Endometriosis: pathogenesis and treatment

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Abstract | Endometriosis is defined as the presence of endometrial-type mucosa outside the uterine cavity. Of the proposed pathogenic theories (retrograde menstruation, coelomic metaplasia and Müllerian remnants), none explain all the different types of endometriosis. According to the most convincing model, the retrograde menstruation hypothesis, endometrial fragments reaching the pelvis via transtubal retrograde flow, implant onto the peritoneum and abdominal organs, proliferate and cause chronic inflammation with formation of adhesions. The number and amount of menstrual flows together with genetic and environmental factors determines the degree of phenotypic expression of the disease. Endometriosis is estrogen-dependent, manifests during reproductive years and is associated with pain and infertility. Dysmenorrhoea, deep dyspareunia, dyschezia and dysuria are the most frequently reported symptoms. Standard diagnosis is carried out by direct visualization and histologic examination of lesions. Pain can be treated by excising peritoneal implants, deep nodules and ovarian cysts, or inducing lesion suppression by abolishing ovulation and menstruation through hormonal manipulation with progestins, oral contraceptives and gonadotropin-releasing hormone agonists. Medical therapy is symptomatic, not cytoreductive; surgery is associated with high recurrence rates. Although lesion eradication is considered a fertility-enhancing procedure, the benefit on reproductive performance is moderate. Assisted reproductive technologies constitute a valid alternative. Endometriosis is associated with a 50% increase in the risk of epithelial ovarian cancer, but preventive interventions are feasible.

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Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity, predominantly, but not exclusively, in the pelvic compartment. It is an estrogen-dependent chronic inflammatory condition that affects women in their reproductive period, and is associated with pelvic pain and infertility.[1] Determination of prevalence and incidence figures has been hampered by exclusive reliance upon surgical visualization of lesions for a definite diagnosis. Analysing the hospitalized instead of the general population presumably distorts estimates.[2–4] Moreover, it is unclear whether the presence of ectopic endometrium, independently of lesion severity or clinical picture, always constitutes a pathological condition. A general consensus exists that the presence of symptoms or of lesion progression that mandates investigation and possibly treatment define 'endometriotic disease', whereas, in the opinion of some experts, very limited forms of endometriosis may occasionally be considered a paraphysiologic or temporary histologic phenomenon.[5–7] The prevalence of endometriotic disease seems to be ~5%, with a peak between 25 years and 35 years of age.[4,5] A 0.1% annual incidence of endometriosis among women aged 15–49 years has been reported.[8] The disease seems frequent in adolescent women with chronic pelvic pain.[9]

Competing interests
The authors declare no competing interests.

A prospective, multicentre survey conducted in 10 European countries demonstrated that the average annual total cost per patient with endometriosis in 2008 was almost €10,000, including health care as well as loss of productivity costs.[10] Affected women have been estimated to lose ~10 h of work weekly, mainly owing to reduced effectiveness whilst working.[11] In the USA, women with endometriosis incur total medical costs that are 63% higher (US$706 per month) than those of average woman ($433) in a commercially insured group.[12] Also in the USA, two-thirds of patients with endometriosis received an endometriosis-related surgical procedure within 1 year of the initial diagnosis.[12] In Canada, the estimated mean annual cost of endometriosis in 2009 was $5,200 per patient, yielding an extrapolated total annual cost to Canadian society of $1.8 billion.[13] Although overestimation of costs cannot be excluded, endometriosis clearly constitutes a substantial burden not only on the health-related quality of life of individual women, but also on the finite health-care resources of national health systems.

Pathogenesis

The pathogenic hypothesis supported by the most robust evidence is based on the so-called retrograde menstruation phenomenon.[1,14] Viable endometrial fragments are driven through the fallopian tubes, possibly by a pressure gradient originating from dys-synergic

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Key points

- Endometriosis is characterized by the presence of ectopic endometrium causing pain, infertility or lesion progression; it affects ~5% of women of reproductive age, with a prevalence peak between 25 years and 35 years of age
- Interaction of the number and amount of menstrual flows with genetic and environmental factors seems to determine the likelihood of development as well as the phenotypic manifestation of the disease
- Although pain can be managed via pharmacological inhibition of ovulation and menstruation, lesions are not eradicated; surgery is generally associated with pain relief, but its benefit is often temporary
- Medical therapy for infertility is inefficacious, whereas laparoscopic elimination of endometriotic lesions and adnexal adhesions increases the chances of conception moderately; *in vitro* fertilization is a valid alternative to surgery
- Endometriosis is associated with a 50% increase in the risk of ovarian cancer; preventive interventions are possible, but screening of patients with endometriosis for ovarian cancer is presently not justified
- Primary prevention of endometriosis is not currently feasible; treatment should be tailored to fit individual needs, and a shared decision-making approach between patient and clinician is encouraged

uterine contractions. Once they reach the peritoneal cavity, they can implant, grow and invade onto pelvic structures. The likelihood of this event is influenced epidemiologically by any menstrual, reproductive or personal factor that would augment pelvic contamination by regurgitated endometrium,[15–37] such as early age at menarche or a long duration of menstrual flows, and biologically by any alteration at the molecular level that favours the stepwise process of cell implantation and growth at ectopic locations (Figure 1).[4,38–61]

Women's reproductive and menstrual patterns have greatly changed in today's affluent Western nations compared with those of our ancestors. Decrease in age at menarche, in number of pregnancies, in duration of breastfeeding, and delay of first birth, all lead to an increase in the overall number of ovulations and menstruations a woman has within a reproductive life-span. Monthly menstruation for decades on end is not the historical norm. Thus, the likelihood of developing a disease directly caused by menstruation might be greater nowadays.[62] Indeed, regular and abundant menstrual flows increase the risk of endometriosis.[4,17]

Familial aggregation of endometriosis is firmly established in humans and nonhuman primates.[18,25,63] The disease has a complex genetic aetiology requiring the interaction of several genetic variants and environmental factors. Genetic factors contribute about half of the variation in endometriosis risk, with an estimate of heredity of 51%.[63] Meta-analyses of the few genome-wide association studies performed in the past few years have provided evidence of a robust association of endometriosis with seven risk loci.[63,64] Of particular interest for their gene-based ranking, known pathophysiology and proximity to single nucleotide polymorphisms with genome-wide significance, the *WNT4*, *CDKN2B-AS1* and *GREB1* genes are strong targets for further studies on endometriosis. *WNT4* encodes a member of the wingless-type MMTV integration site family, which is important for the development of the female reproductive tract and for steroidogenesis. The *CDKN2B-AS1* gene is located in the second-densest gene desert for predicted enhancers in the human genome and is transcribed in a long noncoding RNA in the antisense orientation of

