Endometriosis

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ABSTRACT | Endometriosis is a common inflammatory disease characterized by the presence of tissue outside the uterus that resembles endometrium, mainly on pelvic organs and tissues. It affects ~5–10% of women in their reproductive years — translating to 176 million women worldwide — and is associated with pelvic pain and infertility. Diagnosis is only reliably established through surgical visualization with histological verification, although ovarian endometrioma and deep nodular forms of disease can be detected through ultrasonography and MRI. Retrograde menstruation is regarded as an important origin of the endometrial deposits, but other factors are involved, including a favourable endocrine and metabolic environment, epithelial–mesenchymal transition and altered immunity and inflammatory responses in genetically susceptible women. Current treatments are dictated by the primary indication (infertility or pelvic pain), and are limited to surgery and hormonal treatments and analgesics with many adverse effects that rarely provide long-term relief. Endometriosis substantially affects the quality of life of women and their families, and imposes costs on society similar to other chronic conditions such as type 2 diabetes mellitus, Crohn's disease and rheumatoid arthritis. Future research must focus on understanding the pathogenesis, identifying disease subtypes, developing non-invasive diagnostic methods and targeting non-hormonal treatments that are acceptable to women who wish to conceive.

[H1] Introduction

Endometriosis is a common, often chronic (long-term), inflammatory condition in women in which tissue resembling the endometrium (the lining of the uterus) is found at sites outside the uterus, mainly in the pelvic area including the ovaries, ligaments and peritoneal surfaces as well as the bowel and bladder. The disease is heterogeneous in presentation, varying from superficial peritoneal and serosal lesions to endometriosis cysts in the ovaries (endometrioma) and nodules >5 mm in depth (deep endometriosis) and can often be accompanied by scarring (fibrosis) and adhesions. Endometriosis is associated with severe pelvic pain (during and after sexual intercourse, cyclically and throughout the menstrual cycle) as well as infertility. The growth of the endometriotic tissue is oestrogen-dependent; accordingly, the condition features primarily between menarche and

menopause, but the disease has been described in premenarcheal girls[1] and can recur after menopause.

The origin of endometrial tissue in endometriosis is widely accepted to be retrograde menstruation (backward flux of menstrual debris that contains viable endometrial cells through the fallopian tubes into the pelvic cavity) in most cases. This reflux, in part, accounts for the accumulation of lesions in the gravitationally dependent regions of the pelvic cavity. However, retrograde menstruation is a very common physiological process, occurring in >90% of menstruating women with patent Fallopian tubes[2]. Accordingly, research has focused on understanding the processes in which endometrial cells adhere to ovaries, ligaments and peritoneal surfaces and how, once adherent, these cells proliferate, acquire blood supply and result in endometriosis only in some women. Other types of endometriosis include scar endometriosis, the formation of which is thought to occur via the iatrogenic transplantation of endometrial cells during surgery, particularly surgery that required incision on a gravid uterus (caesarean section)[3]. In addition, rare extra-pelvic locations have been described[4].

Diagnosis of endometriosis can only be established reliably through visualization at surgery, most commonly laparoscopically, although endometrioma and deep endometriosis can also be detected using imaging techniques (ultrasonography or MRI). Histological confirmation of excised endometriotic lesions, in which the presence of endometrial glands and stroma is confirmed, is typically recommended. Indeed, guidelines for the diagnosis and treatment of endometriosis have been endorsed by specialist consensus groups in Canada, Europe and the United States, which provide recommendations on different aspects with substantial variation between the documents[5]. Endometriosis is typically classified according to revised criteria formulated by the American Fertility Society (AFS) and American Society of Reproductive Medicine (ASRM) including lesion size, location and extent of adhesions, into four stages from ‘minimal’ to ‘severe’ according to extent of disease observed (Fig. 1)[6]. However, no correlation exists between the severity of symptoms and the staging sytem[7]. The main treatment of endometriosis involves the surgical removal of ectopic tissue and/or hormonal treatment (for example, with oral contraceptives, progestins or gonadotropin-releasing hormone (GnRH) analogues) to reduce symptoms of pain and inflammation; however, these treatments are associated with many unwanted adverse effects including menopause-related symptoms and contraception.

This Primer discusses the epidemiology of endometriosis, current knowledge about its pathogenesis and pathophysiology and current best-practice methods of diagnosis and treatment. Key research questions that need to be answered to improve the clinical problem are also discussed.

[H1] Epidemiology

The rates of endometriosis in the general population are difficult to quantify because the definitive diagnosis requires surgical visualization. Accordingly, estimates vary widely among different population samples and modes of diagnosis — all influenced by presenting symptoms and access to care. Despite this limitation, a study of women undergoing their first laparoscopic investigation in 10 countries across 5 continents showed that endometriosis is a common global problem with an incidence ranging from 35–100% in symptomatic women[8]. Currently, no robust evidence can confirm that population-based prevalence varies among different ethnic groups because any observed variations cannot be disentangled from differential access to health care[9].

The prevalence estimated among women and adolescents (whereby adolescence is defined by the WHO as those aged 10–19 years and by the United Nations as those aged 15–24 years) whose symptoms warrant surgical evaluation is higher than the true prevalence in the general population; the prevalence estimated among asymptomatic women incidentally found to have endometriosis (for example, during a tubal sterilization procedure, in which fallopian tubes are removed, cut and tied or burnt) is an underestimate. In women investigated for infertility, endometriosis prevalence varies widely (5–50%). For example, in studies of fertile women undergoing a laparoscopy for tubal sterilization, 4% were found to have endometriosis[10] and in a population cohort of unscreened women, 11% were diagnosed with endometriosis via MRI[11]. Among the few studies that have investigated adolescents with severe dysmenorrhea (pelvic pain during menstruation), 50–70% were diagnosed with endometriosis[12]. On the basis of the prevalence of pelvic pain and infertility in the general population, the estimated population prevalence of all endometriosis stages is 5–10%, and <2% for moderate and severe disease (AFS/ASRM stages III and IV)[13] — equating to an estimated 176 million women with endometriosis globally[14]. Endometriosis can also recur in post-menopausal women or after bilateral oophorectomy (removal of the ovaries), in particular those on hormone replacement therapy, although data mainly originate from case-reports and accurate prevalence estimates are lacking[15].

Incidence data in the general population are affected by the same information biases that hamper accurate prevalence estimation. The incidence of clinically diagnosed endometriosis in Rochester,

Minnesota was 187 per 100,000 person years from 1987–1999 (Ref.[16]). Similar incidence was found in the Nurses' Health Study II (NHSII, a prospective nationally representative cohort of US female nurses 25–42 years of age at the time of enrolment in 1989), among whom the 10-year incidence of laparoscopically confirmed endometriosis was 298 per 100,000 person years[17].

[H2]Risk Factors

Given the need for surgery for a definitive diagnosis, determining risk factors and identifying aetiological associations will be influenced by the population from whom data and biological samples are collected. Phenotypical differences (between women diagnosed by a pain specialist, at an infertility centre, at hysterectomy or tubal sterilization or in the general population), study design, sample collection, statistical analyses and, perhaps most importantly, results interpretation must be taken into account. Despite this heterogeneity and these complicating factors, risk factors for endometriosis have been identified.

[H3]Menstrual and reproductive history. Earlier age (<12 years) at menarche[18] and shorter menstrual cycles (<26 days) have been consistently associated with endometriosis[19], perhaps through greater frequency of retrograde menstruation or hormonal milieu. Case–control studies[20] and one cohort study (NHSII)[19], have shown a lower risk of endometriosis among parous women. Additionally, although the NHSII found that women with endometriosis had a two-fold greater risk of infertility, 83% of all women with endometriosis were parous by the age of 40 years[21]. Similar findings have been reported in the ENDO study[22]. Among parous NHSII participants, for every 3 months of breastfeeding, the rate of endometriosis was reduced by 3% (*P* trend <0.0001)[23]. However, the interpretation of association between parity and endometriosis is particularly complex given temporality issues (for example, endometriosis may have been present prior to pregnancy, or endometriosis is identified only once she is diagnosed with infertility). Thus, having children is not definitively 'protective'[24].

[H3] Anthropometry. An inverse association between endometriosis and adult body mass index (BMI) has consistently been observed[25]. Evidence also supports that the greater risk of endometriosis associated with leanness in adulthood is mirrored in the association of endometriosis risk with leanness in childhood[26]. One case–control study and the NHSII cohort observed an inverse association[25,27] between body fat distribution (waist-to-hip ratio) and endometriosis. Genetic studies have further reinforced this association[28], consistent with the observation that women with a higher ratio of oestrogens to androgens have been found to have lower waist-to-hip ratio[29].

[H3]Cigarette smoking. The association between cigarette smoking and endometriosis is unclear and might differ by infertility status[17]. Some studies (see, for example, Ref.[30]) have shown an inverse association whereas others have found no association. Although women who smoke have lower oestrogen levels[31], they are also exposed to higher levels of oestrogenic endocrine disruptors in the form of dioxin, which exert aryl hydrocarbon receptor-mediated oestrogenic activity through interactions with the oestrogen receptor (ER)[32], potentially complicating the association.

[H3]Diet. An Italian hospital-based case–control study observed a statistically significant inverse association between odds of endometriosis and current consumption of green vegetables (OR 0.3, 95%CI 0.2–0.5) and fruit (OR 0.6, 95%CI 0.4–0.8) as well as a significantly greater likelihood of endometriosis with red meat consumption (OR 2.0, 95%CI 1.4–2.8)[33]. However, a US population-based case–control study found greater odds of endometriosis associated with higher fruit consumption (OR 1.5, 95%CI 1.2–2.3) and no association with red meat intake — perhaps due to reverse causation. That is, deliberate dietary changes among women with endometriosis in the study may be an important limitation when quantifying associations with current diet[34].

In the NHSII (who reported diet prospectively for more than a decade, rather than one cross-sectional measurement), women who consumed the most long-chain omega-3 fatty acids were 22% less likely to be diagnosed with endometriosis compared with those who consumed the least (95%CI 0.62–0.99)[35], a finding that was replicated in a case–control study[36]. Also in the NHSII, women who consumed the most trans-unsaturated fats were 48% more likely to be diagnosed with endometriosis (95%CI 1.17–1.88), although this finding was not found within a case–control study[34]. Although omega-3 fatty acids have an anti-inflammatory influence, trans-unsaturated fats increase IL-6 and tumour necrosis factor (TNF) system activation[37], which are thought to be involved in the pathogenesis of endometriosis (see below)[38].

