exploratory laparoscopy should no longer be used to diagnose endometriotic lesions. Instead, diagnosis of endometriosis should be based on a structured process involving the combination of patient interviews, clinical examination and imaging. Notably, a diagnosis of endometriosis often leads to immediate surgery. Therefore, rethinking the diagnosis and management of endometriosis is warranted. Instead of assessing endometriosis on the day of the diagnosis, gynaecologists should consider the patient's 'endometriosis life'. Medical treatment is the first-line therapeutic option for patients with pelvic pain and no desire for immediate pregnancy. In women with infertility, careful consideration should be made regarding whether to provide assisted reproductive technologies prior to performing endometriosis surgery. Modern endometriosis management should be individualized with a patient-centred, multi-modal and interdisciplinary integrated approach.

Ureterohydronephrosis
The dilatation of the renal pelvis and/or calyces and ureter as a result of obstruction.

[1]*Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Paris, France.*

[2]*Assistance Publique – Hôpitaux de Paris (AP-HP), Hôpital Universitaire Paris Centre (HUPC), Centre Hospitalier Universitaire (CHU) Cochin, Department of Gynecology Obstetrics II and Reproductive Medicine, Paris, France.*

[3]*Department 'Development, Reproduction and Cancer', Institut Cochin, INSERM U1016, Université Paris Descartes, Paris, France.*

**e-mail: charles.chapron@aphp.fr*

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Endometriosis is defined as the presence of endometrial-like tissue (that is, the tissue that lines the uterine cavity) outside of the uterus[1]. The disease, which is oestrogen dependent, arises during the reproductive years of women and is challenging to diagnose and manage. As such, determination of the incidence of endometriosis is not straightforward; however, the prevalence ranges from 6% to 10%[2]. Notably, the symptoms of endometriosis include pelvic pain[3] and/or infertility[4], although asymptomatic cases do arise[5]. Subsequently, endometriosis generally has a substantial effect on the quality of life of patients[6–8], with negative consequences on daily life activities, sexual function and personal relationships[9]. In addition, the disease is associated with depression[10] and fatigue[11], thereby leading to a loss of work productivity[8,12,13] and causing a major economic burden[7,14]. In light of these effects, endometriosis should be considered a public health issue rather than a disease of individuals.

Endometriosis is a heterogeneous disease with three well-recognized phenotypes: superficial peritoneal lesions (SUP), ovarian endometriomas (OMA) and deep infiltrating endometriosis (DIE) (FIG. 1). The least severe form of the disease is SUP, in which superficial endometrial lesions occur on the peritoneum (the tissue lining the pelvic cavity). By contrast, OMA are cystic masses that arise from ectopic endometrial tissue and grow within the ovary. The most severe phenotype is DIE, which is defined as subperitoneal lesions that penetrate tissue deeper than 5 mm under the peritoneal surface (such as the uterosacral ligaments) or as lesions that infiltrate the muscularis propria of the organs that surround the uterus, for example, the bladder, intestine with or without occlusion, and ureter with or without ureterohydronephrosis[15]. In addition, endometriosis can occur in extragenital locations, for example, pleural, diaphragmatic or umbilical[16]. Of note, DIE nodules are rarely isolated, instead presenting as a multifocal distribution[17], for which DIE is considered an 'abdominal-pelvic multifocal disease' rather than a single organ pathology[15] (FIG. 1). In addition, the presence of OMA is an indicator of more severe DIE[18,19]. Endometriosis is stratified by the American Society for Reproductive Medicine (ASRM) classification into four stages (I, II, III and IV) according to surgical evaluation of the size, location and severity of endometriotic lesions and the occurrence of extensions of adhesions[20,21].

Adenomyosis, a disease characterized by infiltration of endometrial tissue into the myometrium (that is, the muscular outer layer of the uterus) (FIG. 1), is frequently associated with endometriosis[22–24] (BOX 1). Importantly, adenomyosis contributes, independently of endometriosis, to pain[25,26], infertility[27,28] and bleeding (including menorrhagia and metrorrhagia)[29], and has substantial negative effects on the quality of life of patients[30,31].

Key points

- Endometriosis is a chronic, inflammatory, hormonal, immune, systemic and heterogeneous disease with three different phenotypes (superficial, ovarian endometrioma and deep infiltrating endometriosis), which is associated with adenomyosis in 30% of patients.
- Diagnosis of endometriosis (and adenomyosis) should be based on patient interviews, examination and imaging; endometriosis diagnosis should no longer be considered synonymous with immediate surgery.
- Modern management of endometriosis should be patient focused rather than focused on the endometriotic lesions; medical treatment can be administered without histological confirmation.
- Pain symptoms should be treated without delay to avoid central sensitization, as this can become autonomous, occurring independently of the peripheral stimulus, and can explain coexisting chronic pain syndromes.
- Medical treatment should be the first therapeutic option for patients with pelvic pain who have no immediate desire for pregnancy; assisted reproductive technologies can be performed without previous surgery for selected patients with infertility.
- Endometriosis management should be individualized according to the patient's intentions and priorities; management strategies can vary from country to country as pain perception and health-care systems differ around the world.

Adenomyosis is also a heterogeneous disease with different configurations[24,32]. However, further studies are necessary to determine whether diffuse and focal adenomyosis (BOX 1) are two distinct entities[24].

In this Review, we introduce the concept of the 'endometriosis life' of patients (FIG. 2). We discuss the mechanisms, diagnosis and management of endometriosis, setting these topics in the context of the 'endometriosis life' model. We suggest a new approach to modern endometriosis management, which should be individualized to the patient through an interdisciplinary integrated approach.

Mechanisms

Models of endometriosis. The most well-accepted pathophysiological hypothesis for endometriosis is based on retrograde menstruation, which is observed in the majority of patients. In this process, menses transports viable endometrial fragments through the fallopian tubes to the peritoneal cavity, where they are able to implant, develop and sometimes invade other tissues of the pelvis[1]. These pathological endometrial fragments might result from disrupted ontogenetic endometrial programming, which is a potential consequence of in utero and early neonatal exposure to certain maternal characteristics, gynaecological factors and postnatal feeding patterns, for example, endometriosis or associated uterine fibroids, smoking during pregnancy, preeclampsia during pregnancy, formula feeding and premature birth[33]. Of note, all known factors that increase menstrual flow are also risk factors for endometriosis, including early age at menarche, heavy and long periods as well as short menstrual cycles[34]. The anatomical distribution of endometriotic lesions is the strongest evidence in favour of the retrograde menstruation hypothesis[1,35]. For example, endometriotic lesions tend to have an asymmetrical distribution, which could be explained by the effect of gravity on menstrual flow, the abdominopelvic anatomy and the peritoneal clockwise flow of menses[36]. Furthermore, in the pelvis, endometriotic lesions are more frequently observed in the posterior compartment and on the left side, whereas lesions in the abdomen and the thorax are located mostly on the right side. Pleural endometriosis is thought to be due to the combined action of retrograde menstruation, the clockwise flow of peritoneal fluid[37] and transdiaphragmatic passage of endometrial tissue through a porous diaphragm[38]. Other hypotheses have been proposed such as Müllerian metaplasia, lymphovascular emboli of endometrial cells, and proliferation of endometrial stem cells or bone marrow progenitors[34,39–43]; however, none of these models takes into account the anatomical distribution of the lesions. These alternative theories might be at play in endometriosis in unusual locations (for example, brain, liver or lung)[44].

Of note, retrograde menstruation does not explain the mechanism of endometrial tissue grafting onto the peritoneum. Therefore, it is plausible that several other mechanisms, such as inflammatory factors, dysregulated immunity, hormones, genetic and epigenetic factors as well as environmental factors, might act in unison to cause endometriosis[34] (FIG. 2). In addition, pre-existing endometrial abnormalities might also favour the implantation and growth of pathological endometrial fragments outside the uterine cavity, for example, impaired steroid biosynthesis (such as hyperestrogenism, progesterone resistance or aromatase overexpression), increased endometrial invasive potential associated with neoangiogenesis, endometrial neurogenesis and a proinflammatory profile in endometrial tissue compared with disease-free endometrium[45,46]. However, how the aforementioned mechanisms contribute to the different phenotypes of endometriosis remains unclear.

Genetically, endometriosis is considered a complex trait that exhibits familial aggregation, with an up to six-fold increased risk for first-degree relatives of patients with endometriosis[47]. Furthermore, according to large studies of twins[48,49], heritability is ~50%. Despite this clear heritability, the identification of the genetic factors driving the disease is still incomplete. For example, classic genetic association studies are not reproducible owing to very few tested variants and limited populations under study with mixed phenotypes and/or disease stages[50,51]. Genome-wide linkage studies have focused on major susceptibility chromosomal regions in familial endometriosis. Two chromosomal areas of significant linkage were observed on 10q26 and 7p13–15 (containing genes such as *CYP2C19*, *INHBA*, *SFRP4* and *HOXA10*). However, the logarithm of the odds scores (a statistical estimate of the probability that two genes are located closely together) observed were not of the magnitude seen for monogenic traits, which suggests that the existence a 'major gene' that accounts for the majority of familial endometriosis risk is unlikely[52–54]. Interestingly, genome-wide association studies have reported a dozen susceptibility regions, although these regions only account for just over 4% of the heritability[55]. The role of environmental factors in endometriosis, such as endocrine disrupting chemicals, remains highly controversial[56–58]. Currently, no direct evidence exists showing that endocrine disrupting chemicals are involved in endometriosis[59].