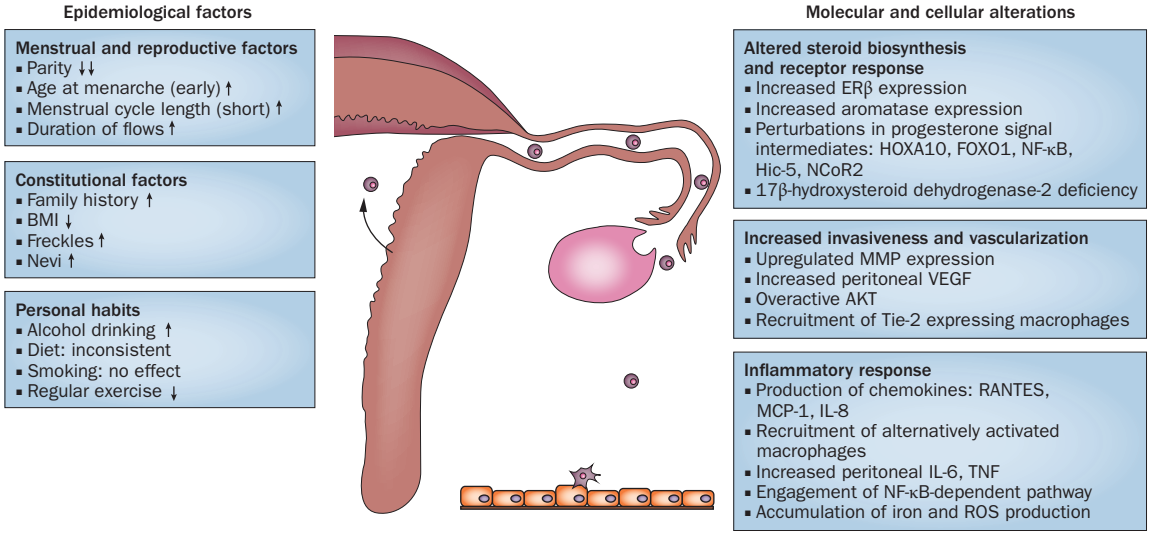

Figure 1 | Epidemiological factors and molecular mechanisms involved in endometriosis development. Viable endometrial fragments are driven through the fallopian tubes by retrograde menstruation owing to a pressure gradient originating possibly from dyssynergic uterine contractions. Once they reach the peritoneal cavity, they can implant, grow and invade into pelvic structures. The likelihood of this event is influenced epidemiologically by any menstrual, reproductive or personal factor that augments pelvic contamination by regurgitated endometrium, such as early age at menarche or a long duration of each menstrual flow. Biologically, the likelihood of this event is influenced by any alteration at a molecular level that favours the stepwise process of cell implantation and growth at ectopic locations. Arrows indicate risk direction. Abbreviations: ERβ, estrogen receptor β; FOXO1, forkhead box O1; HOXA10, homeobox A10; MCP-1, monocyte chemotactic protein 1; MMP, matrix metalloprotease; NCoR2, nuclear receptor corepresssor 2; NF-κB, nuclear factor κB; ROS, reactive oxygen species; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

the *CDKN2B* and *CDKN2A* gene cluster that encodes three tumour suppressor proteins: p15, p16-INK4a and p14ARF. *GREB1* encodes an early-response gene in the estrogen receptor-regulated pathway.[63,64]

Estrogens fuel ectopic endometrium growth, and alterations of estrogen signalling have been associated with the disease.[53,65] Estradiol is available to promote growth of ectopic tissue via that produced from the known steroidogenic organs and also that produced locally by the expression of aromatase in the endometriotic implants.[38,39] The ectopic tissue has been consistently shown to express different levels of estrogen receptor (ER) α and β than eutopic tissue, with ERβ present in markedly higher levels in ectopic tissue.[45,48,51,65] Deficient methylation of the promoter of the gene that encodes ERβ has been suggested to result in pathological overexpression of ERβ in endometriosis, which in turn suppresses ERα expression and diminishes estradiol-mediated induction of the progesterone receptor in endometriotic cells.[45,65] This mechanism is thought to contribute to the resistance to selective actions of progesterone in these cells, which is manifested by perturbations in a number of downstream progesterone target genes.[47]

Progesterone normally triggers a uterine endometrial response characterized by inhibition of estrogen-dependent proliferation of epithelial cells, secretory maturation of the glands, and transformation of stromal cells into specialized decidual cells. Moreover, progesterone transiently induces a receptive phenotype in endometrial epithelial cells essential for embryo implantation. As a consequence of progesterone resistance, genes critical to these events, such as prolactin for decidual response[66] or glycodelin for embryo implantation,[67] are dysregulated in the endometrium of affected women.[47] On the other hand, inflammation secondary to endometriosis could induce progesterone resistance by altering the progesterone signalling pathway though mechanisms of competition or interference with proinflammatory transcriptional factors. Several signal intermediates, such as the chaperone protein FKBP4 or the co-regulator Hic-5, are perturbed in endometriosis.[55,59] Thus, it cannot be excluded that the inflammatory response to the ectopic cell implantation may contribute to the dynamic steroid hormone expression demonstrated in some lesions. The steroid perturbation is also critical for the entire stepwise process of endometriotic lesion formation, which has been shown to involve tissue-adhesive properties, the activity of matrix metalloproteinases and the triggering of an angiogenic response (Figure 1).[53]

Inflammation is another typical feature of endometriosis, as the presence of ectopic tissue in the peritoneal cavity is associated with overproduction of prostaglandins, cytokines and chemokines.[40,42,43,50,61,68,69] Macrophages infiltrating the ectopic lesions express typical markers of alternative activation, favouring the growth of the lesions and promoting their angiogenesis.[54] The macrophage NF-κB-dependent pathway is also engaged,[70] with transactivation of responsive gene elements controlling angiogenesis and tissue remodelling.[71] Moreover, macrophages are endowed with the ability to internalize and recycle iron derived from refluxed erythrocyte breakdown.[72] Indeed, macrophages in the peritoneal cavity of affected women are known to accumulate iron, probably as a result of excessive pelvic blood collection.[49,52] Nonprotein bound, catalytic iron increases the generation of reactive oxygen species, which in turn favours the progression of endometriosis via peritoneal damage, exposure of submesothelial connective tissue, neoangiogenesis, and enhanced endometrial cell proliferation.[44,49,60] The pathogenic theories supported by current scientific evidence are summarized in Box 1.

Box 1 | Current theories on endometriosis pathogenesis

Retrograde menstruation
The most accepted theory. Endometriosis derives from the reflux of endometrial fragments regurgitated through the fallopian tubes during menstruation with subsequent implantation on the peritoneum and the ovary.

Endometrial stem cell implantation
An expansion of the previous theory. Endometrial epithelial progenitor cells and mesenchymal stem-cell-like cells together with their niche cells are shed into the peritoneum via retrograde menstruation establishing ectopic implants.

Müllerian remnant abnormalities
Mostly suggested for endometriosis infiltrating the cul-de-sac and uterosacral ligaments. Aberrant differentiation or migration of the Müllerian ducts could cause spreading of cells in the migratory pathway of fetal organogenesis across the posterior pelvic floor.

Coelomic metaplasia
Still supported for ovarian endometriosis. The coelomic epithelium covering the ovary and the serosa of the peritoneum could undergo a metaplastic change into endometrium.