[H3]Environmental exposures. Endocrine-disrupting chemicals, such as polychlorinated biphenyl and dioxin, might influence endometriosis through the disruption of circulating hormone levels and/or dysregulation of the immune system[39]. However, findings among women have been inconsistent, perhaps due to small sample sizes, varying windows of exposure and differences in control populations[40].

[H2]Comorbidities and long-term disease risk

Women with endometriosis may be at high risk of developing several other chronic diseases, including cancer and cardiovascular disease[41]. However, most studies investigating endometriosis and chronic diseases use self-reported diagnoses of endometriosis that lack phenotypic detail, symptom experience or treatment course, and suffer from potential bias. Accordingly, understanding these associations requires mechanistic (including genetic) and mediator research to determine which are causal and/or which are driven by shared risk factors.

***[H3]Adenomyosis*.** Many of the symptoms of endometriosis, in particular severe dysmenorrhoea, overlap with those of adenomyosis, a condition characterized by the growth of endometrium into the myometrium that is diagnosed by radiological imaging. Although originally regarded as a form of endometriosis, the two conditions are now defined as separate entities but might share aetiological factors; studies to determine the rate of comorbidity are ongoing[42]. In a study of 227 women seeking treatment for infertility, the prevalence of adenomyosis assessed by MRI was reported as high as 79% (126 out of 160 women) among women with surgically confirmed endometriosis compared with 28% (19 out of 67 women) among women without endometriosis[43]. However, accurate estimates of the prevalence of adenomyosis, or the comorbidity between the two diseases, are not available due to the existing biases inherent in the diagnosis of each[42].

[H3]Cancer. Among the 21 studies that investigated endometriosis in relation to ovarian cancer risk, 20 studies reported a positive association (16 of which had statistically significant findings)[41]. A large international pooled analysis quantified a 50% greater risk overall (relative risk (RR) of 1.46, 95%CI 1.31–1.63)[44], findings that were also supported by a meta-analysis[45]. The greater risk associated with endometriosis seems to be primarily limited to clear cell and endometrioid ovarian cancer, whereas the endometriosis phenotypes conferring this higher risk are yet to be determined.

Among non-gynaecological cancers, cutaneous melanoma has been studied most often. Of the 13 studies to date, seven suggested a positive association with endometriosis[46], whereas five studies reported no clear relationship between endometriosis and cutaneous melanoma risk[41].

[H3]Autoimmune diseases. A cross-sectional survey conducted among patient members of the Endometriosis Association in the United States first noted higher than expected self-reported prevalence of autoimmune diagnoses compared with the general female population[47]. The largest cohort study to date, with >37,000 patients with endometriosis in Denmark, showed a significantly greater risk of systemic lupus erythematosus (SLE), Sjögren syndrome and multiple sclerosis[48] ; the

NHSII also identified a higher rate of SLE and rheumatoid arthritis in women with endometriosis[49]. The biological interpretation of these findings remains unclear and requires further research, particularly given that endometriosis itself does not have autoimmune characteristics.

[H3]Cardiovascular conditions. The NHSII reported greater risk of myocardial infarction (RR 1.52, 95%CI 1.17–1.98), angiographically confirmed angina (RR 1.91, 95%CI 1.59–2.29) and need for coronary artery bypass graft surgery, coronary angioplasty or stent placement (RR 1.35, 95%CI 1.08–1.69) in women with endometriosis; other CVD risk factors such as hypertension (RR 1.14, 95%CI 1.09–1.18) and hypercholesterolaemia (RR 1.25, 95%CI 1.21–1.30) were also associated with endometriosis[50]. The strongest associations for all these cardiovascular conditions were observed among women <40 years of age. One interpretation of these findings is that endometriosis either creates or is the result of a multisystem pro-inflammatory milieu. Indeed, the association between endometriosis and heritable genetic polymorphisms in the gene *CDKN2B-AS1* (also known as *ANRIL*), which has also been widely implicated in coronary heart disease[51], supports a multisystem pro-inflammatory milieu as the cause. Existing data do not demonstrate different risk of cardiovascular disease among women with endometriosis who present with infertility compared with those who present with pelvic pain. However, future research must focus on potential risk differences by endometriosis phenotype, chronic symptoms and treatment exposures and also must compare and contrast cardiovascular disease risk associated with endometriosis to other chronic pain or stigma and health disparities that may confer cardiovascular disease.

[H1] Mechanisms/pathophysiology

The exact origin and pathophysiology of endometriosis are unknown. The main hypotheses of the origins of endometrial cells at ectopic sites include retrograde menstruation, metaplasia of the coelom (the epithelium that lines the abdominal organs), vascular and lymphatic metastatic spread and neonatal uterine bleeding. However, other factors are needed to promote cell survival, proliferation and lesion formation and maintenance, including altered or impaired immunity, factors promoting angiogenesis, localized complex hormonal influences and genetic factors.

[H2]Genetics

Endometriosis is a complex disease likely caused by interactions of many genetic and environmental factors, each with modest individual effects on risk. Aggregation of endometriosis cases within families has been noted since the 1950s, and the increased prevalence of endometriosis among related versus unrelated women strongly suggests the presence of predisposing genetic (heritable)

factors[52]. Identifying genetic variants that influence endometriosis risk could shed light on its pathogenesis. To this end, genetic linkage studies in families have implicated regions on chromosomes 7p15.2 and 10q26 as harbouring rare variants that drive familial endometriosis, but the variants have not yet been identified[53,54].

Hundreds of candidate gene association studies have been conducted, focusing on putative genes of interest but generally not producing replicable results[55]. Eight genome-wide association studies (GWAS) have been conducted for endometriosis to date, seven of which reported genome-wide significant signals (Table 1). The largest meta-analysis involved 17,045 patients with endometriosis and 191,596 controls from 11 independent datasets and confirmed 14 common genetic loci robustly associated with endometriosis[56]. Most of the loci had effects that were much stronger for, or limited to, AFS/ASRM stage III/IV disease, highlighting the heterogeneity of biological pathways involved in the different stages of endometriosis. Together, the loci explained 1.75% of total disease risk variance and 5.2% of stage III/IV variance, whereas 26% of the risk variance was predicted to be caused by common genetic variation[57], leaving many loci to be discovered (a meta-analysis involving >60,000 patients is currently underway).

Genes located nearest to the risk loci suggest perturbations of WNT signalling, cell adhesion, cell migration, angiogenesis, inflammatory and hormone-metabolism pathways are involved in endometriosis. In addition, genome-wide analyses have implicated MAPK signalling in AFS/ASRM stage I/II disease[58], and have identified significant sharing of genetic variants underlying endometriosis and fat distribution (waist-to-hip ratio adjusted for BMI), which implicates WNT signalling as a common pathway[28]; endometriosis and ovarian cancer, through as yet unknown pathways[59]; and endometriosis and endometrial cancer, implicating signal transducer and activator of transcription-3 (STAT3) signalling[60]. However, GWAS loci typically reside in intergenic (in between genes) or intronic (in introns within a gene) regions that regulate gene expression rather than exert direct effects on protein expression[61]. Understanding the exact nature of the effects of these associations on biological pathways requires functional investigations in relevant tissues in the context of detailed phenotypic information[62], for example, through correlation of genetic variants with altered gene expression in endometrium (eQTL studies)[63]. Indeed, the World Endometriosis Research Foundation (WERF) Endometriosis Phenotyping and Biobanking Harmonisation Project (EPHect; https://endometriosisfoundation.org/ephect/) has provided globally standardized tools and protocols for deep (extensive) phenotypic data and biological sample collection for endometriosis to enable such studies to be conducted on large scales[64–67].

The link between endometriosis and ovarian cancer risk has led several studies to conduct targeted somatic mutational analysis in endometriosis-associated ovarian cancer, focusing on *ARID1A* and *PIK3CA*[68,69] as these genes were previously found to harbour somatic mutations in clear-cell ovarian cancer. Whether the endometriotic lesions in the ovary that are assumed to be associated with ovarian cancer due to proximity are different in terms of mutation profile than ovarian endometriosis without associated ovarian cancer or whether the mutations have a role in endometriosis origin or maintenance remain unclear. The first comprehensive somatic mutational screen of endometriotic tissue was conducted in deep endometriosis (in the bowel or peritoneal wall) rather than in the ovary; no specific epidemiological studies report an increased cancer risk in patients with deep endometriosis. In the study, the exomes of 24 deep endometriosis nodules were sequenced and compared with adjacent normal tissue to identify mutations, followed by targeted sequencing of known cancer driver mutations in three lesions and *KRAS* mutation sequencing in a further 12 lesions[70]. Common cancer driver mutations in *ARID1A, PIK3CA, KRAS* and *PPP2R1A* in endometriotic tissue (but not in the adjacent normal tissue) were observed in 21% of the patients whose samples underwent exome sequencing (5 out of 24 patients), whereas *KRAS* mutations were detected in 15% of all 39 samples. The somatic mutations were confined to epithelial cells in lesions. The authors emphasized that despite these findings, no evidence supports that deep endometriosis is associated with increased cancer risk. Indeed, multiple other studies have shown the presence of typical cancer driver mutations in human tissues that do not result in cancer[71].

***[H3]Epigenetics*.** Several studies have investigated epigenetic changes in endometriotic lesions compared with eutopic endometrial tissue, as well as in eutopic endometrial tissues from patients compared with healthy controls; few of the results have been consistently reproduced[52]. An additional consideration is that any variations identified in the endometriotic lesion compared with the eutopic endometrial tissue could have arisen as a response to the ectopic milieu rather than playing a part in pathogenesis[72].

Most epigenetic studies have focused on DNA methylation. Examples of reproduced epigenetic changes are the DNA hypermethylation and silencing of endometrial genes normally expressed during the secretory phase of the menstrual cycle, affecting proliferation and invasion. Implicated genes include those encoding homeobox protein Hox-A10 (*HOXA10*), E-cadherin (*CDH1*) and the progesterone receptor B (*PRB*)[73]. A study of stromal cells from healthy eutopic endometrium and from endometriomas detected differential methylation affecting *HOX* gene clusters, steroid nuclear

receptor genes and expression of GATA family of transcription factors, which seems to facilitate progesterone resistance in endometriosis[74]. Very few studies have investigated the epigenetic mechanisms of histone modification in relation to endometriosis[52]. As indicated above, miRNAs also can impose epigenetic effects. One example is miR-9, which physiologically suppresses the anti-apoptosis gene *BCL2*. In endometriosis miR-9 is downregulated, potentially conferring mitogenic effects in the lesions[75]. However, substantial inconsistency in miRNA studies in endometriosis and in healthy endometrium abound, due to study design issues, cellular heterogeneity and fluctuations related to the menstrual cycle[76].