Adhesions
Fibrous bands of scar-like tissue that form between tissues and organs, connecting structures that are not normally connected.

Menorrhagia
Menstrual periods with abnormally heavy or prolonged bleeding.

Metrorrhagia
Uterine bleeding at irregular intervals, particularly between the expected menstrual periods.

Müllerian metaplasia
Tissues derived from the celomic epithelium, such as the peritoneum, have the potential to differentiate into epithelium and stroma.

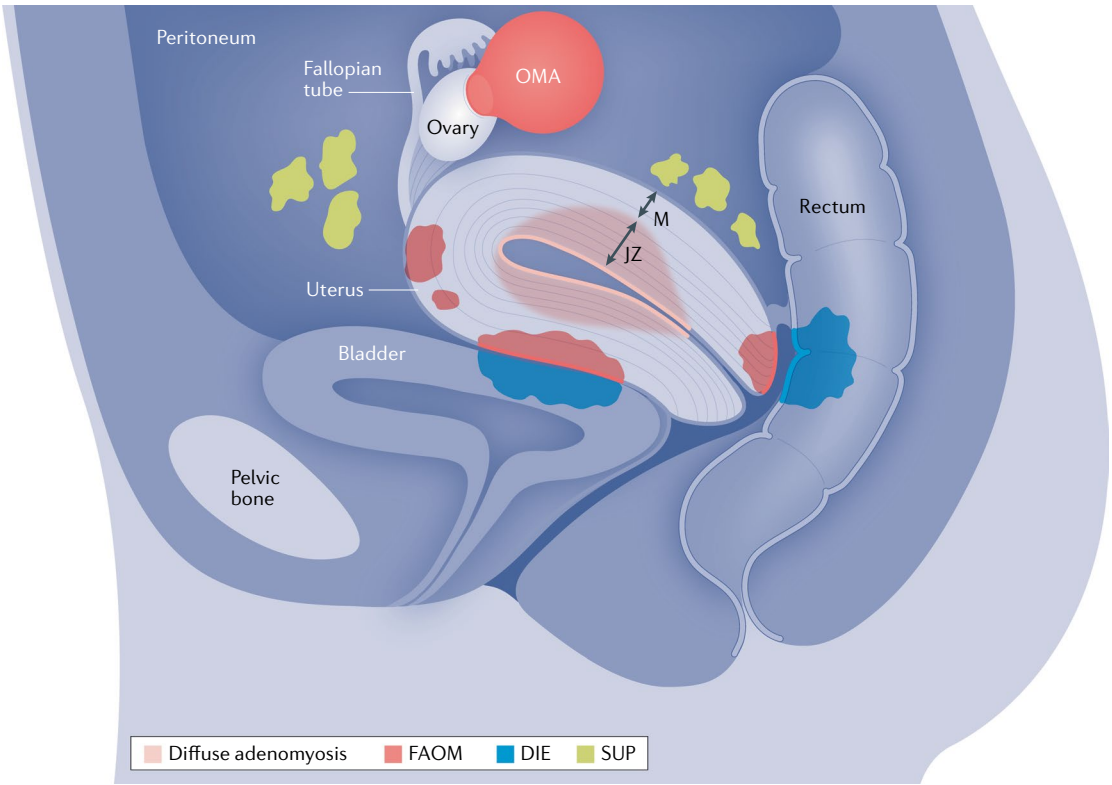

Fig. 1 | **The heterogeneous characteristics of endometriosis and adenomyosis.** During menstrual flow, endometrial debris exits the uterus through the fallopian tubes and attaches itself to the pelvic structures, leading to the establishment of three different endometriosis phenotypes: superficial peritoneal endometriosis (SUP), ovarian endometriomas (OMA), and deeply infiltrating endometriosis (DIE). In addition, the invasion of endometrial tissue into the myometrium leads to the establishment of adenomyosis, a specific entity that differs from endometriosis and has different forms: diffuse adenomyosis and focal adenomyosis of the outer myometrium (FAOM). JZ, junctional zone; M, myometrium.

The natural history of endometriosis. The natural course of endometriosis is unclear because of uncertainty concerning pathogenesis and the evolution of disease. Numerous events can affect the outcome of endometriotic lesions, including hormonal treatments, surgery, pregnancy and ovarian stimulation during treatment for infertility[34]. Endometriosis is defined as a disease because it is characterized by cyclic bleeding[60] with retrograde flux of endometrial tissues that cause inflammation, which contributes to pain and/or infertility. Importantly, hormonal fluctuations (mainly oestrogen and progesterone) and ovulation during the menstrual cycle are crucial for the development of OMA[61,62].

During each menstrual cycle, endometriotic lesions are responsible for repeated tissue injury and repair[22], with local inflammation[63], angiogenesis[64] and neurogenesis[65]. A subsequent cascade of events involving epithelial–mesenchymal transition and fibroblast–myofibroblast transdifferentiation can then contribute to increased myofibroblast contractility, collagen production by endometrial cells, progressive smooth muscle metaplasia and uterine fibrogenesis[66]. This histological progression towards fibrosis in endometriotic lesions is not synonymous with the progression of stages I or II disease into stage III or IV disease according to the ASRM classification[67] and does not correlate with the progression of superficial lesions to the more severe forms (OMA and DIE)[68]. Evidence suggests that endometriosis is a stable disease (as opposed to a proliferative disease such as cancer) (BOX 2) that progresses to fibrosis over time[69–72]. Importantly, surgery in itself could be a risk factor for the progression of endometriosis, as evidenced by the increased risk of endometriosis in patients with a history of surgery[73,74]. This effect might be the result of activation of adrenergic pathways, chronic stress and increased angiogenesis[75,76]. Finally, the occurrence of symptomatic postmenopausal endometriosis could be related to extra-ovarian production of oestrogen by endometriotic lesions and adipose tissue[77].

Endometriosis-related pain. Several mechanisms are proposed to contribute to pain in patients with endometriosis. For example, after retrograde menstruation, refluxed endometrial cells located outside the uterus stimulate the infiltration of immune cells (such as, macrophages and mast cells) into lesions, which secrete inflammatory mediators (such as, proinflammatory cytokines, chemokines and nerve growth factor), finally resulting in an inflammatory peritoneal microenvironment[65]. In addition, a strong topographical relationship exists between endometriotic foci and nerves[78], with perineural and intraneural invasion correlating with the intensity of pain[79]. Importantly, inflammation of the peritoneal fluid in endometriosis can lead to peripheral nerve stimulation and sensitization[80]. Moreover, repetitive and persistent peripheral stimuli contribute to central sensitization[81]

Central sensitization
The amplification of pain by the central nervous system.

Myofascial pain
Pain that originates from myofascial trigger points in skeletal muscle, sometimes in seemingly unrelated parts of the body.

Vulvodynia
Chronic pain that affects the vulvar area and sometimes has no identifiable cause.

Dysmenorrhea
Pain during menstruation.

Myometrial hypertonia
Intense and persistent uterine myometrial contraction.

and myofascial pain[82]. The effect of central sensitization can explain the common coexisting chronic syndromes characterized by pain such as painful bladder syndrome (interstitial cystitis), vulvodynia, myofascial pain and irritable bowel syndrome[83]. Furthermore, central sensitization, which can become autonomous and occur independently of the peripheral stimulus[84], is associated with changes in the regional grey matter volume within the central pain system[85] and with altered brain chemistry[86]. As such, pain symptoms should be treated without delay in order to avoid the occurrence of changes in the central nervous system[87]. Patients with endometriosis can also experience dysmenorrhea, which stems from excessive prostaglandin production by lesions, leading to myometrial hypertonia and secondary ischaemia[88].

Endometriotic lesions (SUP[89], OMA[90–92], DIE[79,93] and adhesions[94]) and adenomyosis[26] contribute to pelvic pain. Although, OMA, per se, are normally associated with mild to moderate pain. As such, the presence of OMA with severe pelvic pain is indicative of associated DIE lesions[95] and severely painful OMA should be seen as an indication to perform an imaging work-up to check for associated DIE[95]. The type of pain is thought to correlate with the location of the endometriotic lesion[96–98], whereas the pain intensity has been reported to be proportional to the depth of the DIE lesions[93,99]. However, no systematic link exists between the pain reported and the extent of the lesions in endometriosis.