Pathology and pain symptoms

Pelvic endometriotic lesions have been schematically subdivided into superficial peritoneal implants (Figure 2a), ovarian cysts (endometrioma; Figure 2b) and deep nodules or plaques (which can individually involve and infiltrate the parametria, Douglas pouch, anterior rectal wall, posterior vaginal fornix, antero-uterine pouch, bladder detrusor, ureters and sigmoid colon; Figure 2c). Controversy exists on a single versus diverse origin of the three lesion types.[73,74] Endometriomas show distinct anatomical characteristics not shared by other benign ovarian cysts, and have been defined as pseudocysts, because they are formed by an extraovarian haematoma, surrounded by duplicated ovarian parenchyma.[75] This finding explains why surgical 'enucleation' of the pseudocapsule actually implies removal of part of the gonadal cortex, follicle loss and reduction of the ovarian reserve.[76] According to some experts, ovulation is crucial in the development of endometriotic cysts.[77,78]

Endometrial fragments refluxed through the tubes generally implant in the pelvis following the principle of gravity in women in the standing or sitting position. This fact explains the frequent involvement of the deepest portion of the Douglas pouch. Moreover, the distribution of lesions onto bilateral organs (ovaries, ureters,

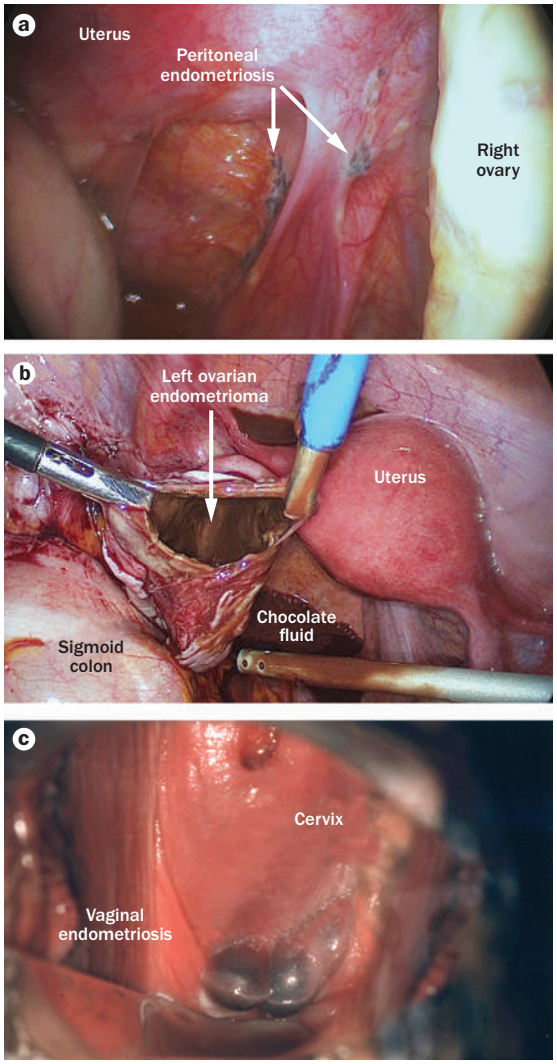

Figure 2 | Visual examples of the most frequent forms of endometriosis. **a** | Endometriotic bluish peritoneal implants on both the medial and lateral aspects of the right utero-sacral ligament, in the postero-uterine Douglas pouch. **b** | A left ovarian endometrioma. The cyst has been opened and the margins are held with two atraumatic microforceps. The wall of the pseudocavity is covered with thick, tarry old blood (chocolate fluid), which also fills the deepest portion of the Douglas pouch. **c** | Endometriotic nodules in the retrocervical area. Distinct bluish endometriotic lesions infiltrate the posterior vaginal fornix.

ascending and descending colon, round ligaments and sciatic nerves) is asymmetrical, probably as a result of anatomical differences in the right and left hemipelves that facilitate implantation on one side. As an example, the left ovary and ureter are more frequently involved than the right ones.[79] Endometriotic lesions are observed in several other organs, including the liver, diaphragm, pleura, lung and umbilicus, although much less frequently compared with pelvic structures.

The two most frequent pain symptoms caused by endometriosis are dysmenorrhoea (80%) and deep dyspareunia (30%).[80–82] Dyschezia, dysuria and inter-menstrual pelvic pain are referred less frequently, and are usually associated with, respectively, rectal and bladder lesions or ovulation.[83] A correlation has been demonstrated between lesion site and pain type.[84] As an example, deep dyspareunia has been associated with deep lesions infiltrating the utero-sacral and cardinal ligaments, the pouch of Douglas, the posterior vaginal fornix and the anterior rectal wall.[81,83–85] Dysmenorrhoea generally also shows a functional origin, as it is based on excessive intraperitoneal prostaglandin production by ectopic endometrium, causing myometrial hypertonus and secondary ischaemia.[80,86]

Moreover, some women with endometriosis experience hyperalgesia, which is the occurrence of excruciating pain when a nonpainful stimulus is applied. Hyperalgesia is characteristic of neuropathic pain, usually related to nerve injury or inflammatory stimuli. In women with deep endometriosis, the sensory nerve fibres are frequently invaded by endometriotic stromal cells,[87,88] and several mediators such as histamine, tryptase, prostaglandins, serotonin and nerve growth factor, are abnormally synthesized and released by activated macrophages, mast cells and leukocytes within the endometriotic lesions, around sensory nerve fibres and in the peritoneal fluid.[86,87,89] Owing to the chronic inflammatory environment caused by ectopic endometrium, a vicious cycle might develop that promotes nociceptor sensitization, neurotrophism, local neo-neurogenesis and activation of sensory nerve fibres, with resulting hyperalgesia.[86] Finally, the presence of endometriosis can be associated with increased pain perception,[90] owing to abnormal modulation of nociceptive input with an increase in the intensity of the neural signal ascending to the cerebral cortex.[91–93]

Diagnosis and classification

With the exception of vaginal endometriosis, obtaining a histological diagnosis requires surgery and, at that point, removal of the lesions is unavoidable. In fact, the therapeutic starting point of most women with endometriosis is a surgical procedure. However, whenever possible, diagnosis of and surgery for endometriosis should be clearly distinguished.[94] Some experts believe that endometriosis can be suspected and should be diagnosed even in the absence of a histological confirmation,[95] and surgery should not be mandatory if clear therapeutic benefits of the intervention cannot be foreseen. This option is included in some but not all international guidelines.[96,97]

Adhesions and superficial peritoneal implants do actually need surgery to be documented, but ovarian endometriomas and deep invasive nodules can be reliably identified with the use of noninvasive diagnostic tools. Gynaecologic bimanual examination can easily detect rectovaginal plaques, and transvaginal ultrasonography is highly accurate in diagnosing ovarian endometriomas, deep nodules and bladder detrusor lesions.[98–100] Recto-sigmoidoscopy, barium enema, MRI and urinary apparatus imaging may be of help in selected circumstances.[101] The role of serum CA-125 levels assessment in primary diagnosis is undefined.

The combination of symptoms, signs and ultrasonographic findings is generally reliable in the nonsurgical diagnosis of endometriosis.[95] In doubtful cases, an

empiric diagnostic trial with gonadotropin-releasing hormone (GnRH) agonists may be considered before resorting to laparoscopy. In fact, symptoms caused by endometriosis generally subside promptly during GnRH agonist treatment, owing to induced hypoestrogenism. However, symptoms relief is suggestive of 'hormonally responsive pelvic pain' and not necessarily endometriosis, as other conditions respond to hypoestrogenism. A diagnosis of exclusion is also important, as lack of pain relief greatly reduces the probability of endometriosis being the cause of symptoms.[86,102]

Endometriosis is classified into four stages according to the American Society for Reproductive Medicine scoring system.[103] In general, minimal and mild stages correspond to peritoneal disease, moderate stage to one endometrioma >3 cm, and severe stage to bilateral endometriomas and/or complete Douglas obliteration. Whereas adhesions affect score attribution substantially, clinical important deep lesions do not receive specific points. Although widely used, this scheme has not been demonstrated to be related to symptoms frequency and severity or reproductive prognosis.[81]