[H2]Histogenesis

[H3]Retrograde menstruation. The most widely accepted hypothesis, at least for peritoneal endometriosis, was first proposed by Sampson in 1927 (Ref.[77]). It states that fragments of menstrual endometrial tissue containing viable endometrial glands and stroma reach the peritoneal cavity through retrograde expulsion of menstrual debris through the fallopian tubes, where they adhere to and invade the underlying mesothelium[77]. This hypothesis is supported by epidemiological evidence showing an increased risk of endometriosis with increased 'exposure' to menstruation (increased menstrual bleeding, shorter cycle length and greater number of menstruations, as well as increased prevalence in women with Müllerian tract outflow obstruction)[19] and by the asymmetry in the anatomical location of the lesions. Indeed, the anatomical characteristics of the upper abdomen, and the spreading of endometrial fragments generated by the clockwise peritoneal flow can explain the higher prevalence of left-sided lesions[78]. In female baboons, retrograde menstruation was observed more often in animals with (83%) than those without endometriosis (51%)[79]. The fact that retrograde menstruation is nearly ubiquitous and that the prevalence of endometriosis is ~10% implicates that many factors probably contribute to the condition (see below).

Understanding how the regurgitated fragments give rise to disease requires understanding of gene expression and regulation, and how these functions rely on the cells being in ectopic sites. However, the characteristics of the interactions between menstrual endometrial fragments and the peritoneal surface remain somewhat controversial. One study suggested that endometrial epithelial and stromal cells can penetrate the intact mesothelium[80], whereas another proposed that adhesion of menstrual fragments only occurs when the underlying mesothelial extracellular matrix is exposed by local injury[80]. Notably , the eutopic endometrium is considered the origin of the majority of endometriotic lesions[81] and a plethora of targeted studies has assessed differences in gene expression and epigenetic modifications between eutopic and ectopic endometrium involving

specific genes, or their regulation by microRNAs (miRNAs). Genes involved in adhesion (such as *ITGB2* (encoding integrin β2) and *ITGB7* (encoding integrin β7)), proliferation (such as *PDGFRA* (encoding platelet-derived growth factor receptor-α) and *PRKCB* (encoding protein kinase C-β1)), invasion (such as those encoding matrix metalloproteinases and relaxin), immune recognition (such as *DEFB4* (encoding β–defensin-4A)), inflammatory response (such as *TNF* (encoding tumour necrosis factor) and *IL1B* (encoding IL-1β)), steroid biosynthesis, biosynthesis response and angiogenesis (such as *VEGF* (encoding vascular endothelial growth factor) and *ANGPT1* and *ANGPT2* (encoding the angiopoietins)) are frequently reported to be aberrantly expressed in ectopic endometrium[82]. Unfortunately, many of these differences likely represent changes in ectopic endometrium as a consequence of its extra-uterine location. Although relevant to understanding the biological features and 'markers' of endometriosis, to what extent the aberrant expression of these genes contribute to the development of endometriosis remains unclear[83].

[H3]Coelomic metaplasia. The hypothesis that endometriosis arises from metaplasia of the coelom — transdifferentiated from mesothelium — was first suggested by Meyer[84] and refined by Ferguson and colleagues[85]. Recent insights suggest this process may involve re-programming of multipotent mesenchymal stem cells[86], derived from the bone-marrow[87] or from a niche within the endometrium itself[88], which may differentiate into endometrial epithelial and stromal cells in ectopic sites. Some investigators[89] argue that although metaplasia can explain deep endometriosis in the rectovaginal septum, it is unlikely to be a dominant mechanism for superficial peritoneal disease because the rate of co-occurrences of the different forms of endometriotic lesions (superficial, deep nodules and endometrioma) is higher than expected if the lesions had different origins[90]. Morphological transitions from the ovarian surface epithelium to endometriotic lesions also support this mechanism[91]. Metaplasia is also suggested as a potential origin of the rare instances in which endometriosis occurs at sites outside the pelvis, including abdominal lymph nodes, lungs, brain, limbs and the nasal cavity[4] and in cases of Müllerian agenesis (that is, the congenital malformation in which the Müllerian duct fails to develop)[92]. In very rare instances, endometriosis has been observed in men[93], which also supports this hypothesis.

[H3]Lymphatic and vascular metastasis. The metastasis hypothesis states that endometrial cells and tissue fragments travel from the uterine cavity through lymphatic channels and veins to colonize distant ectopic sites[94]. This hypothesis best describes the rare occurrence of extra-pelvic endometriosis in women and is supported by evidence of emboli of endometrial cells in sentinel lymph nodes[95].

[H3]Neonatal uterine bleeding. A more recent theory suggests endometriosis originates from stem or progenitor cells potentially present in retrograde neonatal uterine bleeding that occurs as a result of the withdrawal of placental steroid hormones soon after birth. This hypothesis is supported by the observed presence of neonatal uterine bleeding in ~5% of newborns, by the rare occurrence of endometriosis in girls pre-menarche and by the occurrence of severe endometriosis in adolescents[96].

[H2]Establishing and maintaining ectopic lesions

After the 'seeding' of — or metaplastic transformation into — endometrial cells, a number of factors are required to form endometriotic lesions. These factors include attachment and penetration of the peritoneal surface (in cases of retrograde menstruation[97]), cellular proliferation and localized invasion, angiogenesis, neurogenesis and inflammation, all of which are likely to promote pain symptoms. The tissue microenvironment controls these phenomena and its regulation is influenced by a variety of hormonal and cellular factors. Of these factors, ovarian hormones have been extensively studied and form the rationale for most of our current medical therapeutics in the management of women with endometriosis.

[H3]Endocrine and metabolic factors. Oestrogens are key promoters of endometrial cellular growth. Environmental factors, including pesticides and toxicants[40], that affect oestradiol biosynthesis and catabolism in women with endometriosis have been proposed to play a part in aberrant cell growth[98]. Increased expression of steroidogenic factor-1 (SF1), a transcription factor that favours gene expression of aromatase that converts androstenedione to oestrone and testosterone to oestradiol, has been noted in endometriotic stromal cells (Fig. 2). By contrast, ectopic endometrial implants and ectopic epithelium lack expression of 17β-hydroxysteroid dehydrogenase 2 (encoded by *HSD17B2*), which normally oxidizes oestradiol to its less potent metabolite, oestrone. As a consequence, oestradiol accumulates locally, creating an oestrogenic microenvironment around endometriotic lesions. High local concentrations of oestradiol and upregulation of ERα and ERβ receptors activate a network of genes (such as *GREB1*, *MYC* and *CCND1*) that regulate cell mitogenesis[99]. One of the putative cell membrane receptors for oestradiol (G-protein coupled oestrogen receptor, GPER) also can transduce endocrine signals through a kinase cascade[100]. In a mouse model, the increased activity of ERβ in endometriotic lesions promoted endometriosis growth in three ways: by reducing TNF-induced apoptosis, increasing IL-1β-mediated cellular adhesion and proliferation, and increasing epithelial–mesenchymal transition (EMT; see below)[101].

Dysregulation of the progesterone receptors (PRs) or alteration of progesterone signalling pathways in eutopic and ectopic endometrium causes progesterone resistance in up to 30% of women with endometriosis[102]. The phenomenon is associated with the relative suppression of PRB and is manifested by dysregulation of a number of downstream progesterone target genes, including *HSD17B2*, *PAEP* and *TOB1* (Refs.[103]) in endometrial tissues (Fig. 2). PAEP is an immunomodulatory protein and marker of differentiated endometrial function, whereas TOB1 is a cell cycle inhibitor; both confer anti-inflammatory and anti-proliferative effects of progesterone action in healthy endometrium. The steroid perturbation confers additional predisposition that is critical for forming ectopic implants, including unbalanced oestradiol action, enhanced tissue-adhesive properties, increased activity of matrix metalloproteinases and triggering of an angiogenic response[104]. However, a role of inflammation secondary to endometriosis in inducing progesterone resistance cannot be excluded[102]. Whether other hormones involved in menstruation, such as follicle stimulating hormone (FSH), leutinizing hormone (LH) or inhibin B, have a direct effect in endometriosis remains unclear; however, the FSH receptor is reported to be expressed in endometrial stromal and epithelial cells[105] and genetic variants in *FSHB*, encoding the FSH-β subunit of the glycoprotein dimer, are associated with endometriosis[56].

The recent evidence that genetic variants associated with endometriosis also affect fat distribution in women[28], and the known sexual dimorphism of adipose distribution between men and women, suggest further interplay between endocrine and metabolic factors in endometriosis. However, the extent of this interplay on disease causation or maintenance remains unexplored[106]. Other critical metabolic factors include retinoids; on the basis of a recent review on the role of these compounds in endometriosis[107], reduced retinoid acid signalling observed in endometriotic stromal cells can result in high local concentrations of oestradiol due to deficient oxidation and inactivation. That is, reduced retinoid acid signalling could enhance cell proliferation and invasiveness whilst limiting cellular apoptosis. Thus, classic nuclear and membrane-bound steroid hormone receptors, in addition to other metabolic factors, regulate critical growth-promoting genes and paracrine factors in endometriosis.

[H3]EMT. EMT, and its reciprocal counterpart, mesenchymal–epithelial transition (MET), are phylogenetically conserved mechanisms of embryonic development that endow plasticity to cells[108]. EMT — an increasingly recognized phenomenon in endometriosis — occurs in the setting of chronic inflammation, with acquisition of an invasive mesenchymal phenotype (for example, loss of E-cadherin and gain of N-cadherin), and promotes growth factor signalling and increased matrix

metalloproteinase expression required for cellular proliferation. Epigenetic mechanisms, via hypermethylation of CpG islands in the E-cadherin gene promoter, have been suggested to promote EMT in endometriotic epithelium[73]. Other EMT-promoting factors include the presence of stimulating factors (for example, transforming growth factor-β1 (TGFβ1), platelets and a 'stiff' tissue matrix) in the context of endometriotic tissue undergoing repair after bleeding. EMT may also trigger fibroblast-to-myofibroblast transdifferentiation and increased collagen production, further contributing to a stiff matrix and ultimately formation of fibrosis[109].