Endometriosis-related infertility. Endometriosis is clearly associated with infertility, yet a diagnosis of endometriosis is not synonymous with infertility. The disease can adversely affect fecundity by different mechanisms acting at the level of the pelvic cavity, the ovaries and the uterus itself[1]. For example, pathological mechanisms include chronic inflammation of the peritoneal fluid[36,41] that leads to alteration of the fertilization process, disruption of ovarian function, abnormalities of the eutopic endometrium, pelvic adhesions, decreased frequency of sexual intercourse owing to pain during sex (that is, dyspareunia) and possible surgical damage to the ovary after OMA excision[100]. In addition, adenomyosis, which is frequently associated with endometriosis, also contributes to infertility[28] (BOX 1). The relationship between endometriosis phenotypes and infertility is a matter of debate. Evidence suggests that the presence of OMA in itself does not seem to cause infertility[101–103]. Instead, the infertility of patients with OMA could be associated with surgery[101] owing to the negative effect of OMA surgical excision on the ovarian reserve[100,104,105].

Perinatal adverse outcomes. The relationship between endometriosis and pregnancy can be considered from two key perspectives — the influence of endometriosis on pregnancy outcomes and the influence of pregnancy on the natural history of endometriosis. After ovulation, the endometrium undergoes decidualization, which is the process that prepares the endometrial surface for pregnancy. This process, which is mainly induced by progesterone, consists of the transformation of endometrial stromal fibroblasts into specialized secretary decidual cells[106]. In women with endometriosis, decidualization can be compromised, which could contribute to impaired reproductive health outcomes[106]. Fetal membranes have also been reported to show structural changes (endometriosis-like glands) and molecular changes (gene expression and methylation) in the choriodecidual layer in women with endometriosis[107]. In addition, evidence is accumulating of a slightly increased obstetrical risk in women with endometriosis[108,109], irrespective of the use of assisted reproductive technologies (ART)[110,111]. However, the risk of such complications is particularly low and there is no clear evidence that surgery can prevent these risks[112,113]. Adenomyosis can also negatively affect perinatal outcomes[114–117] (BOX 1).

Interestingly, pregnancy seems to have a beneficial, albeit transient, effect on endometriosis-related symptoms[118–120]. Ectopic decidua formation during pregnancy (also named deciduosis and defined as stromal cell transformation of the peritoneum) has been attributed to hormonal effects during pregnancy (mainly increased levels of progesterone) on the ectopic endometrium[121]. This effect could explain a decrease in the size of the lesions previously observed in pregnant women with endometriosis upon clinical examination[122,123]. In addition, severe but rare and unpredictable complications during pregnancy[124] associated with changes in endometriotic lesions during pregnancy have been reported.

Diagnosis

Endometriosis is difficult to diagnose for several reasons. One of the factors is probably a lack of understanding of the disease by health-care professionals. Furthermore, uncertainty exists regarding the pathogenesis of endometriosis. The heterogeneity of the disease, with three endometriosis phenotypes, and the possibility of

Box 1 | Adenomyosis is a heterogeneous disease

Adenomyosis is a specific entity that differs from endometriosis. The disease is defined as the invasion of endometrial tissue into the myometrium, which occurs as different forms: diffuse adenomyosis, focal adenomyosis of the outer myometrium and cystic adenomyoma[32,235,236]. A radiological diagnosis with transvaginal ultrasound and MRI[131–133,237] is now available[23,32,133,238] and different classifications have been proposed[26,32,235,236,239].

Adenomyosis can occur on its own or coexist with endometriosis. A strong clinical relationship exists between these two diseases, which varies according to their respective phenotypes[238]. For example, diffuse adenomyosis, which is common, even in young women[23,238], does not correlate with the presence of endometriosis or with the endometriosis phenotype[238]. By contrast, focal adenomyosis of the outer myometrium is observed statistically significantly more frequently in patients with endometriosis, particularly those with deep infiltrating endometriosis[238]. Although the pathogenesis of both endometriosis and adenomyosis is not well established, both are the consequence of ectopic localization of endometrial cells. The association of these two diseases could be explained by several common molecular deregulated processes that have been observed in these two pathologies[240,241], including immune system dysfunction, PTGS2-facilitated inflammation, neurogenesis mediated by neutrophilin, vasculogenesis mediated by VEGF, epithelial–mesenchymal transition of endometrial cells, and oxidative stress pathways activated through NRF2 or ADAM17–Notch[240,241].

Adenomyosis can cause symptoms (for example, heavy bleeding during and/or between monthly periods, pain and/or infertility[34]) independently of endometriosis, which negatively affect perinatal outcomes[114,115,117] and have a pronounced negative effect on the quality of life of patients[8,242]. Thus, in daily practice, health-care professionals face difficulties in distinguishing whether symptoms (such as pain and infertility) are caused by endometriosis or by coexisting adenomyosis. However, diagnosis of associated adenomyosis for patients with endometriosis is of prime importance in deciding on the best therapeutic option.

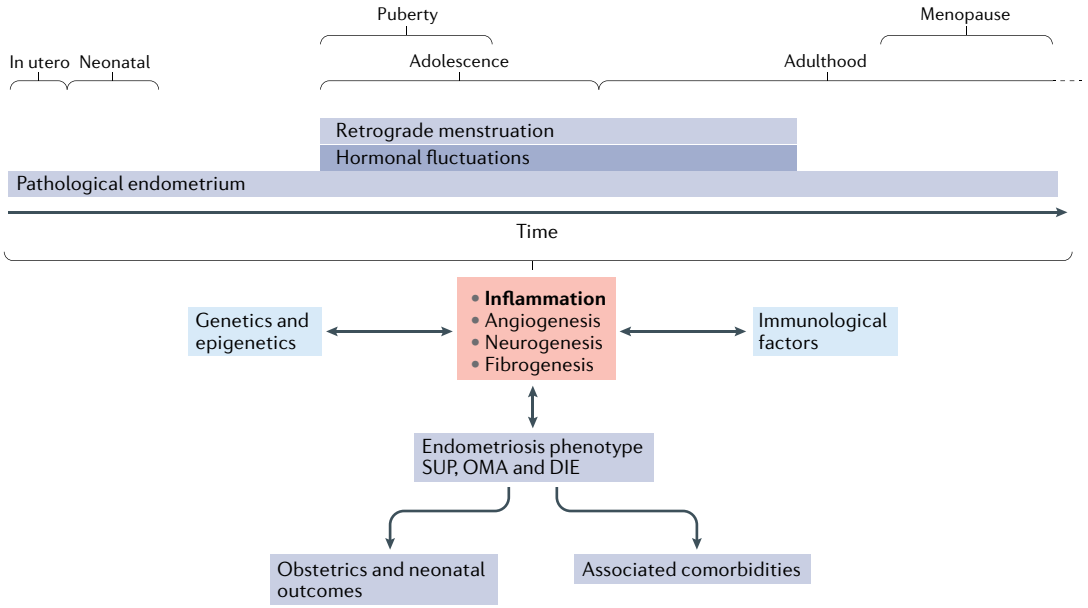

Fig. 2 | **The concept of 'endometriosis life'.** In utero and early neonatal exposures to maternal characteristics, gynaecological factors and postnatal feeding patterns (including endometriosis or associated uterine fibroids, smoking during pregnancy, preeclampsia during pregnancy, formula feeding and prematurity) might contribute to ontogenetic endometrial programming impairment, potentially resulting in a pathological endometrium. During puberty and adolescence, retrograde menstruation of abnormal endometrium generates ectopic lesions. During adulthood, ectopic lesions are sensitive to hormonal fluctuations owing to ovarian function, hormonal therapies and pregnancy. As such, endometriosis is a lifelong disease, the course of which we term 'endometriosis life'. Menopause can lead to quiescence of the lesions that remain exposed to oestradiol production by peripheral adipocytes. During the 'endometriosis life', inflammation, angiogenesis, neurogenesis and fibrogenesis are the main processes involved in the genesis and maintenance of ectopic lesions. These processes are controlled by genetic, epigenetic and immunological factors influenced by the environment and associated diseases. DIE, deep infiltrating endometriosis; OMA, ovarian endometriomas; SUP, superficial peritoneal endometriosis.

asymptomatic disease as well as the potential comorbid presence of adenomyosis (BOX 1; FIG. 1) can complicate diagnosis. In addition, symptoms occuring during the adolescent period might be overlooked by health-care practitioners. Although the aforementioned factors play a part, the main explanation for the difficulty in diagnosis is that pelvic pain is the cardinal symptom of endometriosis. This pain can present in different forms (for example, dysmenorrhea, dyspareunia or chronic pelvic pain), with the potential for overlapping symptoms[125]. However, a painful clinical presentation is not pathognomonic or synonymous with endometriosis[126]. Moreover, such pain can be associated with non-gynaecological symptoms (particularly urinary and/or digestive)[125,127]. Thus, for health-care professionals, the challenge in daily practice is the determination of whether pain is caused by endometriosis or by other gynaecological conditions (for example, an ovarian cyst, myoma or pelvic inflammatory disease sequelae) or syndromes associated with chronic pain (for example, adhesions, irritable bowel syndrome, interstitial cystitis, fibromyalgia and myofascial pain) or by depression and/or a history of sexual abuse.