Treatment for pain

Medical or surgical approaches can be adopted in women with endometriosis-associated pelvic pain. The choice between the two alternatives is influenced by several factors, including the presence of a large ovarian endometrioma or cysts with doubtful ultrasonographic characteristics, as well as ureteral or bowel stenosis.[101] Moreover, the desire for a spontaneous pregnancy is crucial for the final decision, as all the available hormonal compounds used for endometriosis interfere with ovulation. One of the main indications for surgery is thus temporary pain relief in women seeking spontaneous conception.[104]

Although the effect of surgery on pain is usually temporarily satisfactory,[105–107] the risk of complications varies according to the type of lesion extirpated. Peritoneal implants can be safely coagulated or excised with similar benefit.[108–110] Also, conservative ovarian surgery (that is, treatment of ovarian endometriotic cysts without removal of the ovary) is a relatively safe procedure. Excision of ovarian endometriomas seems to be associated with better pain relief as well as lower recurrence and higher pregnancy rates than cyst vaporization or coagulation.[111] However, alternative modalities have been suggested with the objective of limiting damages to the gonadal reserve; these include three-step management (that is, laparoscopy with cyst drainage and biopsy, GnRH agonists for 3 months, second laparoscopy with laser vaporization of the wall of the residual cyst)[112] and a technique combining excision of most of the endometrioma wall, with laser vaporization of the remaining part close to the ilus.[113] In a systematic review, no differences in the number of mature oocytes retrieved and in clinical pregnancy rate were observed between women who underwent endometrioma coagulation and those who underwent standard cystectomy prior to *in vitro* fertilization (IVF) cycles.[114]

Resection of rectovaginal lesions is associated with a relatively high overall risk of complications (around 10%), especially when colorectal resection is performed concomitantly.[101,106] Partial bowel stenosis not causing subocclusive symptoms does not constitute an indication to segmental resection *per se*, and more conservative approaches should be discussed with the patient.[115,116] Different techniques are used to manage rectosigmoid endometriosis, namely, lesion shaving, nodule/disk excision and suture, or segmental resection. However, there are major differences in postoperative complication rate, with lesion shaving being associated with much less frequent complications compared with disk excision and segmental resection.[117,118] Good pain relief is generally reported during the first year after bowel resection for deep endometriosis.[119] In the experience of some surgeons, more than 80% of women achieved short-term and long-term amelioration of symptoms after surgery for bowel endometriosis.[117,120] However, in a systematic literature review, pain recurrence was observed in one out of four patients, and re-intervention was required in almost one out of five of these individuals.[119] Robotic laparoscopy has been introduced among the surgical modalities to treat endometriosis in the past few years,[121] and preliminary results suggest that a robotic approach to deep and colorectal endometriosis is feasible, effective and safe,[122] although uncertainties on cost-effectiveness still remain.

The objectives of medical therapy are inhibition of ovulation, abolition of menstruation, and achievement of a stable steroid hormone milieu, based on the concept that the response of the eutopic and ectopic endometrium is substantially similar.[123,124] In addition, some drugs create a hypoestrogenic (GnRH agonists), hyperandrogenic (danazol, gestrinone), or hyperprogestogenic (oral contraceptives, progestins) environment, with suppression of endometrial cell proliferation. Pharmacological treatments are symptomatic and not cytoreductive: lesions survive any drug, at any dose, for any period of use, ready to resume their metabolic activity at treatment discontinuation.[97,125]

Medical therapy should be conceived as a long-term treatment, similarly to therapy for other chronic inflammatory conditions. Symptom recurrence at drug discontinuation is expected and does not constitute demonstration of inefficacy of hormonal manipulation.[125] The results of systematic literature reviews have consistently demonstrated that, as long as amenorrhoea is achieved, there are no major differences between the various available drugs in terms of pain relief, whereas tolerability, adverse effects and costs vary widely.[123,124] To increase compliance, the lowest effective dose of any drug should be chosen.[125]

Danazol and gestrinone are not suitable for prolonged treatments,[97] mainly owing to androgenic-type adverse effects (for example, seborrhoea, hypertrichosis and weight gain) and unfavourable effects on serum cholesterol lipoprotein distribution (HDL levels decrease, and LDL levels increase). A possible exception is danazol 200 mg per day used vaginally.[126]

GnRH agonists are very effective against pain[127] but are associated with frequent and scarcely tolerable

hypoestrogenic adverse effects (for example, vasomotor symptoms, genital hypotrophia and mood instability), and a negative calcium balance with increased risk of osteopaenia, although bone loss seems to be reversible if treatment is limited to a few months. Moreover, GnRH agonists are the most costly pharmacologic compounds available for the treatment of endometriosis. To limit subjective and metabolic untoward effects, GnRH agonists can be combined with a so-called 'add-back' therapy. Many of the available hormone replacement therapies can be used as add-back therapy, including tibolone (2.5 mg per day orally) or a bone-sparing progestin such as norethisterone acetate (5 mg per day orally), which have both been successfully used.[123,124] This add-back therapy enables the indefinite extension of the treatment period but increases the overall costs further. The use of GnRH agonists plus add-back therapy is suggested only in highly selected women unresponsive to progestins or at very high surgical risk.

Monophasic, low-dose, oral contraceptives and progestins combine demonstrated overall safety, good efficacy, appreciable tolerability and low cost, and seem to constitute the best possible therapeutic compromise for chronic treatment.[123–125] Oral contraceptives are used for multiple reasons, which include decreasing retrograde menstruation (particularly when given continuously), inducing a pseudopregnant state and causing decidualization and subsequent atrophy of the eutopic and ectopic endometrium. No differences have been demonstrated between various oral contraceptives, but it seems sensible to use preparations with the least possible estrogen content to prevent endometrial proliferation.

Several progestins have been studied, with different types of administration, including the oral, subcutaneous, intramuscular, intrauterine and vaginal route.[123–125,128] The two progestins supported by the largest available evidence are norethisterone acetate and dienogest, which have been used orally at the dose of 2.5–5.0 mg per day and 2 mg per day, respectively.[129–134] Norethisterone acetate is partly metabolized to ethinylestradiol,[135] thus limiting the consequences of estrogen deficiency and stabilizing the endometrium, with achievement of amenorrhoea in more than two-thirds of cases.[129,130]

The therapeutic goal is pain relief, not lesion resorption. Treatment should be tailored to the specific symptom that most afflicts the individual patient, as pain is not similar in all women with endometriosis and, more importantly, the same type of symptom may have different implications for different women. If the main problem is dysmenorrhoea, then oral contraceptives should be the first choice, and continuous use is suggested, with the aim of abolishing uterine flows.[123–125] However, irregular bleeding should always be anticipated, and pill discontinuation for 4–7 days suggested in case of prolonged spotting or breakthrough bleeding. Women should be informed that bleeding is usually associated with pain but not with disease progression, and should be instructed to use analgesics with a long half-life (for example, naproxen sodium 550 mg twice per day). The final objective is reducing uterine bleeding episodes as much as possible, from the 13 per year expected with cyclic oral contraceptive use.

An effective alternative is insertion of the levonorgestrel-releasing intrauterine system, which abolishes menstruations in about one-third of users and substantially decreases the amount of bleeding in another third.[123,124] Given the 5-year duration of the system, it is an interesting option for women who have completed their family or those that do not plan to seek conception in the short term. Moreover, the intrauterine system can be inserted at the end of a surgical procedure as a postoperative adjuvant treatment.[136] However, the levonorgestrel intrauterine system is not FDA-approved for the treatment of endometriosis-related pain. In addition, relatively few studies have been performed with this system. Although it does seem to be a promising modality, more data are still needed.