By contrast, MET drives the secretory transformation of endometrium (decidualization) in preparation for embryonic implantation, in a process that seems to be impeded in endometriosis[110]. Specifically, in response to decidualization, endometrial stromal cells acquire epitheloid structure and function, accumulate glycogen, lipids and subcellular organelles and secrete proteins that are characteristically epithelial, rather than mesenchymal. The resultant reprogramming of many cell functions includes changes in steroid hormone receptor expression and steroid metabolism; remodelling of the extracellular matrix and cytoskeleton; modified expression of intracellular enzymes, growth factors, cytokines and their receptors; and induction of decidualization-specific transcription factors such as FOXO1, C/EBPβ and STAT5. The convergence of cAMP signalling and PR-signalling pathways is critical to this phenomenon, as activation of the cAMP pathway confers cellular specificity to progesterone action through the induction of transcription factors (such as FOXO1) that modulate PR function. In endometrial stromal cells from women with endometriosis, PR dysregulation is associated with increased activation of AKT and decreased expression of nuclear FOXO1, resulting in reduced expression of decidualization-specific genes[111].

[H3]Altered immunity and inflammation. Numerous studies provide evidence of altered local and systemic immunity in patients with stage III/IV endometriosis, including T cell and B cell activation and defective natural killer (NK) cell activity, which may be related to platelet dysfunction[112]. Type 1 hypersensitivity and autoimmune disorders are common comorbidities[49].

Two major classes of chemokines have been identified in endometriosis. The CC-chemokine ligands (such as CCL5, CCL2 and CCL11) target monocytes, T cells and eosinophils. The CXC-chemokine ligands (such as CXCL1, CXCL8, CXCL5 and CXCL12) attract monocytes and neutrophils[81]. Although women with endometriosis have increased production of chemokines and, consequently, increased local macrophage recruitment, the potency of the macrophage scavenger function and phagocytotic potential seems to be inhibited[113]. Some reports claim that the cells are polarized towards the anti-

inflammatory, pro-angiogenic M2 phenotype[114], whereas others suggest an increase in the pro-inflammatory M1 phenotype[115]. Activated macrophages secrete a panoply of adhesion molecules, growth factors and pro-inflammatory cytokines into the microenvironment of endometriosis lesions and the peritoneal fluid[81]. Among these factors, fibronectin, intercellular adhesion molecule (ICAM)-1, insulin-like growth factor (IGF)-1, IL-1, IL-6, IL-8, IL-12, platelet derived growth factor (PDGF), VEGF and TNF have been widely reported (Fig. 3); unfortunately, none of these proteins, alone or in combination, have provided reliable biomarkers for diagnosis[116].

The master transcription factor nuclear factor (NF)-κB is a critical regulator of chemokine gene and protein expression[117]. NF-κB has been shown to be activated in peritoneal endometriotic lesions, possibly via increased levels of pro-inflammatory cytokines in the lesion microenvironment. Overexpression of NF-kB has been demonstrated in cultured endometriotic stromal cells and peritoneal macrophages isolated from women with endometrioma. Iron, from in situ menstruation, can accumulate in endometriotic lesions, where it can contribute to the generation of reactive oxygen species. One of its effects is to increase NF-κB activity in endometriotic stromal cells[118]. Other inflammatory pathways (mediated by extracellular-signal-regulated kinase (ERK) 1 and ERK2, p38 MAP kinase and Jun N-terminal kinase (JNK)) are implicated in cytokine production within endometriotic lesions; antagonism of these pathways might provide innovative, non-hormonal therapeutic options in the future.

[H3]Pain. The complex mechanisms that underpin the origin and maintenance of pelvic pain associated with endometriosis are increasingly well understood, and relate to the interplay between the peripheral and central nervous system[119]. Angiogenic (for example, VEGF) and neurogenic (for example, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)) factors are reported to be overexpressed in the peritoneal fluid of women with endometriosis and are thought to support the survival, vascularization and nociceptive sensitivity of the endometriotic lesions (Fig. 3). These factors also are responsive to oestradiol, prostaglandin and cytokine stimulation and sensitise sensory nerve fibre terminals. Endometriotic lesions send noxious signals to dorsal root spinal cord neurons and activate spinal microglia to maintain pain stimuli, resulting in complex, lasting engagement of interconnected neurons in the brain via ascending and descending inhibitory and excitatory synapses in the central nervous system (central sensitization[120]). This central sensitization in turn is influenced by many factors (such as cortisol levels) that affect how the brain processes pain. Thus, the complex endocrine and inflammatory microenvironments surrounding the implants are thought to contribute to the mechanisms of pain in endometriosis.

[H2]Model systems

Endometriosis occurs spontaneously only in humans and non-human primates, which has necessitated the development of various experimental models, including in vitro endometrial cell cultures and sophisticated animal models. These approaches have been used to investigate the processes by which menstrual endometrial fragments implant and grow at ectopic sites[121] to identify new diagnostic and therapeutic opportunities. However, poor alignment of many models to the presentation of endometriosis in humans has likely limited progress. Importantly, the majority of model studies in endometriosis are performed in systems that do not take into consideration the extreme variability in phenotypes and forms characteristic of the disease. Conventional clinical classifications of the disease are of very limited use in elucidating the mechanisms underlying this variability, with the consequence that experimental data are often contradictory or of uncertain interpretation.

Although the placement and attachment of endometrial stroma and glands in the peritoneal cavity of an animal is in general considered a reliable approach to recapitulate the human condition, endometriosis lesions include a variety of cellular (for example, macrophages, leukocytes and smooth muscle cells) and extracellular components (for example, fibrosis) that are rarely present in these models. Similarly, current in vitro studies use traditional 2D cell culture conditions on polystyrene dishes that cannot approximate the complex cell–cell interactions of endometriosis. Future in vitro models will likely incorporate collagen–Matrigel hydrogel matrices, microfluidic devices[122] or other tissue-on-a-chip approaches to overcome these limitations.

[H3] Primary cell cultures. Epithelial and stromal cells isolated from endometrial biopsy specimens and endometriotic lesions can be used to compare cellular and molecular characteristics of eutopic and ectopic endometrium to identify targets for therapeutic intervention[123]. Generally isolated from endometrioma via mechanical and enzymatic procedures, the purity of endometriotic cells can be verified by immunocytochemistry for vimentin expression on stromal cells and cytokeratin expression on epithelial cells[124]. However, fibrous stromal cells of the ovarian cortex also stain intensely with anti-vimentin antibodies, so immunocytochemical staining for CD10 (a marker of endometrial stroma) is recommended to distinguish endometriotic cells[123]. Primary cultures, mostly the stroma, have been used extensively to identify dozens of molecules differentially expressed between eutopic and ectopic endometrial cells[125], particularly collected from the ovary . Unfortunately, to date, translation of these findings to the clinic has been limited. Additionally,

556 interactions between endometrial and peritoneal cells, including adhesion and invasion, have been
557 effectively studied using primary and immortalized mesothelial cells[125].
558
559 ***[H3] Immortalized cell cultures.*** To address experimental limitations of using primary cells, expand
560 the number of cells and mitigate subject-to-subject variability, attempts have been made to
561 immortalize human endometrial and endometriotic cells by oncogenic transformation or
562 prolongation of cell division by introducing human telomerase reverse transcriptase[125]. Such cells
563 have been derived from ovarian endometriomas and peritoneal lesions[125]. However, the synergistic
564 effect of progestin and cAMP on decidualization tends to be attenuated in these cell lines.
565 Additionally, several immortalized endometrial lines are reported to be contaminated with HeLa
566 cells that can obscure the results in terms of gene and protein expression, pathways involved and
567 response to drugs[126]. Thus, studies must validate the cell purity, confirm steroid responsiveness and
568 be linked to the specific endometriosis phenotype[125] to be useful.
569
570 ***[H3]Autologous rodent models.*** Mouse and rat models have been developed via intraperitoneal or
571 subcutaneous transplantation of autologous endometrial tissue from the same or syngeneic
572 donors[127]. In mice, rats and hamsters, 'endometriosis' is induced surgically by suturing fragments of
573 uterine tissue to the peritoneum and omentum (the membranous double layer of fatty tissue
574 covering the intestines and organs in the lower abdominal area); these sutured specimens then
575 develop well-vascularized cystic lesions with typical endometriosis-like histomorphology.
576 Localization, graft number, size and volume as well as histological and molecular changes within the
577 lesions can be evaluated over time[128]. However, limitations of these rodent models include that they
578 do not develop endometriosis spontaneously and potential therapeutic effects observed might be
579 the result of phenomena underlying the induction method rather than a response toward specific
580 endometriosis-related processes.
581
582 In mice, an alternative procedure is to inject fragments of minced uterine horns from donor mice
583 into the peritoneal cavity of syngeneic recipient animals; fragments from each horn are sufficient to
584 inoculate up to two mice, minimizing variability in the model. The lesions consist of isolated or
585 multicystic vascularized nodules bulging from and loosely attached to serosal surfaces. Similar to
586 humans, the distribution of lesions is influenced by gravity, with most found on the anterior
587 abdominal wall and around the uterus[129]. However, unlike human endometriosis, the omentum is
588 commonly colonized in this model. Deeply infiltrating lesions have never been observed in this
589 model.

Tissue from human eutopic endometrium, endometriotic lesions and menstrual effluent as well as isolated stromal and epithelial cells have been injected or transplanted into the peritoneal cavity or subcutaneous space of immunodeficient mice[125]. These lesions maintain human histological endometrial characteristics[130] and can be evaluated for responsiveness to steroid hormones or steroid modulating drugs[131]. Furthermore, owing to their chimeric nature, human/mouse xenografts are extremely useful for investigating species-specific factors involved in lesion formation. Angiogenic and anti-angiogenic compounds have been extensively studied in this model (for example, Ref.[132]). Certainly, the absence of a normal immunological response represents a limitation and such models might not be suitable for testing hypotheses related to inflammation in endometriosis. By contrast, immunocompetent mouse models can be used to study the effect of immune-modulating drugs and anti-inflammatory agents[125]. Immunomodulators, cyclooxygenase-2 inhibitors, vitamin D analogues and N-acetyl-cysteine have all shown various degrees of lesion growth inhibition in these models [129,131,133].

One of the most important advantages of murine models is the vast availability of genetic modifications that can be applied to specific target genes. For examples, to demonstrate the role of ERβ activity in endometriosis progression, the disease was surgically induced in mice carrying genetically modified ERs[134]. Recently, a mouse model was developed using hormone withdrawal to induce a menses-like event to derive donor tissue for injection into the peritoneum of syngeneic immunocompetent recipient mice[135]. 'Menstrual' endometrium may represent a more authentic tissue source than surgically dissected intact uterine fragments to establish endometriotic lesions.