History-taking by patient interviews is essential for diagnosing endometriosis. Detailed history indicators of endometriosis and questions that practitioners should ask patients during a clinical interview are presented in BOX 3.

This key step is often neglected during the initial clinical examination of women with endometriosis. Of note, the cyclic nature of the pain is the key feature of the disease[5]. Moreover, during clinical examination, health-care professionals should check for the following abnormalities: visible bluish lesions on the vaginal fornix; palpable sensitive nodules or a thickened area involving any of several pelvic locations (the torus uterinus, uterosacral ligament(s), the upper third of the posterior vaginal wall[128], the pouch of Douglas or vaginal cul-de-sac(s)); adnexal masses; fixed retroverted uterus; and/or pelvic pain upon mobilization. However, a normal physical examination does not rule out endometriosis[129] and physical examination during menstruation can improve detection[130].

Biological tests currently have little or no merit in the diagnosis of endometriosis and no biomarker tests have been identified to date[87]. By contrast, medical imaging has led to substantial improvements in the diagnosis of endometriosis. Importantly, transvaginal ultrasound (TVUS) (FIG. 3) and MRI (FIG. 4) are not only suitable for diagnosing two phenotypes of endometriosis (OMA and DIE)[131–135] but also for evaluation of adenomyosis[133,136], which is useful given the frequent association of endometriosis and adenomyosis[23,24]. In addition, sigmoid, ileocaecal and urological lesions can be detected with supplementary radiological techniques such as transrectal ultrasonography, multidetector CT scan with

Adnexal masses
Lumps in tissues of the adnexa of the uterus (such as the ovaries and fallopian tubes).

Retroverted uterus
The position of the uterus, tipped backwards so that its fundus is aimed towards the rectum.

retrograde colonic opacification and late urography, and/or uro-MRI[135]. Moreover, scintigraphy can be used to explore renal function in cases of suspected ureteral endometriosis[137,138]. Of the aforementioned techniques, TVUS should be the first-line imaging approach for the evaluation of suspected endometriosis[139,140]. Notably, SUP cannot be visualized by imaging since the size of the lesions is below the threshold for detection[135]. In cases of diagnostic uncertainty, prescription of a continuous ovulation-blocking medication should be used as a clinical test[141]. If the symptomatology persists despite cessation of menstruation, an aetiology other than endometriosis should be investigated[5]; this strategy allows unnecessary diagnostic laparoscopies to be avoided.

Management

Endometriosis is a chronic inflammatory disease that requires lifelong management[142,143]. Three main therapeutic options exist for endometriosis management, including medical treatment, surgery and ART.

Medical treatment. Available medical therapies for endometriosis include non-hormonal treatments, such as painkillers and NSAIDs[144], and hormonal treatments, such as combined oral contraceptives (COCs), progestins and gonadotropin-releasing hormone analogues (GnRHa)[145]. Several arguments can be made for the use of medical treatment in endometriosis for lifelong management. For example, both hormonal and NSAID treatments decrease inflammation, which is a key aspect of the pathogenesis of endometriosis[146]. Numerous inadequate and unnecessary surgical procedures are performed for endometriosis; however, surgical exeresis of endometriotic lesions has no effect on retrograde menstruation. In addition, high rates of symptom and lesion recurrence are observed after surgical treatment and surgery is not effective for treating pain owing to central sensitization. Therefore, medical treatment should be considered for the management of pain and inflammation associated with endometriosis for patients who do not want to become pregnant.

Hormonal treatments for endometriosis act by suppressing hormonal fluctuations (gonadotropin and ovarian hormones)[147], resulting in inhibition of ovulation and menstruation and a downstream decrease in inflammation[63]. However, these treatments are not indicated in patients who wish to try for pregnancy because all female sex hormone treatments are contraceptive. Of note, hormonal treatments are effective for the treatment of symptoms but are not curative, that is, they relieve pain without eliminating the endometriotic lesion[34,148,149]. In rare cases, patients can be refractory to treatment with COCs, progestins and GnRHa, in which case the use of danazol and aromatase inhibitors can be considered, but these therapies have a high rate of adverse effects[150]. For patients who do not respond to hormonal therapy, emerging drugs (particularly GnRH antagonists[151], selective oestrogen or progesterone receptor modulators, anti-angiogenic drugs, antioxidants, immunomodulators and epigenetic agents) are promising new treatments, though they require more thorough evaluation[150].

Although the various hormonal treatments have similar efficacies for pain relief, independently of their mechanism of action, they differ in terms of safety, tolerability and cost[152]. In the context of endometriosis-related pain in patients with no current plans to become pregnant, a personalized stepwise approach is necessary[153]: COCs or progestins are low cost drugs that should be considered as a first-line medical therapy. However, between a quarter to a third of patients either do not respond to these treatments[150], have intolerances or have contraindications. In these patients, high-cost drugs (GnRHa[154]) are provided as a second-line therapy[152] (FIG. 5). Of note, patients who take GnRHa for more than 6 months can be at risk of loss of BMD and an add-back therapy (using oestroprogestative hormonal replacement) should be prescribed to prevent this[155,156].

Prevention of pain[157–159] and the recurrence of OMA[160–164] after surgery are the main indications for hormonal treatment in patients who do not wish to become pregnant. Better results, in terms of pain relief and recurrence rates, are achieved when the hormone therapy-free interval is as short as possible[165]. The medical management of endometriosis-related persistent pelvic pain should be integrated into an interdisciplinary approach that includes treatment targeting the central nervous system (for example, pain education, neuromodulators, physiotherapy, mindfulness strategies, mood treatments and sleep restoration) and treatments of peripheral nociceptors (for example, pelvic floor relaxation, physiotherapy, trigger point injections and diet)[166].

Surgery. Surgery is a suitable therapeutic option for endometriosis for the effective treatment of both pelvic pain and infertility. Two surgical modalities should be considered. The first is conservative surgery, defined as the exeresis of endometriotic lesions without removal of the uterus and/or the ovaries. Conservative surgery can be complete (with no residual endometriotic lesions) or incomplete (with persistent endometriotic lesions after the surgery)[17]. The second modality is definitive surgery, which encompasses the removal of all the endometriotic lesions associated with concomitant hysterectomy with or without oophorectomy (removal of one or both ovaries)[17]. Importantly, in patients who undergo conservative surgery, pregnancy can occur shortly after

Box 2 | Ovarian cancer and endometriosis

Based on epidemiological studies[243], an association exists between endometriosis and ovarian cancer, with a moderately increased risk of 1.34 in women with endometriosis compared with the general population[244,245], especially for endometrioid and clear-cell types of ovarian cancer. Endometriosis and ovarian cancer share common risk factors (for example, early menarche, incessant ovulation and menstruation, and chronic stress) and protective factors (for example, tubal ligation, hysterectomy and physical activity)[64,246,247]. However, the temporal continuum between endometriosis and cancer is far from clear[244]. Given the low incidence of ovarian cancer with endometriosis, there is no rationale to propose a risk-reduction strategy or screening of patients with endometriosis[244]. In women with endometriosis and ovarian endometriomas who have reassuring imaging with no suggestion of malignancy, no scientific data exist to support systematic ovarian endometrioma surgery before assisted reproductive technologies to prevent the development of ovarian cancer later in life[244,248].

Operative laparoscopy
Minimally invasive surgery for therapeutic interventions with a few small cuts in the abdomen.

the surgical procedure[167]. Surgery for endometriosis is performed by operative laparoscopy, except for in rare cases of DIE with multifocal lesions and numerous previous surgeries, which might require laparotomy.

Although surgery remains an important management strategy for endometriosis, several limitations should be considered by health-care professionals. For example, surgery enables exeresis of endometriotic lesions, however, it does not treat the underlying cause of the disease and is associated with a high rate of recurrence[168], the latter mainly due to incomplete endometriotic lesion exeresis[74,169]. Of note, surgery can have major complications, specifically in cases of DIE surgery (for example, postoperative infection, rectovaginal fistula, neurogenic bladder and bowel dysfunction), which could affect the quality of life of patients[167]. Also of importance is the potential negative effect on the ovarian reserve after OMA laparoscopic cystectomy[100], specifically in patients with bilateral cysts[170]. As such, the dogma that OMA laparoscopic cystectomy must be the systematic first-line therapeutic option for OMA needs to be revisited[101,171]. Following surgery, postoperative hormonal treatment is required to prevent recurrence of the disease and pain (as long as the patient has no desire for pregnancy). In addition, following surgical excision of endometriosis, pelvic pain is statistically significantly more likely to persist in patients with associated adenomyosis[26,172].