When deep dyspareunia is the main problem, treatment should be suggested according to the presence or absence of rectovaginal endometriotic lesions. When deep plaques are identified, surgery and the use of norethisterone acetate (2.5 mg per day) are associated with a similar degree of pain relief and satisfaction with treatment after 1 year; however, these two therapeutic approaches exhibit different patterns of efficacy: immediate after surgery, but followed by partial recurrence with time, or more gradual with progestin therapy, but progressively better with duration of use. In the absence of rectovaginal lesions, norethisterone acetate seems to offer better results than surgery.[130] A drawback of progestin therapy is reduction of libido in about one-fifth of women.[129,130]

Overall, medical therapy with oral contraceptives and progestins enables satisfactory long-term pain control in around two-thirds of symptomatic women.[123–125] The remaining third may benefit from conservative or definitive surgery, according to the desire to conceive. When pregnancy is no more an issue, hysterectomy with bilateral salpingectomy relieves dysmenorrhoea and can reduce deep dyspareunia, as the parametria as well as deep lesions are concomitantly resected, while avoiding the consequences of premature castration. However, ovarian preservation exposes to the risk of pain persistence owing to continued estradiol production, especially in case of nonradical treatment of endometriotic implants. If both ovaries are removed and hormonal replacement therapy is deemed appropriate, combined preparations are generally suggested to avoid hyperplasia of residual foci exposed to unopposed estrogens.

Treatment for infertility

In women with endometriosis, infertility arises mostly as the consequence of chronic pelvic inflammation.[137] Adhesions secondary to this flogistic phenomenon may disrupt pelvic anatomy, and inflammatory molecules can create a local milieu that is unfavourable to conception. Interference has been hypothesized with the complex mechanisms of ovulation, oocyte pick-up by the fallopian tubes, spermatozoa function, fertilization

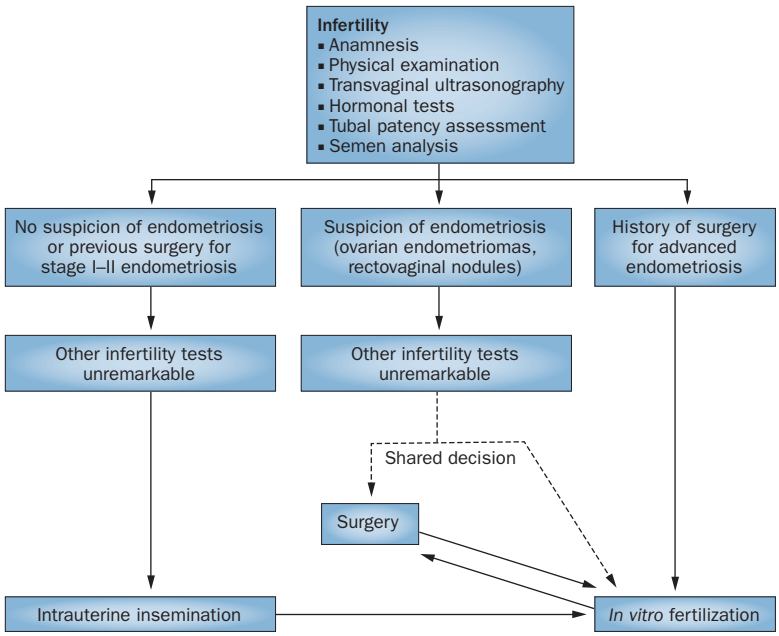

Figure 3 | Flow-chart of infertility treatment from an endometriosis-centred perspective. Women with past intervention for endometriosis stage I–II and those with unexplained infertility (one-third of whom have endometriosis stage I–II) should receive intrauterine insemination and, if failed, *in vitro* fertilization (IVF). Diagnostic laparoscopy to identify early stages of the disease is not mandatory because effectiveness is very limited. By contrast, a history of surgery for advanced endometriosis should orient towards IVF. There is no definitive evidence on the most suitable approach in unoperated infertile women who are diagnosed with ovarian endometriomas or rectovaginal nodules. If all the other infertility tests are unremarkable, surgery or IVF may both be considered. Women should receive complete information on the pros and cons of both treatments and a shared and personalized decision with the patient should be taken (dotted line). Factors to be considered include age, cyst bilaterality, cyst dimension and sonographic appearance, detection of hydrosalpinx at ultrasonography, presence of associated pain symptoms and results of ovarian reserve tests. Of note, IVF and surgery are not final treatments, and both IVF after failed surgery or surgery after failed IVF can be considered.

process, tubal transport of the embryos and, possibly, embryo implantation.[137]

On the basis of these pelvic inflammatory effects, two possible therapeutic options can be envisaged, surgical 'normalization' of the altered anatomy or bypass of the unfavourable pelvic environment. In the former case, adhesiolysis may re-establish normal relationships between pelvic organs, and removal of endometriotic lesions may discontinue the permanent inflammatory trigger. In the latter case, IVF can be performed, thus overcoming problems with adhesions and tubal patency. Oocytes are retrieved directly from the ovaries and embryos are replaced within the endometrial cavity, thus avoiding direct exposure to the detrimental effects of the pelvic milieu. However, this approach may not fully overcome the unfavourable effects of endometriosis, given that both folliculogenesis and endometrial receptivity might at least in part be influenced by the adjacent detrimental peritoneal milieu.[137] A possible therapeutic algorithm for endometriosis-related infertility is shown in Figure 3.

Hormonal medical treatment has no effect on infertility in women with endometriosis. According to a Cochrane meta-analysis, the odds ratio of pregnancy following ovulation suppression versus placebo or no treatment was 0.97 (95% CI 0.68–1.34) for all women, and 1.02 (95% CI 0.70–1.52) for subfertile couples.[138] These results fit with the modern view of the disease. Both eutopic and ectopic endometrium have outstanding capacity of remaining quiescent even for years under suppressive hormonal therapy, but only until exposed again to gonadal activity. Even if the steady hormonal condition obtained with ovary-suppressing agents improves the pelvic milieu by reducing inflammation, the potential benefits are rapidly lost at drug discontinuation; thus, the fertility potential remains unchanged.

Overall, the effect of surgery for endometriosis-associated infertility is supported by evidence of limited quality. A small benefit has been demonstrated for early, peritoneal disease. A meta-analysis of the two randomized controlled trials (RCT) conducted on women with stage I–II endometriosis, documented an odds ratio for pregnancy of 1.64 (95% CI 1.05–2.57) in favour of laparoscopic surgery.[139] However, the cumulative pregnancy rate at 9–12 months increased only from 18% to 26%, corresponding to a number of women needed to be treated of 12. This finding means that, in real-world conditions, the number needed to be treated is actually doubled at least, considering that the prevalence of early stage endometriosis is between 30% to 50% in women with unexplained infertility, and that peritoneal implants cannot be reliably diagnosed before surgery.[140] On this basis, in clinical practice, the value of diagnostic laparoscopy in women with unexplained infertility is limited.[141]

Data regarding more advanced endometriosis, that is, stage III–IV disease, are less robust, as no RCTs have investigated the benefit of surgery as a conception-enhancing procedure in these women. Only case series have been published on the effect of treatment of ovarian endometriotic cysts. Overall, the likelihood of pregnancy following endometrioma excision has been estimated to be around 50%.[137] However, this figure is most probably an overestimate, considering the poor design of the available studies, and the inclusion in some of them of women who were not infertile at the time of surgery, as well as of those who achieved a conception through IVF.[140]