Transgenerational rat studies, whereby female offspring of animals with surgically induced endometriosis are used, have exhibited reproductive abnormalities (reduced oocyte quality and embryo development and early pregnancy loss) similar to those of the operated dams indicating heritability of the impaired fecundity phenotype[136]. In addition, rats bearing grafted uterine fragments onto the peritoneum have been used to explore the association between endometriosis and increased pelvic nociception, which led to the demonstration that the animals had vaginal hyperalgesia (increased sensitivity to pain) suggestive of altered pain responses in the central nervous system[125].

[H3]Non-human primate models. Non-human primates, such as rhesus macaques and baboons, have menarche, menstrual cycles and (eventually) menopause. Endometriosis in these animals

resembles the human condition in terms of laparoscopic appearance, pelvic localization and microscopic aspects[137]. In some colonies of ageing rhesus macaques with regular menstrual cycles, a high prevalence of spontaneous endometriosis has been observed[138]. However, in the wild, endometriosis develops with low frequency and slow progression, which has led to the development of an induced model via injection of autologous menstrual effluent into the pelvic cavities of baboons[139]. Stage III/IV endometriosis can also be induced experimentally by the intrapelvic injection of menstrual endometrium, resulting in obliteration of the Pouch of Douglas (Fig. 1) and presence of adnexal adhesions; the ovary is rarely involved.

These animals are expensive, require specialized facilities and their use is limited by ethical considerations[140]. However, the effects of endometriosis on subfertility, clinically proven by a reduced pregnancy rate in more-severe disease and at a molecular level by abnormalities in progesterone responsiveness and decidualization, has been clearly manifested in these models. As such, non-human primates likely represent the model that most closely mimics human endometriosis[141]. Indeed, the development of progesterone resistance has been associated with alterations in both endometrial PRB expression (at the gene and protein level) and the chaperone immunophilin FKBP52 (also known as peptidyl-prolyl *cis-trans* isomerase FKBP4, encoded by *FKBP4*), which has been shown to be critical for a functional PR response[141]. Finally, given the highly evolved behaviours of these species, assessment of 'pain' associated with endometriosis has been attempted but lack of rigorous end points for such evaluations have hindered progress[142].

[H1] Diagnosis, screening and prevention

Endometriotic tissue predominantly presents in the abdominal cavity, particularly in the pelvis (Fig. 1). Whilst endometrioma in particular are quite easily detectable using conventional imaging techniques such as transvaginal or abdominal ultrasonography, detecting or ruling out peritoneal lesions often poses a considerable diagnostic challenge. Furthermore, clinical signs and symptoms are commonly not endometriosis-specific, which — coupled with a lack of awareness of this common condition (Box 1) — may slow diagnosis. To date, no clinically relevant biomarker or combination of biomarkers are available for either screening or patient stratification. Thus, laparoscopic visualization, ideally with histological verification, is still considered the gold standard for the diagnosis of endometriosis. However, it is generally not necessary to perform invasive surgery solely for diagnostic purposes if there is no intention to treat surgically[137]. As a principally non-malignant condition, a reasonable first-line approach to avoid a costly and invasive surgical intervention — associated with potential morbidity and even mortality[143] — is to clinically diagnose

(or rule out) the presence of endometriosis and to treat the patient empirically (see Management, below). To date, no studies exist investigating the potential benefit of interventional strategies for primary disease prevention.

[H2] Signs and symptoms

[H3] Pain and associated symptomatology. No endometriosis-specific symptoms exist; women may be asymptomatic or present with a single or a combination of pain symptoms of variable intensity that can be attributed to many other conditions. Endometriosis is associated with dysmenorrhoea, cyclical or non-cyclical abdominal pain and pelvic pain during or after sexual intercourse (deep dyspareunia). Women also frequently report considerable effects on their bowel habits, including alternating constipation and diarrhoea, painful emptying of their bowels (dyschezia) or blood in the stool (in particular peri-menstrually). Some women experience recurrent painful urination (dysuria) and/or cyclical blood in the urine (macrohaematuria) and have been treated with multiple courses of antibiotic therapy despite a lack of direct evidence of urinary tract infection. Such symptoms may be caused by interstitial cystitis/painful bladder syndrome, which can be associated with endometriosis[144].

Diaphragmatic endometriosis has been associated with chest and shoulder pain[145] whereas endometriosis in the ileo-caecal or peri-appendiceal region has been described to result in abdominal pain, nausea, vomiting and diarrhoea[146]. Another frequently present, but often neglected, symptom in women with endometriosis is chronic fatigue[51] although the exact mechanism remains elusive. One study showed no differences in pain symptoms experienced by adolescent women diagnosed with endometriosis compared with adult patients, but adolescents experienced nausea with pain more frequently and were more likely to report pain starting at menarche[147]. Additionally, multiple studies now indicate that no correlation exists between pain intensity and location and the extent and location of the endometriotic lesions[7]. Similarly, individual pain areas are widely unrelated to the extent and area of endometriosis found during surgery[148]. Indeed, medical and surgical treatment do not result in full cessation of symptoms[149] (see below), which suggests that endometriosis-associated pain is a complex symptom.

To add a further level of complexity, some ‘endometriosis-associated’ symptoms including painful and heavy periods may originate from concomitant adenomyosis. Finally, and crucially, studies have shown that a combination of peripheral pain sensitizers including various chemokines and cytokines abundantly present in peritoneal fluid might be involved in endometriosis-related pain; additionally,

central sensitization mechanisms (such as structural and volume changes of the brain, modifications within the autonomic nervous system and alterations in the behavioural and central response to noxious stimulation) are probably involved[150,151] . However, it remains to be seen if earlier diagnosis and treatment of endometriosis (for example, during adolescence) provides long-term benefit[152]. Small case series have described endometriosis in adolescent girls as predominantly minimal and mild with mostly superficial lesions[153], although AFS/ASRM stage IV in 31% of adolescent girls was reported in one series[154].

[H3] Fertility issues. Approximately 30–50% of women with endometriosis have fertility problems, in particular those <35 years of age (who generally have good ovarian reserve and oocyte quality)[21]. Reciprocally, endometriosis is identified in approximately one-third of women in infertile couples. Thus, endometriosis should be suspected a potential cause of infertility, particularly in women who present with pain symptoms. However, the underlying mechanisms linking endometriosis and infertility remain elusive.

Disruption of pelvic anatomy owing to extensive endometriosis-associated adhesions can reasonably be assumed to result in a mechanical obstacle that prevents the fertilization. However, the molecular processes are less clear. In addition, structural changes in the pelvis do not explain the increased incidence of miscarriages and obstetric complications in women with endometriosis[155]. Endometriosis is thought to have a detrimental effect on oocyte quality[156]. A small, but seminal study using donor oocytes demonstrated the lowest pregnancy rates per embryo transfer when the donors had a history of endometriosis compared with women with tubal factor infertility, polycystic ovary syndrome and idiopathic infertility[157]. Women with endometriosis undergoing in vitro fertilization (IVF) have decreased numbers of retrieved oocytes during ovarian stimulation and need higher gonadotrophin doses than women without endometriosis[158]. Endometriosis in these women may impart a direct toxic effect on the ovarian cortex, or the ovaries may be damaged as a result of ovarian surgery (for example, to remove and/or obliterate endometrioma or other ovarian cysts). Such surgical interventions have been shown to reduce postoperative levels of anti-Müllerian hormone (AMH), the hormone involved in follicle maturation[159].

Considerable debate abounds about the effect of endometriosis on uterine receptivity[160,161]. A small prospective study demonstrated that donated oocytes from healthy women are just as likely to result in pregnancy when implanted in women with endometriosis compared with healthy recipients[162]. However, another study could not replicate these findings[163]. Molecular and genetic

pathway analyses also demonstrate conflicting results suggesting that further well-designed studies are needed to better understand potential association between endometriosis and uterine receptivity[164]. The fact that surgical excision or eradication of lesions in women with mostly peritoneal lesions only marginally increases spontaneous pregnancy rates supports this demand[165].

[H2] Diagnosis

Most clinicians use the aforementioned classification system by the AFS and ASRM to describe the extent, depth and location of endometriotic lesions[6]. This system uses a point system that results in categorization into stages I–IV (Fig. 1). Disease severity according to the AFS/ASRM staging system does not correlate with the severity and location of symptoms; that is, women with stage I (mild) disease may experience severe pain symptoms and/or infertility, whereas some women with stage IV (severe) endometriosis can be asymptomatic. This discordance can be partially explained by the fact that even experienced clinicians fail to report and classify endometriosis consistently[166]. In addition, the AFS/ASRM classification system fails to acknowledge any extra-pelvic endometriosis. Other classification systems have been proposed. For instance, the ENZIAN system describes the location and extent of deep endometriosis[167]. However, its general use is currently not accepted everywhere possibly due to its complexity[168]. Another challenge in diagnosing the condition is the predominantly pelvic presentation of endometriotic tissue involving the parietal peritoneum and the pelvic organs because lesions are small (a few millimetres diameter).

Pelvic endometriosis can be divided into in three different entities: superficial peritoneal endometriosis, endometrioma (‘chocolate cysts’) and deep endometriosis (Fig. 4)[169]. This categorization is based on factors such as possible differences in the pathogenesis, the anatomical distribution and morphological differences (for example, in the distribution of glandular epithelial and stromal cells). Such characterization is not always straightforward and poor agreement exists between the colour, shape and depth of the ectopic tissue (C.M.B., unpublished data). However, with the emergence of novel molecular data, and the availability of a standardized approach to deep phenotyping and biological sample collection and processing as developed by WERF EPHect[64–67], it is expected that functional subcategorizations for endometriosis will emerge similar to conditions such as cancer or auto-immune diseases, leading to a better targeted management approach.

The presence of endometriotic tissue has been described involving most organs. Rare abdominal locations include scars (in particular after caesarean section), the umbilicus and the sub-phrenic region. Despite the lack of large cohort studies, pleural endometriosis — also known as thoracic

endometriosis syndrome — is generally considered the most common extra-abdominal location[170]. Despite its rarity, a meta-analysis of case reports and series suggests that women present predominantly with (sometimes recurrent) pneumothorax (menstrual and non-menstrual; 72% of cases) and less commonly with haemoptysis (coughing of blood; 14% of cases), haemothorax (12% of cases) and a lung mass (2% of cases)[171].