The benefits of surgery for patients with infertility might be overestimated[173]. For these patients, the indications for surgery and ART are a matter of debate. Although some studies have indicated that endometriosis surgery before ART can be beneficial[174,175], insufficient data exists to recommend systematic surgery before ART to increase the chances of pregnancy[113]. Notably, evidence suggests that a previous history of surgery for endometriosis, with or without ovarian surgery, might negatively affect ART pregnancy and live birth rates[176,177]. Moreover, the management of ART failure is highly controversial[178]. Only a small number of studies have reported that surgery can improve pregnancy rates after ART failure[179,180]. In these situations, spontaneous conception was only rarely observed and most pregnancies were obtained with additional ART after endometriosis surgery[180].

Assisted reproductive technologies. In patients with endometriosis-related infertility, ART (that is, in vitro fertilization (IVF) and intracytoplasmic sperm injection) are suitable options to achieve pregnancy. ART can bypass the inflammation-related processes occurring

Box 3 | **Specific patient history indicators of endometriosis**

The described factors are detailed history indicators of endometriosis and questions that practitioners should ask patients during clinical interview.

Family history of endometriosis
- First-degree relative with endometriosis[47]

In utero or early childhood factors
- Patient was born prematurely[33]
- Neonatal uterine bleeding or low birth weight[33,249]
- Formula-fed infant[33]
- Early-life small body size[250]
- Sexual and emotional abuse during childhood[251]

Adolescent history[252]
- Severe primary dysmenorrhea with negative effects on life activities[253]
- School absences due to pain[252,253]
- Poor and/or no response to medications used to treat pain: NSAIDs and/or combined oral contraceptives[253]
- Migraines[254]

Phenotype[255]
- Low BMI
- Cutaneous naevi
- Pigmentary traits (for example, freckles)

Infertility[34]

Pain characteristics
- Cyclic pain that worsens during the menstrual cycle[5]

Menstrual symptoms[96]
- Gastrointestinal pain
- Urological pain
- Diaphragm pain
- Pulmonary pain
- Sciatic pain

Fatigue syndrome[11]
- Pain
- Insomnia
- Depression
- Occupational stress

Associated comorbidities[256]
- Autoimmune diseases (for example, systemic lupus erythematosus, scleroderma, rheumatoid arthritis, Sjögren's syndrome, multiple sclerosis and fibromyalgia)
- Endocrine diseases (for example, hypothyroidism and Basedow disease)
- Asthma, atopic diseases and allergic disorders (hay fever, food allergy and sinus allergic rhinitis)
- Migraines
- Inflammatory bowel diseases (for example, ulcerative colitis and Crohn's disease)
- Cardiovascular diseases (for example, hypertension and hypercholesterolaemia)
- Cancer (for example, ovarian, breast or melanoma)

Previous obstetrical history
- Adverse pregnancy and perinatal outcomes[108,109]
- Miscarriage(s)[257]

Previous history of pelvic surgery
- For endometriosis[74]
- For other indications[73] (for example, laparotomy or caesarean section)

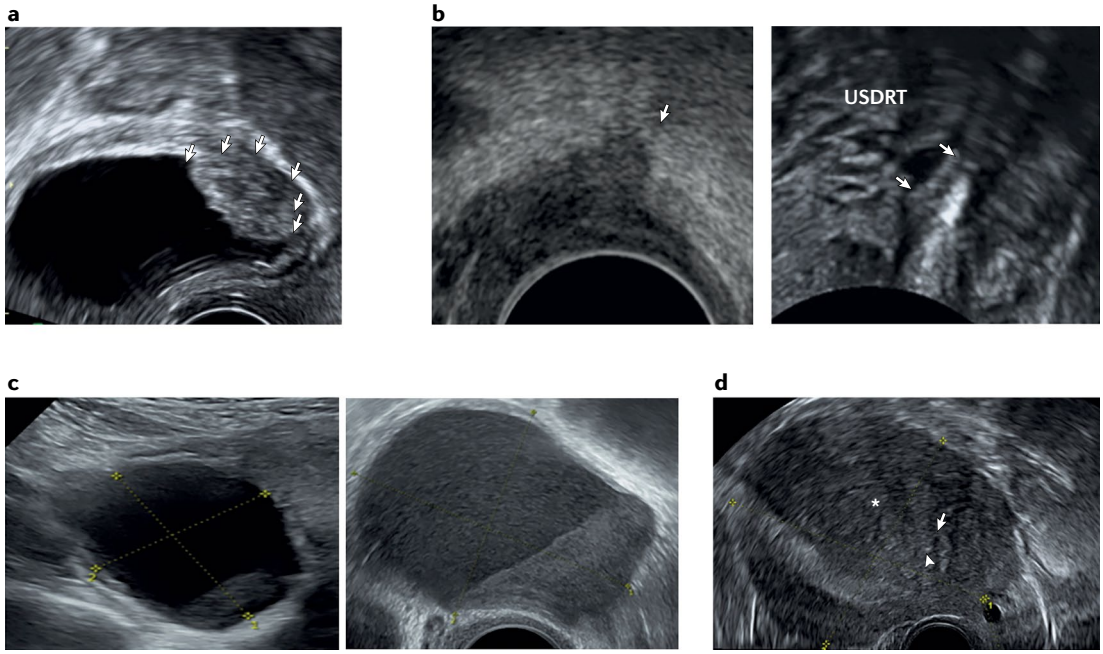

Fig. 3 | **Imaging of endometriosis and adenomyosis by TVUS. a** | Transvaginal ultrasound (TVUS) of anterior deep infiltrating endometriosis (DIE) with bladder involvement. This image shows a sagittal view with hypoechoic nodular involvement of the wall of the bladder (white arrows). **b** | TVUS of involvement of the uterosacral ligament in DIE. The left panel shows involvement of a uterosacral ligament appearing as an irregular hypoechoic thickening of the ligament (white arrow). The right panel shows a normal right-side uterosacral ligament (USDRT), which is a thin hyperechoic structure, more readily identifiable when surrounded by peritoneal fluid (white arrows). **c** | Ovarian endometriomas. The left panel shows a unilocular hypoechoic non-specific cyst by transabdominal ultrasound. The right panel shows a ground glass unilocular cyst (TVUS). **d** | TVUS of adenomyosis. The image shows the typical presentation of adenomyosis in a uterus in the sagittal plane. The greyscale image reveals non-homogeneous irregular myometrial echotexture with hyperechoic (white arrowhead), and hypoechoic (white arrow) irregular myometrial areas and a radiating pattern of linear striations (white asterisk). Images courtesy of A.-E. Millischer.

in the pelvic cavity that are secondary to retrograde menstruation in endometriosis[4]. Such inflammation decreases the chance of in vivo fertilization by disruption of sperm–oocyte interactions[4]. In striking contrast, clinicians generally regard intrauterine insemination (IUI, defined as the injection of semen into the uterus) as unable to overcome the negative effect of endometriosis-related inflammation[4]. Thus, the basis for using IUI in endometriosis is controversial and its indication in the management of endometriosis-related infertility seems to be minimal[4,113], especially as IUI seemingly entails a potential risk of disease progression[181,182].

Comparison of the results of ART for patients with infertility associated with endometriosis and those with other causes of infertility has not revealed any difference in live birth rates[176,183–185]. Although the effect of endometriosis ASRM classification[20] stages is controversial[176,183–186], ART outcomes seemingly do not correlate with endometriosis phenotypes (SUP, OMA or DIE)[177]. However, the presence of OMA might affect ovarian responsiveness during controlled ovarian stimulation during ART. Compared with women without endometriosis, the presence of OMA was associated with a higher cycle cancellation rate, higher required doses of gonadotropins, a lower mean number of oocytes retrieved, a lower mean number of metaphase II oocytes retrieved and a lower total number of embryos formed; however, pregnancy rates and live birth rates were similar[187–190]. A previous history of surgery for endometriosis (with or without ovarian surgery) statistically significantly decreases ART results[176,177]. Of note, adenomyosis, which is frequently associated with endometriosis[24] (BOX 1), independently and negatively affects ART outcomes, with reduced chances of pregnancy and live birth as well as an increased risk of miscarriage[191,192].