Indirect evidence suggests that surgery may not be of major benefit for deep infiltrating endometriosis.[142] In a patient preference trial comparing women with rectovaginal endometriosis opting for surgery ($n = 44$) with those choosing expectant management ($n = 61$), the cumulative pregnancy rate was, respectively, 34% and 36%.[143] On the other hand, it has been shown that, even when bowel surgery was needed because of infiltrative endometriosis, one-third of infertile women conceived spontaneously.[117]

Intrauterine insemination (IUI) is commonly advocated for infertile women with endometriosis stage I–II who fail to become pregnant following surgery. This approach is theoretically illogical, as the procedure does not overcome the negative effect of a detrimental pelvic milieu. On the other hand, limited peritoneal endometriotic implants may be unrelated to infertility

in a considerable proportion of women. Endometriosis stage I–II was observed in 19% of women undergoing tubal ligation and in 32% of those with an azoospermic partner.[144,145] Thus, minimal or mild endometriosis might be an incidental finding in women with infertility. IUI, which is typically prescribed for unexplained infertility, may thus be effective. Moreover, most studies involve IUI in combination with controlled ovarian hyperstimulation, not IUI alone.[146,147] Probably, the combination of both modalities is the factor that increases pregnancy rates in patients with tubal patency and the partner's reasonable-quality sperm.

Endometriosis is a classic indication for IVF, as the tubes are bypassed, and oocytes as well as spermatozoa are not directly exposed to the abnormal peritoneal environment. Therefore, anatomical distortion and biochemical insults are mostly overcome. Nonetheless, endometriosis seems to be associated with lower than normal chances of success. According to a meta-analysis of available data published in 2002, the pregnancy rate was significantly lower for patients with endometriosis (OR 0.56, 95% CI 0.44–0.70) compared with control individuals with infertility related to tubal factors.[148] Moreover, pregnancy rates for women with severe endometriosis were significantly lower than for women with mild disease (OR 0.60, 95% CI 0.42–0.87).[148] A second, adjourned meta-analysis confirmed the above findings, as the relative risk of pregnancy in women with endometriosis stage I–II and III–IV undergoing IVF was 0.93 (95% CI 0.87–0.99) and 0.79 (96% CI 0.69–0.91), respectively.[149]

At least two main reasons explain this reduced performance. Firstly, as mentioned above, the detrimental effects of chronic pelvic inflammation might act beyond the limits of the peritoneal cavity. Follicular development may be altered and the quality of the oocytes may be affected even if a direct exposure to the peritoneal fluid is avoided. Furthermore, endometrial receptivity might also be negatively influenced. One suggestion is that therapy with a GnRH agonist for 2–6 months before initiation of an IVF cycle (ultralong protocol) 'switches off' the inflammation, thus improving the chances of pregnancy. A meta-analysis of three small RCTs documented an odds ratio of pregnancy of 4.28 (95% CI 2.00–9.15) in women allocated to the ultra-long protocol, compared with women allocated to the normal protocol.[150] Interestingly, another suggestion is that similar benefits may be obtained with oral contraceptives, but more robust evidence is required.[151] Finally, some evidence also indicates that, in women with endometriosis failing to become pregnant with IVF, surgery enhances the chances of both spontaneous or IVF-mediated pregnancy.[152] It may be speculated that, similarly to what is observed with medical ovarostatic treatments, surgery also reduces the inflammatory-mediated detrimental effects of endometriosis, at least in the subgroup of patients refractory to IVF treatments.

Secondly, endometriosis may affect ovarian reserve, a crucial factor for IVF success. However, laparoscopic excision of endometriomas, rather than the disease itself, has been shown to cause follicle loss,[153–155] and women operated on for bilateral cysts are at particularly increased risk.[156,157] Potential mechanisms leading to damage include accidental removal of adjacent healthy ovarian tissue, vascular injury, heat damage consequent to diathermy-coagulation, and local inflammation.[158] This poses a clinical dilemma as, paradoxically, surgery can improve spontaneous pregnancy rate while it can damage the gonads.[111,137,140] Considering that the success rate of surgery and IVF are similar, infertile women with ovarian endometriomas may be scheduled directly to receive IVF without prior surgery. However, given the lack of robust data, the decision between surgery and IVF must be discussed and shared with the patient, also considering that IVF is associated with complications such as ovarian hyperstimulation syndrome, haemorrhage, thrombosis, and twinning with increased risk of preterm birth.[159] Women should receive comprehensive information illustrating the potential benefits and risks of both approaches. Additional factors to be taken into consideration in the decision-making process are age, surgical history, cyst sonographic appearance, cyst bilaterality, ultrasound detection of hydrosalpinx, results from tests of ovarian reserve, and presence of pain symptoms.[158] Research is now aimed at improving the surgical technique to preserve follicles while maintaining the benefits of surgery.[112,113] Some clinicians suggest that the injury to the ovarian reserve depends on surgical skilfulness and that an accurate and faultless intervention could actually prevent the damage.[160]

Emerging pharmacological therapies

Emerging pharmacological therapies are mostly based on targeting the molecular steps relevant for the pathogenic mechanisms or selective hormonal receptiveness. Medications interfering with the inflammatory condition, hormone responsiveness, cell survival, proliferation, neoangiogenesis and invasion have been tested mostly in preclinical models, but also in humans.[161]

Several antiangiogenic agents (soluble Flt-1, cabergoline, rapamycin, endostatin, βpep-25, TNP-470, angiostatin, SU5416 and SU6668) have been tested in animal models, with promising results on the establishment and maintenance of the lesions; however, owing to their severe adverse effects related to interference with physiologic angiogenesis, their translation into human research has been limited.[161] Statins have also been used in a preclinical setting for their ability to inhibit proliferation in a number of biologic systems. In addition, as aberrant methylation of the progesterone receptor gene seems to take part in the process of specific gene silencing in endometriosis, demethylation agents and histone deacetylase inhibitors have been proposed as possible medications. Trichostatin A and valproic acid have been tested in animal models and in a very limited number of patients,[161] but any beneficial effect must be confirmed in large controlled trials. Aromatase inhibitors have also been tested in some clinical trials.

In general, novel medications proposed to date are associated with uncertain or no efficacy and potentially severe adverse effects.[162] A list of the pharmacological agents

Box 2 | Nonconventional therapies proposed for endometriosis

Aromatase inhibitors

The rationale for their use is based on the higher expression of aromatase in endometriotic implants than in normal endometrium. In premenopausal women, they should be used with other drugs, as alone they stimulate gonadotropin elevation. Two RCTs have been published. One RCT reported a longer pain-free interval but significantly more adverse effects after 6 months postsurgical treatment with anastrozole and a GnRH agonist versus GnRH agonist alone.[163] The other RCT reported similar pregnancy rate and endometriosis recurrence rate at 12 months after 2 months postsurgical treatment with letrozole or a GnRH agonist or no medications.[164]

Selective estrogen receptor modulators (SERM)

Rationale for their use is based on the tissue selection activity, enabling these molecules to have estrogen receptor antagonism in the uterus and agonism in other tissues. A single RCT has been published, which reported shortening of the time to return of chronic pelvic pain after 6 months postsurgical treatment with raloxifene versus placebo.[165]