[H3] Imaging. Common imaging modalities used to investigate endometriosis-associated symptoms are ultrasonography and MRI (Fig. 5). Where appropriate, transvaginal ultrasonography should be part of first-line management to investigate pelvic endometriosis, as it can reliably identify or exclude endometrioma[165]. Blood in these ovarian cysts on ultrasonography can be functional (haemorrhagic, that is, often caused by spontaneous bleeding into a cyst or corpus luteum) and usually resolve spontaneously within 6–8 weeks. Thus, repeat ultrasonography is generally recommended. Endometrioma are rarely the only manifestation of endometriosis and are often indicative of more extensive and often deep endometriosis[172]. Ultrasonography, when performed by an experienced operator also has a high sensitivity (91%) and specificity (98%) for detecting and ruling out deep endometriosis[173]. A prospective study of 198 women undergoing transvaginal ultrasonography before laparoscopic surgery demonstrated a high negative predictive value for both endometrioma and deep endometriosis[174]. Of note, this study was performed in a highly specialized centre and it remains unclear whether the findings for deep endometriosis are applicable in the general setting. MRI is almost equally successful for detecting deep endometriosis[175], but is costly and should be regarded as the second-line imaging technique[176].

Using ultrasonography for the identification of peritoneal endometriotic lesions is unreliable mostly owing to their small size. Dynamic surrogate markers of endometriosis-associated adhesions, such as the immobility of pelvic organs during transvaginal ultrasonography (negative 'sliding sign'), can be indicative of disease, but are unreliable and may only be successful in expert hands[177]. Similarly, a prospective study in 2003 demonstrated low sensitivity and specificity of MRI in the diagnosis of peritoneal disease[178]. Data from a recent large multi-centre randomized controlled trial on the usefulness of MRI to detect endometriosis overall are eagerly awaited (ISRCTN13028601).

[H3] Laparoscopy. Laparoscopic surgery remains the gold standard in identifying and excluding pelvic endometriosis[179]. However, similar to imaging, this modality can be highly operator dependent[165]. Available guidelines in assessing the abdomen and pelvis in a standardized fashion should be applied[64]. A negative laparoscopy performed by an experienced and meticulous surgeon is

highly sensitive and should generally reassure the patient that no endometriotic lesions are present[180]. However, two studies have shown that in 6% of women with a negative laparoscopy, peritoneal biopsies taken from normal-looking peritoneum have been histologically confirmed as endometriosis[181]. A small study including 45 women with or without pelvic pain showed that intraoperative use of intraperitoneal methylene blue can help to visualize subtle peritoneal lesions that are invisible to the eye otherwise[182]. Other methods that involve different wavelengths of light during laparoscopy are currently being tested for their wider applicability[183]. Endometriosis identified visually should ideally be confirmed by histology[165].

[H1] Management

When aiming to improve fertility as the primary objective, medical treatment is not recommended because all current medications used for endometriosis are hormonal and block ovulation. By contrast, when targeting pain as the primary problem, medical treatment is beneficial although surgery might also be indicated for certain patients. Endometriosis is viewed as a long-standing disease, the natural history of which is unknown and which may require long-term management depending on the patient's age, symptom profile and desire for fertility[184]. The descriptions below are based on international guidelines such as by the ASRM[184], the European Society of Human Reproduction and Embryology (ESHRE)[165] as well as a a systematic guideline review[5].

[H2] Infertility

Mechanically, extensive pelvic endometriosis can cause anatomical distortion that potentially impairs oocyte 'pick-up' by the fallopian tubes. Biochemically, endometriosis may have a detrimental effect on oocyte quality[156] or on endometrial receptivity[160], although the molecular process is less clear. Treatment options for women trying to conceive are either expectant management, surgery or assisted reproductive techniques (ARTs) (Fig. 6). The use of hormonal treatment, one of the pillars of endometriosis-associated pain treatment, is contraindicated in women trying to conceive as it has contraceptive effects. As part of the general infertility check-up, ovarian reserve, ovulation, tubal function and partner's semen should be assessed.

[H3]Expectant management. In women with infertility without notable pelvic pain and with normal baseline parameters (ovarian reserve, ovulation, fallopian tubal patency and partner's semen), expectant management (watchful waiting) is not unreasonable, especially for young patients with only a short period of infertility. In older patients, in particular those in whom clinical examination, imaging or previous surgical history suggests more-extensive disease resulting in anatomical

distortion, it may be beneficial to reduce the time of expectant management and consider ART and/or surgery.

[H3]Surgery. Surgical treatment aims to remove endometriotic tissue, normalize or improve the anatomy and eliminate lesions that contribute to an unfavourable inflammatory milieu in the pelvis, potentially enhancing fertility. Ideally, surgery should be performed by infertility specialists in specialized centres. However, surgery may not completely correct anatomical distortion and biochemical insults, and might even negatively affect fertility by impairing ovarian function (decreasing in ovarian reserve) or resulting in further adhesions. When considering surgery, the benefits and the harm should be balanced; alternative treatment modalities (such as ART) must be discussed with the patient.

In patients with AFS/ASRM stage I/II endometriosis, operative laparoscopy (ablation or resection of endometriosis) significantly increases spontaneous pregnancy rates compared with diagnostic laparoscopy[185]. However, the cumulative pregnancy rate at 9–12 months increased only from 18% to 26%[186] and the number needed to treat to achieve an extra pregnancy is 12–13 patients[165]. One may also question whether this modest increase in the pregnancy rate justifies the costs and risks of surgery, especially given that a single ART attempt usually generates a similar success rate[187]. Thus, although there is objective evidence that surgery is better than no treatment, surgery may not always be the best choice to improve fertility in patient with AFS/ASRM stage I/II endometriosis. In patients with AFS/ASRM stage III/IV endometriosis, no randomized trial has assessed the value of surgery. However, the benefit is smaller in those with AFS/ASRM stage IV endometriosis with tubal adhesions compared with those with stage II endometriosis[188]; thus, alternative therapies such as ART should be considered for these patients unless they have severe pain or a large endometrioma (that might cause rupture or limit the oocyte retrieval) or suspected malignancy.

For endometrioma, laparoscopic resection increased the subsequent spontaneous pregnancy rate with lower recurrence rate of both cysts and pain symptoms compared with ablation in women who had documented prior subfertility[189]. This finding suggests that in women with endometrioma who have no other identifiable infertility factors, surgery may increase the chance of spontaneous pregnancy; however, one should be aware of compromised ovarian reserve as a possible adverse consequence[190]. For deep endometriosis (such as rectovaginal endometriosis and bladder/bowel endometriosis), the benefit of surgery for infertility is controversial[191], although recent retrospective

observational studies suggest a benefit (for example, Ref.[192]). These possible benefits should be weighed against major complication risks, especially in surgery with bowel resection.

A clinical tool, the Endometriosis Fertility Index (EFI), which includes parameters such patient's age, duration of infertility and pregnancy history, as well as endometriosis severity according to rASF/ASRM score and tubal, fimbrial and ovarian appearance, has been developed and subsequently validated in different centres. The tool predicts spontaneous pregnancy rates in women with surgically documented endometriosis[193] and is useful to provide reassurance to those patients with good prognoses and to avoid wasted time and treatment in those with poor prognoses.

[H3] Non-assisted reproductive technology. Evidence supports that superovulation/intrauterine insemination (SO/IUI) in women with endometriosis can be effective (for example, Ref.[194]). Indeed, both the ASRM[186] and ESHRE[165] recommend SO/IUI as non-ART methods, especially in patients with AFS/ASRM stage I/II endometriosis who are seeking fertility treatment. However, the UK National Institute for Health and Care Excellence (NICE) did not recommend the routine offer of IUI[195] in their 2013 guidelines. Alternatively, others suggest 'first-line ART' (going straight to ART prior to attempting SO/IUI) rather than first attempting SO/IUI, in particular in patients with endometriosis with diminished ovarian reserve[196]. The reasons for this approach stem from findings that the benefit of SO/IUI in women with endometriosis is lower than in women without endometriosis[197]. Furthermore, SO/IUI has been deemed to be not cost effective[198], especially for endometriosis-associated infertility[199].

[H3]ART. ART such as IVF can bypass the fallopian tube and is currently the most successful treatment that can be offered to those with endometriosis-associated infertility[165,186]. As mentioned earlier, endometriosis is suggested to negatively affect ART results[200]; however, in comparison with non-ART treatments, ART increases cycle fecundity for those with endometriosis, especially in those with distorted pelvic anatomy. ART can also minimize the time to achieve conception and is, therefore, recommended for those whose ovarian reserve is reasonably diminished. Medical treatment in the form of prolonged hormonal downregulation with a GnRH agonist[201] or combined oral contraceptives (COCs)[202] prior to ART seems to benefit ART outcomes and is recommended to be considered by the ASRM[186] and ESHRE[165]. However, the studies were small and one should also be aware that the medical treatment delays the commencement of ART, which might affect the outcome, particular in patients of advanced reproductive age. Cryopreservation of embryonal or

ovarian tissue is currently discussed as an alternative for patients at high risk of ovarian insufficiency, although evidence is sparse[203].

[H3]Surgery prior to ART.

The benefit of surgical treatment of endometriosis prior to ART is controversial. With regard to endometrioma, there is no evidence that removal prior to ART improves pregnancy rates (as opposed to spontaneous pregnancy rates, see above)[201]. In addition, many studies have shown that ovarian surgery decreases ovarian reserve, which results in unfavourable ART outcomes[204] . Accordingly, the rule of 'no surgery before ART' is proposed by both the ASRM and ESHRE guidelines[165,186], especially for patients with diminished ovarian reserves[196]. However, endometrioma kept in place during ART can become infected, rupture and limit the accessibility to follicles; clinicians should be aware of these issues when opting for conservative management.

For deep endometriosis, surgical removal prior to ART is proposed to improve pregnancy rates [205], but the evidence is very limited. Surgery may also reduce pain and detect occult malignancy, but must be balanced against the operative risks[44]. Collectively, surgery prior to ART is not warranted for all patients, but should be considered for those with pain, large endometrioma or when malignancy cannot reliably be ruled out[196].

[H3]Obstetrical outcomes. Recent literature has focused on the relationship between endometriosis and obstetric and neonatal outcomes, reporting a correlation with placenta previa (in which the placenta sits low in the uterus, next to or covering the cervix), preterm birth, babies who are small for their gestational age and need for caesarean delivery[206]. Spontaneous haemoperitoneum in pregnancy (unprovoked intraperitoneal bleeding) is a rare but potentially lethal complication of pregnancy that is also strongly associated with pelvic endometriosis[207]. Some of these observations may be explained by the high frequency of concomitant adenomyosis in terms of myometrial displacement of endometrial glands and stroma among women affected by endometriosis[208]. The pro-inflammatory environment may also contribute to poor obstetrical outcomes, as the consequences of inflammation can manifest at endometrial and systemic levels. Additionally, patients with endometriosis have uterine contractions with higher frequency, amplitude and basal pressure tone and feature alterations in the inner third of the myometrium compared with controls, which may contribute to poor obstetrical outcomes[209] .