Health-care professionals should keep several points in mind with regard to ART modalities for patients with infertility and endometriosis. Several stimulation protocols are available to induce controlled ovarian hyperstimulation, which is necessary to achieve the growth of multiple ovarian follicles. The oocytes are collected transvaginally, under the guidance of ultrasonography, in order to obtain embryos by IVF before their transfer into the uterus. To improve pregnancy rates, patients should undergo pretreatment with GnRHa agonist for a period of 3–6 months[193] or have continuous use of oestrogen and progestin contraception[194] prior to starting ART. Studies suggest that, to prevent premature ovulation during ART-controlled hyperstimulation, both agonist or antagonist protocols seem to be equally effective[195–197]. However, research suggests that GnRHa agonist ovarian triggering, which can occur in antagonist protocols, limits pain symptom progression in the period immediately after ART[198]. Interestingly, preliminary results

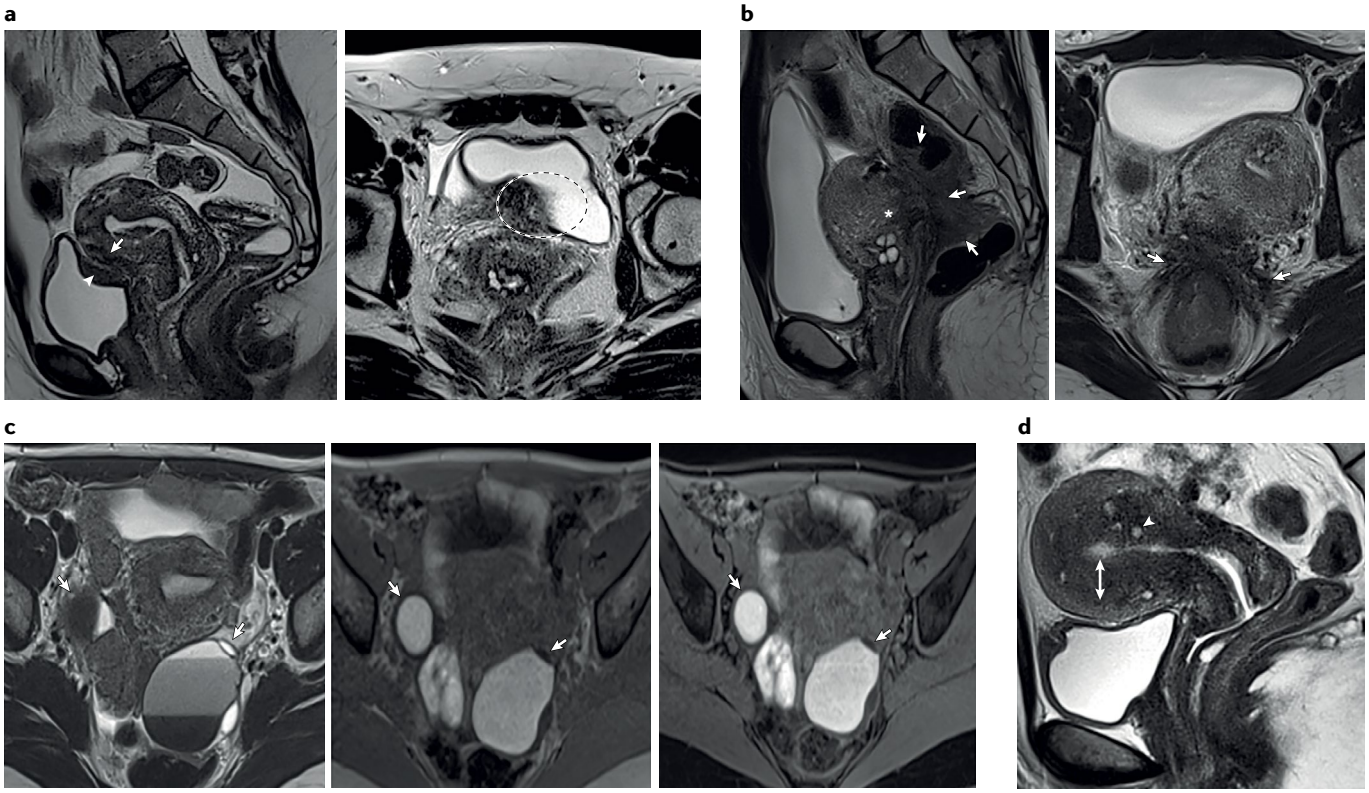

Fig. 4 | **Imaging of endometriosis and adenomyosis by MRI. a** | MRI showing anterior deep infiltrating endometriosis associated with anterior focal adenomyosis of the outer myometrium (FAOM). The left panel shows an MRI image of bladder infiltrating endometriosis. A sagittal T2-weighted image revealing obliteration of the vesicouterine pouch and abnormal thickening of the posterior bladder wall (white arrowhead) with a reciprocal development of anterior FAOM (white arrow). The right panel shows an axial T2-weighted section indicating the nodule in the wall of the bladder (dotted circle). **b** | MRI of posterior deep infiltrating endometriosis and bowel endometriosis associated with posterior FAOM. The left panel shows a sagittal T2-weighted image illustrating obliteration of the posterior cul-de-sac and asymmetric wall thickening of the lower third of the sigmoid colon (surrounded by white arrows). The endometriotic plaque infiltrates the sigmoid colon wall and also the uterine posterior wall, leading to attachment between the colon and the uterus. The posterior FAOM appears as an area of hyposignal T2 (white asterisk), contiguous to the nodule in the wall of the bowel. The right panel shows an axial T2-weighted section illustrating involvement of bilateral uterosacral ligaments in hyposignal T2 thickening (white arrows). **c** | MRI of ovarian endometriomas. Axial sections of bilateral ovarian endometriomas (white arrows). Adnexal lesions exhibit 'shading' on T2-weighted images (left panel), with three haemorrhagic fluid levels due to successive aggregation of blood components. Axial T1-weighted imaging with (right panel) and without (middle panel) fat suppression reveals multiple hyperintense bilateral adnexal lesions. **d** | MRI of adenomyosis. The typical presentation of adenomyosis in a uterus by sagittal T2-weighted MRI: diffuse thickening of the area as well as of the entire myometrium ventrally and dorsally correlates with severe diffuse adenomyosis; the white arrowhead indicates small foci of high signal intensity that represent a heterotopic endometrium with an abnormal enlargement of the junctional zone (white double arrow). Images courtesy of A.-E. Millischer.

suggest that, in women with endometriosis, deferred embryo transfer (that is, embryo transfer postponement to avoid the detrimental effects of ovarian stimulation on endometrial receptivity), is a potential option that might increase ART success rates[199].

The risks posed to patients with endometriosis by ART are not clear (TABLE 1). However, IVF and intracytoplasmic sperm injection do not exacerbate symptoms nor do they promote progression or recurrence of endometriosis[200–202]. In women with endometriosis who undergo ART, tubo-ovarian abscesses can occur after oocyte retrieval (<1% of women); these abscesses are not necessarily related to oocyte retrieval and can occur sporadically[203]. The risk of unfavourable outcomes with ART pregnancy is generally higher; compared with spontaneous conception, singleton[204–206] and multiple[207] ART pregnancies are associated with a high risk of pregnancy-related complications. However, the interpretation of these global ART outcome results should take into account the ART indication.

Endometriosis is a potential indication for fertility preservation[208]; however, few clinical studies have examined this approach in endometriosis[209–211]. Owing to the high level of clinical heterogeneity with endometriosis, the challenge lies in defining the patient groups who can be expected to derive a degree of benefit from fertility preservation. However, evidence suggests that women of reproductive age with endometriosis might benefit from fertility preservation before treatment, as these procedures, along with endometriosis itself,

Fertility preservation
The procedure used to help retain the ability to procreate, including gamete and/or gonad cryopreservation.