Anti-inflammatory agents

Rationale for their use is based on activity on chronic peritoneal inflammation. Four RCTs have been published and report: more effective symptom control with the COX2 inhibitor rofecoxib compared with placebo in minimal or mild endometriosis;[166] a similar pregnancy rate after 12 months postsurgical treatment with pentoxifylline versus placebo;[167] similar pregnancy and sign and symptoms recurrence rates after 6 months postsurgical treatment with pentoxifylline versus placebo;[168] significant improvement of pain relief after 6 months postsurgical treatment with pentoxifylline versus placebo.[169]

Immunomodulators

Rationale for their use is based on impairment of peritoneal immune surveillance. Three RCTs have been published and report: lower recurrence rate at 21 months after postsurgical intraperitoneal interferon-α2b treatment versus saline;[170] longer time to recurrence after intracystic IL-12 injection versus placebo in women with endometriomas treated with a GnRH agonist;[171] similar pain score, nodule volume and pelvic tenderness after 3 months treatment with the anti-TNF infliximab versus placebo.[172]

Abbreviations: COX2, cyclo-oxygenase 2; GnRH, gonadotropin-releasing hormone; RCT, randomized controlled trial; TNF, tumour necrosis factor.

tested for which randomized clinical trials in humans have been performed are presented in Box 2; unfortunately, most results are either disappointing or limited.[125,161–172] As compounds able to achieve a long phase of disease remission are already available for endometriosis, a new medical treatment should ideally eradicate the disease rather than merely relieving its symptoms. However, the pharmacological eradication of ectopic endometrium would carry a high risk of damage to normal endometrial mucosa from which endometriosis originates, with potential consequences on fertility. A compound with selective properties only against the ectopic cells is not yet at hand. Moreover, it is unclear how adhesions and fibrotic tissue could be eliminated pharmacologically.

Despite the numerous clinical trials on endometriosis registered, results are infrequently published. At the end of 2012, 35 registered interventional trials were completed. Results were not published for 24 of them (68.5%). Trials sponsored by industry were nearly four times less likely to have their results published than were non-industry-sponsored studies.[173] Reasons for not reporting data may be various, including safety and efficacy issues. However, as no published industry-sponsored trial has to date reported a 'negative' result, it can be inferred that greater difficulties than originally envisioned have been found in the development of therapeutics to treat endometriosis. In general, the untoward effects associated with the majority of drugs tested are unacceptable in healthy women affected by a benign condition. At present, hormonal manipulation remains the principal modality to effectively inhibit lesion growth and limit endometriosis progression.[125]

Recurrence: management and prevention

As surgery does not affect the pathogenic mechanisms of endometriosis, symptoms and lesion recurrences are frequent (between 40% and 50% at 5-year follow-up) when no postoperative adjuvant treatment is used.[174] In particular, the probability of endometrioma reappearance is about 10% per year in the triennium following surgery.[62] About 50% of women who had undergone surgery needed analgesics and/or hormonal therapy within 2 years.[106,107,175]

Although the surgical approach to the management of endometriosis recurrences is not dissimilar to that adopted for primary lesions, outcome and risk of complications are different. As a consequence, the therapeutic balance can change, and counselling as well as decisions on choice of treatments vary. The likelihood of conception at second-line surgery for ovarian endometriomas in infertile women is about half (~25%) that at primary intervention (40–50%).[104,176] This reduction is probably due to selection of a patient population with a worse reproductive prognosis than those at first-line surgery, but also because of repeated surgical gonadal insults. Therefore, in women without severe pain seeking pregnancy, and without recurrent cysts >4 cm[177] or with suspect sonographic findings, IVF is preferred rather than repeat laparoscopy.[97,178] Probably also owing to the patients selected, second-line surgery for pain generally achieves substantially inferior results compared with the primary intervention, at the cost of increased morbidity.[107,175] Morbidity is particularly a concern in the case of deep lesions. Technically demanding procedures should be offered only when medical treatment is ineffective, not tolerated or contraindicated.

After first-line surgery, pain symptoms and endometriotic lesion recurrence can be limited using oral contraceptives or progestins for prolonged periods of time.[179,180] During treatment, the risk of endometrioma reappearance is reduced by >80%, indirectly supporting the role of ovulation in the pathogenesis of this cyst type.[181] However, a misunderstanding exists on the definition of postoperative adjuvant therapy, which has been conceptually mediated from the oncological environment. In fact, the most 'powerful' compounds (GnRH agonists), are still used for only 3–6 months, with the objective of 'sterilizing' endometriotic remnants that were not identified or could not be excised at surgery. Conversely, postoperative medical therapy should be considered for extended periods, preferably until conception is desired.

Endometriosis-associated ovarian cancer

Endometriosis is a risk factor for epithelial ovarian cancer.[182] In a large international collaborative study,

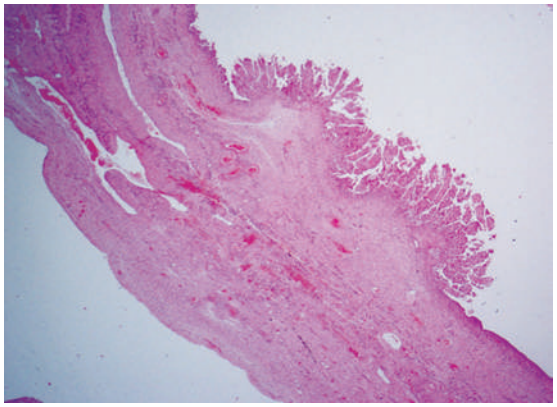

Figure 4 | An ovarian endometriotic cyst with a papillary clear cell carcinoma. The cyst wall beneath the cancer lesion is lined by cylindrical endometrial-type epithelium. Haematoxylin and eosin staining; magnification, 4×.

self-reported endometriosis was associated with an overall risk increase of nearly 50% (OR 1.46, 95% CI 1.31–1.63).[183] The association was limited to clear cell (OR 3.05, 95% CI 2.43–3.84), endometrioid (OR 2.04, 95% CI 1.67–2.48) and low-grade serous (OR 2.11, 95% CI 1.39–3.20) tumours. In other words, endometriosis is associated with an increased risk of most type I epithelial ovarian cancers, although the association with low-grade serous ones could be explained by concomitant, but independent, pelvic contamination by tubal epithelial cells.[184]

Endometriosis in general has been indicated as the putative precursor lesion of the majority of endometrioid and clear cell ovarian cancers, and a risk-reducing, surgical approach has been suggested.[183,185] However, it has been argued that only cytologically and/or structurally atypical endometriosis constitutes a true pre-neoplastic condition.[186,187] Atypical endometriosis is observed in 1–3% of endometriomas with no preoperative ultrasonographic findings suggestive of ovarian cancer.[188]

Whereas endometriotic implants are observed all over the pelvis, endometriosis-associated malignancies typically arise in endometriomas (Figure 4), thus suggesting that the local ovarian cyst environment facilitates neoplastic derailment.[189] Red blood cells collected within the endometrioma pseudocavity are phagocyted and haemolysed by macrophages, but when their iron storage capacity is overwhelmed, non-protein-bound 'free' or 'catalytic' iron and haem are released in the cyst fluid, where they can damage proteins, lipids, cell membrane and cause carcinogenic DNA mutations or gene deletions as well as genetic instability, as reactive oxygen species are generated via the Fenton reaction typical of redox cycling.[190–192] Oxidative stress appears to contribute in inducing random deletion of some tumour suppressor genes, such as *ARID1A*, or activating proto-oncogenes.[193,194]