[H2]Pain

928 Endometriotic implants are often associated with fibrosis and mechanical distortion of adjacent
929 structures that can result in pain[210]. Endometriosis also induces the growth of nerve fibres into the
930 lesion, which could have an influence of the activity of neurons throughout the central nervous
931 system[120]. However, in women with persistent pelvic pain, observations of minimal endometriosis
932 could also be coincidental rather than causal. Both medical and/or surgical approaches can be
933 adopted for endometriosis-associated pain (Fig. 7).
934
935 ***[H3]Medical treatment.*** As endometriosis is an oestrogen-dependent disease, medical treatments
936 for endometriosis have focused on establishing either a hypo-oestrogenic or hyper-progestogenic
937 milieu. Medical treatment, however, does not eradicate the disease, and lesions and symptoms
938 commonly reappear at therapy discontinuation[102]. The choice of treatment depends on
939 effectiveness, adverse effects, long-term safety, costs and availability[165].
940
941 Combined oral contraceptive (COC) pill contains oestrogen and progestin; COCs induce central
942 inhibition of gonadotropin secretion, inhibiting ovulation and reducing ovarian oestrogen secretion.
943 COCs can establish a hyper-progestogenic milieu and induce decidualization and subsequent atrophy
944 of ectopic endometrium[211]. In addition, the oestrogen component results in central inhibition of
945 gonadotropin secretion, inhibiting ovulation and overall reducing serum oestrogen levels.
946 Continuous rather than cyclic administration of COCs often results in amenorrhea, which is
947 particularly beneficial in women with dysmenorrhea[165]. Evidence supports the efficacy of COCs for
948 endometriosis-associated pain[212] and currently COCs are prescribed as a first-line treatment choice
949 for long-term treatment[102], although COCs are used off-license for the indication of endometriosis.
950 Similar to COCs, progestin-only pills (POPs) or other progestins induces atrophy of endometrial
951 implants[211]. Medroxyprogesterone acetate, norethisterone acetate[213] and dienogest[214] are
952 supported by evidence and are commonly prescribed for women with contraindications to COC use
953 or as first-line treatment[215]. The levonorgestrel-releasing intrauterine system (LNG-IUS) is also
954 effective for reducing dysmenorrhea[216].
955
956 GnRH agonists that are administered continuously to suppress pituitary function produce a hypo-
957 oestrogenic milieu and are very effective against pain[217]. However, adverse effects include bone
958 mineral density loss and vasomotor symptoms, such as hot flashes and night sweats[218], which limit
959 the long-term use of these medications. As discontinuation of GnRH agonists results in symptoms
960 recurrence, 'add-back' therapy (addition of low levels of oestrogen and progestin) has been
961 advocated for extending the duration of use of GnRH agonists[219]. However, GnRH agonist plus add-

back therapy is expensive and is recommended only in selected patients who are unresponsive to first-line therapy or with conditions (such as obesity and pulmonary disease) that render them high-risk surgical candidates[102].

A 2017 randomized controlled trial showed that the oral GnRH antagonist elagolix was effective for endometriosis-associated pain[220]. Similar to GnRH agonists, GnRH antagonists inhibit the secretion of gonadotropin and produce a hypo-oestrogenic state, but have the advantage of inducing a rapid drop of oestrogen avoiding the initial increase in FSH and LH secretion (so-called flare effect of GnRH agonists). If these drugs are approved by the US FDA, it will be important to see which restrictions the agency will impose for their use long-term use, and to await further trials against other treatments[221]. Hormonal therapy is often accompanied by direct analgesia using NSAIDs, paracetamol (acetaminophen) or various opioids. Other drugs currently under investigation include aromatase inhibitors, selective progesterone (or oestrogen) receptor modulators, immune-modulators and anti-angiogenic agents[222].

[H3]Surgery. Surgery for endometriosis aims to remove or destroy all visible disease and restore the anatomy; the effect on pain is usually satisfactory[223], although symptoms may recur after surgery. Accordingly, the benefits and the risks of complications and recurrence should be balanced. Conservative surgery (that is, resection of lesions without removal of the ovaries and the uterus) is usually preferred as most women with endometriosis wish to retain the ability to conceive. Peritoneal endometriosis and endometrioma can be safely removed with considerable benefit of fertility enhancement and pain relief[165]. Excision of deep endometriosis involving the uterosacral ligament, bladder or vagina is also effective but the procedures are complex, and are associated with higher rates of complications, particularly when bowel resection is concomitantly performed[208]. Deep endometriosis that causes bowel or ureteral obstruction requires resection and/or anastomosis as medical treatment is ineffective due to the irreversible fibrosis[210]; in these patients, a multidisciplinary approach with colorectal and urological surgery must be considered[210]. Laparoscopic uterosacral nerve ablation does not improve pelvic pain nor offers any added benefit[224]. Presacral neurectomy involves interrupting the sympathetic innervation to the uterus and is proposed for reducing dysmenorrhea, but substantial risk of bleeding and postoperative constipation should be noted[184].

Despite its temporarily satisfactory effects, disease and symptoms may recur after surgery[225], although symptom recurrence does not always imply disease recurrence; instead concomitant

adenomyosis or central pain sensitization might be evident. Medical therapy following conservative surgery is, therefore, crucial[184] to limit recurrence[226]. Using COCs or progestins in the long-term, preferably until conception is desired, should be considered[226].

[H1] QUALITY OF LIFE

The symptoms associated with endometriosis are known to exert substantial burden on the lives of women with endometriosis and their families. A systematic review of 20 health-related quality of life (HRQOL) studies in endometriosis published in 1999–2006 showed that endometriosis was associated with pain and significant impairment of psychological and social functioning[227]. However, disease-specific instruments to characterize HRQOL in endometriosis were not used by many studies and few assessed the influence of infertility on HRQOL, or the effect of endometriosis on adolescents.

In 2011, a study in 1,418 women undergoing their first laparoscopy for pain or infertility symptoms suggestive of endometriosis, or for tubal sterilization, at 16 clinical centres in ten countries in five continents reported a significantly reduced physical (but not mental) HRQOL —measured using the generic Short-Form (SF)-36 instrument — in symptomatic women with endometriosis compared with those without endometriosis and compared with asymptomatic women undergoing tubal sterilization[8]. Diagnostic delay (Box 1) was significantly associated with reduced HRQOL, even after adjustment for number of symptoms. Each woman with endometriosis lost on average 11 hours of work per week, mainly owing to reduced effectiveness while working rather than absence from work[8], measured using the Work Productivity and Activity Index (WPAI), which is a tool to assess the impact of symptoms on effectiveness at and absence from work and ability to carry out other non-work activities. As a consequence, endometriosis has a substantial socioeconomic impact on the individual and on society in general. In 2012, a prospective study involving 12 referral centres in ten countries calculated the average annual costs and HRQOL per woman with endometriosis-associated symptoms at €9,579, with two-thirds of this sum solely owed to the loss of productivity, putting it into a similar category as other chronic conditions such as type 2 diabetes mellitus, Crohn's disease and rheumatoid arthritis[228].

Generic HRQOL instruments such as the SF-36 are unlikely to capture all aspects important to women with endometriosis. An endometriosis-specific quality of life outcome tool has been developed, the Endometriosis Health Profile (EHP)-30 [229], and a shorter form, the EHP-5, also has been validated[230]. The EHP-30 has been translated and validated in 19 languages. The tool measures

endometriosis-related health status in a core questionnaire with 30 items and five scales relevant to the disease (the core questionnaire): pain, control and powerlessness, emotional well-being, social support and self-image. A further 23 questions (the modular questionnaire) examine the areas of sexual intercourse, work, relationship with children, feelings towards the medical profession, treatment and infertility. The EHP-30 has been shown to be sensitive to change in patient outcomes[231], making it a useful tool in endometriosis-specific clinical trials. The EHP-5 was developed for clinical settings in which short, economical health status measures are required, and contains 11 items: five items from the core questionnaire and six items from the modular questionnaire.

A recent systematic review amalgamated outcome reporting in randomized controlled trials on endometriosis up to November 2014 (Ref.[232]), including 54 trials with 5,427 participants and reporting 164 outcomes and 113 outcome measures. As expected, the most commonly reported primary outcomes were dysmenorrhea (10 outcome measures; 23 trials), dyspareunia (11 outcome measures; 21 trials) and pregnancy (3 outcome measures; 26 trials). However, variation in outcome reporting prohibited comparison and synthesis of data, limiting the meaningfulness of research to inform clinical practice. The authors of the above systematic review are in the process of developing a core outcome set for endometriosis as part of the CROWN initiative, which aims to standardize reported outcome measures in trials across the entire field of women's health[233]. Standardized, validated pain outcome measures are also included in the WERF EPHect patient questionnaires[65].

Additionally, an endometriosis-related pain diary has been developed, the EPDDv3 (11 items), consisting of five core items relating to dysmenorrhea, non-menstrual pelvic pain and dyspareunia, and six additional items relating to sexual activity, daily activities and use of rescue medication[234]. The tool is based on a range of sources, including an existing Endometriosis Pain and Bleeding Diary, a review of literature, interviews with clinical experts and interviews with patients in the United States and Japan. Content validation of the EPDDv3 has been assessed through translatability across 17 languages, and US and European regulatory authorities for clinical trials have also provided feedback. Reliability of the instrument, construct validity and ability to detect change remain to be tested.

[H1] Outlook

Endometriosis is an enigmatic disease in which a wide range of research questions remain to be answered to improve the lives of patients. The most recent World Endometriosis Society (WES)

Research Directions Workshop involving 60 global key opinion leaders in the field identified and ranked 107 research priorities to be addressed, covering pathogenesis and pathophysiology, symptoms, diagnosis, classification, prognosis, disease and symptom management and research policy[235]. In the United Kingdom and Ireland, the James Lind Priority Setting Partnership on endometriosis set out to identify the unanswered questions about endometriosis that patients, advocates and clinicians agree are most important; a 'top 10' of priorities was ascertained (Box 2)[236] and showed overlap with themes covered by WES.