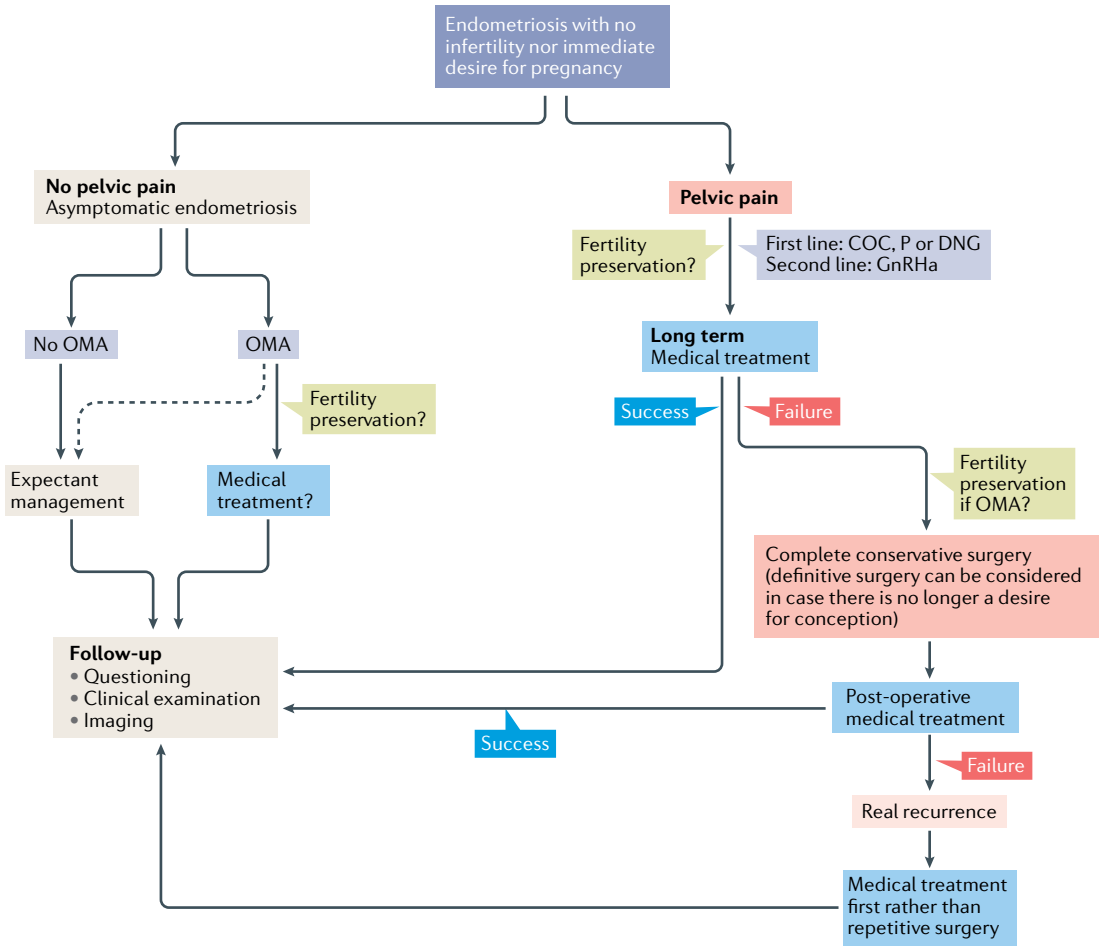

Fig. 5 | **Endometriosis management algorithm for patients without an immediate desire for pregnancy.** This novel algorithm can be used by health-care professionals for the management of patients with endometriosis who have no immediate desire for pregnancy. COC, combined oral contraceptive; DNG, dienogest; GnRHa, gonadotropin-releasing hormone analogues; OMA, ovarian endometriomas; P, progestins.

can adversely affect the ovarian reserve and hence result in an increased risk of premature ovarian insufficiency and infertility[208]. Of note, fertility preservation can be offered at a younger age than 35 years to increase the likelihood of success[212].

Time to change the paradigm

The paradigm in current practice that is widely broadcast for endometriosis management is based on first-line surgery[213]. We believe that the current management of patients with endometriosis-related health issues should be changed for the following three main reasons: first, using medical imaging, a diagnosis of endometriosis can now be made without surgical exploration; second, medical treatment can be safely prescribed without histological confirmation of endometriosis[214–218]; and third, three different therapeutic options exist (medical treatment, surgery and ART), each of which provides satisfactory clinical outcomes according to the situation.

Rethinking endometriosis diagnostic modalities. In light of the progresses made regarding the epidemiology of endometriosis and imaging, diagnostic laparoscopy should no longer be used. The most appropriate and up-to-date approach to diagnosing endometriosis is based on a combination[219] of patient interviews and clinical examination to enable the selection and identification of patients suspected of having endometriosis. Individuals identified by this step then undergo imaging (TVUS and/or MRI) (FIGS 3,4), which allows the endometriotic lesion phenotypes (OMA and/or DIE) and possible associated adenomyosis (diffuse and/or focal) to be identified. More than 20 years have passed since Brosens[60] suggested in 1997 that "noninvasive techniques such as colour Doppler ultrasonography and particularly MRI seem more suitable for diagnosis and follow-up of the recurrent ectopic bleeding of endometriosis". Importantly, models based on non-surgical parameters that can predict endometriosis with a fair degree of accuracy are being devised[220,221]. Also of note, surgery (laparoscopy) does not appear to be a factor associated with the time to endometriosis diagnosis[222]. Rather, a better understanding of the clinical signs and symptoms and patient history indicators of the disease allows patients who merit having a suitable imaging assessment to be more readily identified.

Rethinking endometriosis management. Globally, for the majority of gynaecologists, the current approach to endometriosis management favours performing surgery from the outset for diagnostic and therapeutic purposes[213] (FIG. 6a). This approach should be reworked considering the several sound scientific arguments. Not least, numerous learned societies have made recommendations that medical treatment can be prescribed for endometriosis without prior histological confirmation[214–218]. As such, in patients who do not have an immediate desire to become pregnant, medical treatment should be the first-line therapeutic option[223] (FIG. 5). Our opinion is that clinical diagnosis of endometriosis (obtained by a combination of patient interviews, clinical examination and imaging) should no longer be an indication for immediate surgery. Moreover, ART results in satisfactory fertility outcomes[224], irrespective of the endometriosis phenotype[177], even without prior surgical removal of OMA[225] and DIE nodules[226]. Also of note, the optimal time to perform ART after endometriosis surgery is within 2 years[227,228]. It would be highly desirable to reduce the number of unnecessary and/or inappropriate surgeries for endometriosis, as they entail a risk of recurrence and complications and can negatively affect the ovarian reserve[74]. As a result, patients might not be able to become pregnant spontaneously and a prior history of endometriosis surgery also has a negative effect on ART pregnancy rates[177]. Finally, in patients with endometriosis-associated infertility, pregnancies can occur soon after conservative surgery to remove lesions[229]. However, fertility outcomes after repeated surgeries are not higher than those observed with ART[230]. Finally, independently of endometriosis diagnosis, studies observed an increase in patient age at first birth, during the last decade for all women[231].

In modern endometriosis management, the patient needs to be at the centre of therapeutic decisions. As such, health-care professionals should focus on the patient rather than on the endometriotic lesions. As the endometrium is diseased in women with endometriosis[232,233], the patient is 'endometriotic' for their entire life, what we call the patient's 'endometriosis life' (FIG. 2). For this key reason, ultimately, the therapeutic strategy needs to have a long-term perspective and not be limited to immediate and systematic surgery after diagnosis. The challenge in the coming years will be how to best determine the moment to perform surgery, which ideally should only have to be done once during the entire endometriosis life. Determination of the best time to perform the surgery is one of the main indications for long-term medical treatment.

According to this new approach, we propose that a number of new strategies can be used according to the clinical situation and patient intentions. These strategies vary according to the desire of a patient for pregnancy. In patients with pain but with no immediate desire for pregnancy, medical treatment should be the first-line therapeutic option[223] (FIG. 5). The only indications for immediate surgery are the following rare situations: first, if doubt exists regarding the nature of OMA after imaging (for example, a suspected borderline or malignant lesion); second, in bowel DIE with occlusion; and third, in ureteral DIE with ureterohydronephrosis[137].

In women with endometriosis and a desire for pregnancy, there are two key questions. First, the health-care provider should ascertain when the patient wishes to become pregnant. If the desire for pregnancy is not immediate, medical treatment should be prescribed first, without surgery until the patient wishes to become pregnant (FIG. 6b–d). Second, if the patient decides to become pregnant and does not succeed spontaneously, the question then lies on how the health-care professional should choose between surgery and ART as the first option, as both result in satisfactory fertility outcomes[4] (TABLE 2). We propose that the dogma that surgery is the systematic first-line therapeutic option in cases of endometriosis-related infertility warrants being revisited. The key issue for health-care professionals

Table 1 | **The respective advantages and risks of surgery and ART**

Treatment	Fertility results	Potential risks and limits	Advantages
Surgery	Satisfactory	• Negative effect on the ovarian reserve • Reduced responsiveness to controlled ovarian stimulation • Major complications, specifically in cases of DIE surgery • Recurrence of endometriosis and/or pain • Incomplete and repetitive surgeries	• Treatment of painful symptoms • Avoids very low risk of ovarian cancer, in rare cases of doubt concerning the nature of the OMA at the imaging work-up
ART	Satisfactory	• Less than 1% of tubo-ovarian abscess secondary to oocyte retrieval • Low risk of disease progression • In cases of multiple embryo transfer, multiple pregnancies with a risk of adverse pregnancy and perinatal outcomes • Compared with spontaneous pregnancy, singleton ART pregnancies are at higher risk of obstetric and perinatal complications • Not suitable for management of associated pain	Possible without surgical exeresis of OMA and DIE lesions

ART, assisted reproductive technologies; DIE, deep infiltrating endometriosis; OMA, ovarian endometriomas.