Although the iron-mediated, local chronic inflammation has been generally indicated as the main single promoter of the oncogenic process, endometrioid and clear cell histotypes seem to follow a dualistic developmental model, that is, a hormone-dependent pathway in the endometrioid histotype and an hormone-independent pathway in the clear cell histotype.[195,196] In fact, endometrioid adenocarcinomas are predominantly positive for estrogen and progesterone receptors, whereas clear cell carcinomas typically exhibit very low receptor expression. Moreover, clear cell carcinomas show overexpression of hepatocyte nuclear factor 1β, a transcriptional factor that increases the survival of endometriotic cells under iron-induced oxidative stress conditions, thus inhibiting apoptosis of cells carrying DNA mutations. No hepatocyte nuclear factor 1β overexpression is generally observed in endometrioid carcinomas.[190] The estrogen-dependent pathogenesis of ovarian endometrioid carcinomas associated with endometriosis is corroborated also by the repeated observation of higher than expected occurrence of synchronous primary endometrial (type I, estrogen-dependent[197]) and ovarian, endometriosis-associated, endometrioid adenocarcinomas.[198–200]

Only limited data are available to evaluate the effect of medical and surgical preventive interventions. Modugno *et al.* pooled information on the self-reported history of endometriosis from four population-based case–control studies of incident epithelial ovarian cancer.[201] The use of oral contraceptives for >10 years was associated with 80% reduction in risk among women with endometriosis. A dose–response effect was observed related to duration of use.

Rossing *et al.* assessed the risk of ovarian malignancy associated with a prior diagnosis and surgery for ovarian cysts and endometriosis.[202] Compared with women without a history of endometriosis, the odds ratio was 1.6 (95% CI 1.1–2.3) among those with endometriosis but no surgery, and it was 1.2 (95% CI 0.5–2.5) among women

Box 3 | Prevention of endometriosis-associated epithelial ovarian cancer

The dualistic carcinogenic model[190,195,196] has practical implications because, if this hypothesis is confirmed, chemoprophylaxis via long-term oral contraceptive use would mainly affect the endometrioid histotype, in which expression of both estrogen and progesterone receptors is observed. By contrast, clear cell carcinomas, which are double negative for both receptors, could be effectively prevented only by extirpative surgery. In Western countries, endometrioid adenocarcinomas represent about 10–20% of all epithelial ovarian cancers, whereas clear cell carcinomas are less frequent (5–10%). For unknown reasons, the reverse is true in Asian countries and in Japan in particular. This difference might translate into a different prophylactic approach to ovarian cancer in women with endometriosis, mostly based on oral contraceptive use in Western countries and on surgery in Asian countries.

In the absence of contraindications, low-dose, second-generation oral contraceptive use could be the best option in women up to their early forties, unless tolerance is low or pain symptoms are not relieved. After that age, unilateral oophorectomy plus bilateral salpingectomy could be the best risk-reducing approach, as this would imply not only prevention of endometrioid and clear cell tumours, but also of high-grade serous ones. Moreover, it has been demonstrated that longstanding endometriosis is associated with a progressive increase in ovarian cancer risk.[182] In the case of bilateral endometriomas, bilateral cystectomy plus bilateral salpingectomy should be considered, unless the woman is willing to use hormone replacement therapy after surgery. Finally, surgical risks (mainly bowel and ureteral lesions) and the possibility of developing the ovarian remnant syndrome should be carefully weighed up in patients who have already undergone difficult procedures for extensive endometriosis associated with severe adnexal adhesions.

with endometriosis and surgery. The reduction in risk was more evident in women who had undergone a unilateral oophorectomy than in those who reported cystectomy.[202]

Melin *et al.* identified all Swedish women with a first time diagnosis of endometriosis between 1969 and 2007 and, by linkage with the National Swedish Cancer Register, all women diagnosed with epithelial ovarian cancer at least 1 year after the endometriosis diagnosis.[203] A protective effect was observed for both one-sided oophorectomy (OR 0.19, 95% CI 0.08–0.46), as well as radical excision of all visible endometriosis (OR 0.30, 95% CI 0.12–0.74).[203]

Unfortunately, the magnitude of the effect of extirpative surgery is not yet completely clear, because salpingectomy is usually performed together with oophorectomy, thus substantially reducing also the risk of high-grade serous tumours (type II), which are not related to endometriosis, but comprise about 70% of all epithelial ovarian cancers. Surgery is indicated when large endometriomas are present. The dilemma is what to do when small endometriomas are identified in women not wanting children or that have completed their family. Any specific cut-off threshold in cyst diameter not based on a dose–response risk increase seems arbitrary, and the wisest approach should be based on a balance between several factors, including patient preference after detailed information (Box 3).

In the worst-case scenario, the lifetime probability of not developing ovarian cancer is decreased from 99% to 98%.[187] Thus, the risk of epithelial ovarian cancer is only moderately augmented in women with endometriosis, and the magnitude of the increase does not currently justify screening of asymptomatic individuals.[204,205]

Conclusions

The past decade has witnessed a progressive but substantial modification in therapeutic approaches for endometriosis.[96,97,178,206] A gradual shift occurred toward the use of pharmacological compounds with the most favourable therapeutic profile. New drugs that cure endometriosis definitively or that relieve pain without interfering with ovulation, thus allowing conception, are badly needed. However, future trials on new drugs for pain should include patient satisfaction as the main outcome, and use a progestin or a continuous oral contraceptive as comparator.[125]

The surgical approach has also changed, from the model of radicality at whatever cost, to a wiser approach aimed predominantly at achieving outcomes that matter to women, namely, pain relief and pregnancy.[207] The decrease in bowel resection in favour of more conservative techniques is one example of this process.[115,116] Endometriosis is not a cancer. Therefore, risky procedures should be undertaken only if unavoidable or dictated by otherwise untreatable symptoms. Moreover, the published results of the best surgeons, in terms of fertility improvement, pain relief and complication rate may not be replicated by the average gynaecologist.

Endometriosis constitutes a paradigm for the new model of patient-centred medicine. In fact, several clinical situations exist in women with endometriosis in which one treatment modality clearly more advantageous than the alternatives cannot be identified. In this context, patient preference is of utmost importance for the final choice that, after complete and unbiased information, should be pursued within the framework of a truly shared decision-making process.[208] Women must be reassured and encouraged with empathy through their possibly long medical journey. Frequently, lifelong management plans should be foreseen, avoiding short-sighted temporary solutions.[102] Many patients will finally overcome their endometriosis-associated problems,[209] whereas others should be gradually persuaded that achievement of a reasonable compromise in their health-related quality of life is possible and acceptable.

Endometriosis may be associated with severe pyschosocial consequences such as anxiety, depression, isolation, familial and intimate implications including unfavourable emotional impact in partners, decreased quality of life, inability to cope with everyday activities, reduced work productivity, and greatly increased expenditure on health care.[10,210,211] Women with endometriosis should not be ignored or patronized by society and the medical profession at large. In this regard, a major cultural change is needed.

Review criteria

For this Review, the best quality evidence was selected with preference given to the most recent and definitive original articles, randomized controlled trials, systematic reviews, meta-analyses, as well as international guidelines. Information was identified by searches of MEDLINE and references from relevant articles, using combinations of MESH terms “endometriosis”, “epidemiology”, “etiology”, “pathogenesis”, “infertility”, “pain”, “medical treatment”, “oral contraceptives”, “progestins”, “surgery”, “ovarian cancer” and “costs”. The search was limited to peer-reviewed, full-text articles in the English language. For most clinical issues, papers published between 2000 and May 2013 were considered. Other databases, including the Cochrane Database of Systematic Reviews, were also searched.

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