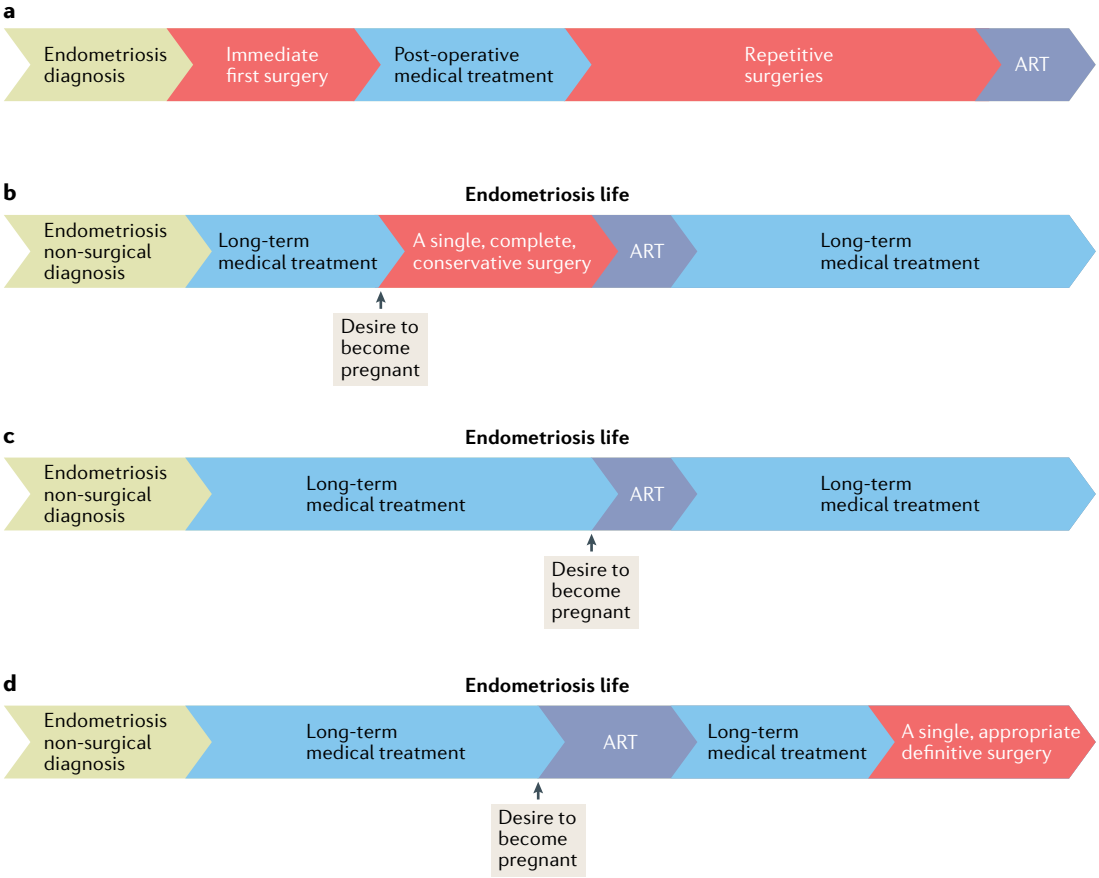

Fig. 6 | **Approaches for management of endometriosis. a** | The conventional and current approach followed by most clinical centres for endometriosis management. **b** |Timeline for a proposed management strategy that takes into account endometriosis as a lifelong condition (endometriosis life). This is the first option that can be followed if the patient wishes to become pregnant but is unable to do so spontaneously. The difference with the conventional and current approach (FIG. 6a) is that assisted reproductive technologies (ART) are provided to younger patients who have only undergone a single operation, which increases their likelihood of becoming pregnant. After childbirth, medical treatment can be provided until the patient wishes to become pregnant again. **c** | This panel shows a management strategy that can be followed if a patient refuses or is unsuitable for surgery. In this context, the patient can be given ART without previous endometriosis surgery. In this situation, it is possible for the patient to avoid undergoing surgery for their endometriosis if medical treatment is effective and well tolerated. **d** | For the third option, the criteria are met for undertaking ART before surgery. In this context, surgery can be provided at the end of the treatment process for patients with pain for whom hormonal treatment is ineffective and/or poorly tolerated and for those who no longer wish to undergo medical treatment. This situation is particularly relevant for patients with adenomyosis associated with endometriosis[22–24].

when dealing with patients whose priority is to become pregnant is to know how to select those for whom it would be preferable to perform first-line ART (TABLE 2). In these patients, the most important criterion is evaluation of the ovarian reserve and, if it is decreased, ART should be performed as the first-line therapeutic option[4], without surgery (except for salpingectomy or tubal occlusion in cases of hydrosalpinx). Another important consideration is the patient's preference, as for a variety of reasons they might prefer one treatment over the other. As such, health-care professionals should provide a clear explanation of the advantages and disadvantages of surgery and ART so that the best decision is made in accordance with the patient's perspective[2,3,4] and the clinical situation. With the patient's consent, surgery is usually provided to young patients for whom the duration of infertility has been fairly short, the ovarian reserve is adequate, there are no associated factors for infertility or a previous history of surgery for endometriosis, severe pelvic pain is reported, and neither endometrioma nor adenomyosis are present (FIG. 6b). For patients who fall outside of these indications, first-line ART seems to be preferable (FIG. 6c,d).

Conclusions

We propose that modern management for patients with symptomatic endometriosis should take into account certain scientifically established principles. Importantly, endometriosis should be considered as a chronic inflammatory disease, thereby justifying the need for a lifelong management plan. Moreover, patients with endometriosis can now be identified without surgery using non-invasive tools (for example, a combination of patient interviews, clinical examination and imaging). Subsequently, a diagnosis of endometriosis should not be considered synonymous with immediate surgery.

Table 2 | **The decision-making process for choosing between surgery and ART**

Factor	In favour of surgery	In favour of ART
Ovarian reserve[a]	Satisfactory	Decreased
Patient's intentions and priorities	Patient choice[b]	Patient choice[b]
Age	Young	Old
Infertility duration	Short	Long
Associated infertility factors (male infertility or tubal blockage)	No	Yes
Previous surgery for endometriosis (specifically OMA)	No	Yes
Pelvic pain intensity	Intense	Low
Ovarian endometrioma (specifically whether bilateral)	No	Yes
Associated adenomyosis	No	Yes

ART, assisted reproductive technologies; OMA, ovarian endometriomas.[a]Hormonal levels and antral follicle count at day 2 or 3 of the menstrual cycle[b]Influenced by culture, religion, educational level and the health-care system

Furthermore, surgical exeresis of endometriotic lesions has no effect on disease pathology (that is, retrograde menstruation) and therefore lesions can reoccur. Of note, medical treatment can be prescribed without prior histological confirmation, which is important as there is a need to reduce the number of inappropriate surgeries for endometriosis. Surgery entails a risk of complications, decreased ovarian reserve and incomplete primary conservative surgery in particular is associated with an increased risk of 'pseudo-recurrence' (that is, persistence of endometriotic lesions that are not completely removed during a first inappropriate surgery).

Following these principles, modern endometriosis management requires a broad-based approach, centred on a patient's symptoms and priorities. Importantly, endometriosis is a heterogeneous disease with three phenotypes (SUP, OMA and DIE) that might or might not be associated with adenomyosis (diffuse and/or focal). As such, disease management is highly dependent on the lesion (or lesions) that are observed and is also based on the recognition that OMA are the key lesions owing to the implications for a patient's future fertility. A multidisciplinary approach should be the current standard practice. For patient management, specialized referral centres are the gold standard. These centres should aim to provide an efficient diagnosis, which implies close collaboration with specialized radiologists. Moreover, all possible therapeutic options can be explored by a multidisciplinary team of health-care professionals (for example, gynaeco-endocrinologists for medical treatment, a multidisciplinary team of surgeons, ART specialists, pathologists and psychologists). In these centres, surgery and ART should be performed by skilled practitioners in order to obtain satisfactory results that enable a genuine choice between these two therapeutic options.

The gold standard for modern endometriosis management is an individualized approach. Subsequently, the choice of therapeutic options (that is, medical treatment, surgery and ART) depends on the clinical situation and the patient's intentions or priorities. It is important that gynaecologists stop considering surgery for patients upon diagnosis as an immediate fix. Instead, a better approach is that women with endometriosis receive care throughout their entire 'endometriosis life'. The decision is not whether the patient should undergo surgery (most patients will at some point), but when such surgery should take place. Ideally, the patient should undergo endometriosis surgery only once in her 'endometriosis life'. We propose that, if the surgical approach is selected, the best time to operate is when the patient wishes to become pregnant. Moreover, by providing effective relief of pelvic pain, medical treatment enables the best time for the surgery to be scheduled.

We hope that these scientifically demonstrated propositions will contribute to changing the paradigm regarding endometriosis management. Nevertheless, although there is a call for action along these lines, management strategies for endometriosis can be influenced by culture, religion, educational level and health-care systems around the world.

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C.C. supervised the project. All of the authors researched data for the article, substantially contributed to discussions of the content and wrote the article. C.C. and P.S. carried out the review and editing of the mauscript.

Competing interests
Until recently, C.C was the president of the Society of Endometriosis Disorders (SEUD) and of the Society of Gynecological and Pelvic Surgery (SCGP). Over the past 3 years, C.C. has been a consultant for AbbVie, Bayer, Gedeon Richter and Ipsen. P.S. has been a consultant for Gedeon Richter and Ipsen. L.M. has been a consultant for Ipsen. B.B. has no potential conflicts of interest to disclose.

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