The development of improved, non-invasive, diagnostic options to enable earlier effective treatment and novel, non-hormonal therapies with fewer adverse effects and are amenable to conception are urgently needed. Research aimed at understanding the pathogenesis of endometriosis needs to take into account that it is a heterogeneous condition for which subtypes are likely to be identified that have different aetiologies and require different treatments; such subtypes will require different diagnostic markers and markers for stratification. This vision for endometriosis is similar to, for example, the cancer field in which improved biological characterization of tumours, correlated with risk-factor profiles and treatment outcomes, have resulted in treatments targeting specific subtypes[237] and in large-scale programmes aimed at such characterization, such as The Cancer Genome Atlas[238]. Endometriosis subtype identification will require the integrated analysis of extensive molecular profiles (proteomic, metabolomic, transcriptomic and (epi)genomic) from biological samples obtained from women with and from women without endometriosis, with detailed phenotypic data that has been validated and replicated.

Regarding biomarkers for endometriosis, a set of recent Cochrane reviews concluded that despite the existence of potentially promising candidates no single or panel of diagnostic screening, prognostic or predictive biomarkers presently exists that is clinically relevant[116,239–241]. The reviews confirmed earlier observations of problems with data interpretation, including generally small sample sizes, lack of data validation and substantial heterogeneity within and between studies[165,242,243]. The aforementioned WERF EPHect data and sample collection protocols will enable urgently needed large-scale, standardized, multi-centre, robust and reproducible studies to identify endometriosis subtypes and associated biomarker panels. Indeed, many potential clinical applications for biomarkers have been identified (Table 2). Ideally, biomarkers should be obtained by non-invasive or minimally-invasive means, such as from biological samples (including blood, urine, saliva and endometrium), but can also include imaging and clinical parameters or a combination of the above. Biomarkers should be stable across the menstrual cycle (or have a well-characterized

cyclical variability), with or without hormonal contraception use, and in the presence of other pathologies such as uterine fibroids.

All therapies currently available for endometriosis are hormonal. Their adverse-effect profiles aside, these treatments are not viable long-term options for women hoping to conceive. Accordingly, new treatments need to focus on alleviation of symptoms and should be based on a better understanding of the mechanisms underlying the associated pelvic pain and infertility. Although novel medical treatments are under development, the important role of surgery will remain, in particular for women with AFS/ASRM stage III/IV disease. However, awareness that surgery requires trained, skilled professionals must improve to avoid damage to pelvic organs and tissues, repeated operations and poor outcomes.

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Author contributions

Introduction (K.T.Z.); Epidemiology (S.A.M.); Mechanisms/pathophysiology (R.N.T. and P.V.); Diagnosis, screening and prevention (C.M.B.); Management (K.K.); Quality of life (K.T.Z.); Outlook (K.T.Z.); Overview of the Primer (K.T.Z.).

Competing interests

K.T.Z. has received grant funding from the Wellcome Trust, Medical Research Council UK, the US National Institutes of Health (NIH), the European Union and the World Endometriosis Research Foundation. She also has scientific collaborations with, and received grant funding from, Bayer AG, MDNA Life Sciences, Roche Diagnostics and Volition Rx , and has served as a scientific consultant to AbbVie and Roche Diagnostics. She is secretary of the WES, the ESHRE Special Interest Group in Endometriosis and Endometrial Disorders, and of Wellbeing of Women; and she is chair of the WES Research Directions Working Group. C.M.B. is a member of the independent data monitoring group for a clinical endometriosis trial by ObsEva. He has received research grants from Bayer AG, MDNA Life Sciences, Volition Rx and Roche Diagnostics as well as from Wellbeing of Women, Medical Research Council UK, National Institutes of Health (US), the National Institute for Health Research (UK) and the European Union. He is the current chair of the Endometriosis Guideline Development Group of the ESHRE and was a co-opted member of the Endometriosis Guideline Group by the NICE

in the UK. K.K. has received grant funding from the Ministry of Education, Culture, Sports Science and Technology Japan, the Ministry of Health, Labour and Welfare Japan, Takeda Research Support and MSD. She has also served as a scientific consultant to Bayer AG. She is an ambassador of the WES and a member of the Guideline Development Group of the Japan Society of Obstetrics and Gynecology. S.A.M. has received grant funding from the NIH and the Marriott family foundations, and served as an advisor to and has scientific collaborations with AbbVie, Celmatix and Oratel Diagnostics. She is a treasurer of the WES, secretary of the WERF; Chair of the ASRM Endometriosis Special Interest Group, and member of the NIH Reproductive Medicine Network Data Safety and Monitoring Board. R.N.T. has received grant funding from Bayer AG, Ferring Research Institute, the NIH and Pfizer and served as a scientific consultant or advisor to AbbVie, Allergan, the NIH, ObsEva SA and the Population Council. He is the immediate past honorary secretary of the WES. P.V. has received grant funding from Bayer AG and Merck Serono and has served as a scientific consultant to Ferring Pharmaceuticals and Roche Diagnostics. She is a board member of the WES.

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Related links
WERF Endometriosis Phenome and Biobanking Harmonisation Project
https://endometriosisfoundation.org/ephect/

Box 1. Awareness and advocacy.

Despite its high prevalence in women and its effects on daily life (including economic burden), public and professional awareness of endometriosis remains poor[244]. Compounding this issue is the notion that women are reluctant to disclose their symptoms to avoid stigmatization[245]. However, most women diagnosed with endometriosis report a history of pain and seek health care at some point. In a large cross-sectional study of self-reported survey data, approximately two-thirds of these women were told by at least one physician at some stage that nothing was wrong with them; false assessment by gynaecologists was more frequent than by general practitioners (GPs)[246]. A large study of symptomatic women in 10 countries undergoing their first laparoscopy showed that the average time between symptom onset and first medical consultation was 1 year, with subsequent referral to a specialist taking another 6 years; women visited their GP on average seven times before referral[8]. Longer delays were associated with greater number of pelvic symptoms (chronic pelvic pain, dysmenorrhoea, dyspareunia and heavy periods).

The cause–effect relationship is clear: education programmes for the public and medical professionals are urgently needed to significantly boost research funding for this common, but widely neglected, condition[235]. Such programmes will lead to an improvement in the lives of millions of affected women and their partners and families[247]. Local and national support groups are actively helping to raise awareness through political lobbying and information events[248]. Some affected celebrities are now starting to use social and traditional media to openly declare their experiences with the condition, which may help symptomatic women to ask their physicians about the possibility of endometriosis. Although the ever-growing plethora of freely available information presents an enormous resource for patients with endometriosis, the general public, medical personnel and policy makers, the accuracy of content is unclear; any treatment suggestions should be based on robust evidence[249].

Box 2. Top ten research questions for endometriosis in the UK and Ireland

1. Can a cure be developed for endometriosis?
2. What causes endometriosis?
3. What are the most effective ways of educating health-care professionals throughout the health-care system, resulting in reduced time to diagnosis and improved treatment and care of women with endometriosis?
4. Is it possible to develop a non-invasive screening tool to aid the diagnosis of endometriosis?
5. What are the most effective ways of maximizing and/or maintaining fertility in women with confirmed or suspected endometriosis?
6. How can the diagnosis of endometriosis be improved?
7. What is the most effective way of managing the emotional and/or psychological and/or fatigue impact of living with endometriosis (including medical, non-medical and self-management methods)?
8. What are the outcomes and/or success rates for surgical or medical treatments that aim to cure or treat endometriosis, rather than manage it?
9. What is the most effective way of stopping endometriosis progressing and/or spreading to other organs (for example, after surgery)?
10. What are the most effective non-surgical ways of managing endometriosis-related pain and/or symptoms (including medical and non-medical methods)?

Identified by James Lind Alliance Priority Setting Initiative for Endometriosis[247], which aimed to identify the top 10 unanswered research questions through collaboration between patients, carers and clinicians, and use of standardized survey and focus group methodology[195].

Figure 1. Staging of endometriosis.

The revised American Fertility Society and American Society of Reproductive Medicine staging system of endometriosis is based on a points system that takes into account location, extent and depth of disease in relation to pelvic structures[6]. Organs such as the uterus, fallopian tubes and ovaries as well as structures that include the ovarian fossae (the shallow depression on the lateral wall of the pelvis in which the ovary lies), uterosacral ligaments, rectovaginal septum, Pouch of Douglas (the portion of the peritoneal cavity between the rectum and the posterior wall of the uterus and the uterosacral ligaments) and uterovesical fold (the shallow depression of the peritoneum between the uterus and bladder) are often affected. Lesion size can range from punctate spots millimetres in size to nodular structures of a few centimetres and ovarian cysts (endometrioma) the size of grapefruits. Stage I (minimal, 1–5 points) is usually comprised of few superficial endometriotic spots or adhesions. Stage II (mild, 6–15 points) can be few, solely deep peritoneal lesions or in combination with superficial lesions and filmy adhesions. Stage III (moderate, 16–40 points) often includes an endometrioma by itself or in combination with superficial or deep endometriosis and/or dense adhesions. Stage IV (severe, >40 points) is often characterized by all of the above, as well as bilateral ovarian endometrioma and/or dense adhesions that can lead to a partial or complete obliteration of the lesser or true pelvis (the structure that contains all the pelvic organs). Importantly, the severity of the disease according to this system does not correlate with the severity and location of symptoms.

Figure 2. Hormone signalling in endometriosis.

Oestradiol is a critical growth activating, angiogenic and mitogenic steroid hormone in endometriosis. The interaction between the stroma and the epithelium is critical for several endometrial functions including proliferation, migration and decidualization (the secretory transformation of endometrium). Paracrine factors are secreted by one compartment and can activate different signalling pathways of the other compartment. For example, in situ accumulation of oestradiol is mediated in part by reduced local epithelial levels of the catabolic enzyme HSD17B2, which converts oestradiol into oestrone. The actions of oestradiol are mediated via classic oestrogen receptors (ERα and ERβ) and also through the membrane-associated G-protein coupled oestrogen receptor (GPER). Examples of oestrogen-responsive genes upregulated in endometriosis are *GREB1*, *MYC* and *CCND1*. By contrast, progesterone receptor signalling (relayed through the progesterone receptors PRA and PRB) tends to be reduced in endometriosis and progesterone-regulated genes, such as *PAEP* (encoding glycodelin), *HSD17B2* and *TOB*, are underexpressed. Prostaglandin E_2 (PGE_2) signalling (which leads to steroidogenic factor-1 (SF1)-mediated upregulation of aromatase

expression) is also involved in maintaining the oestrogenic milieu. More controversial is that the gonadotropin follicle-stimulating hormone (FSH) might have direct effects on endometrial or endometriosis cells. COX2, cyclooxygenase 2; ERK, extracellular-signal-regulated kinase; JAK, Janus kinase; PI3K, phosphoinositide 3-kinase; PTGER2, Prostaglandin E2 receptor EP2 subtype; STAT3, signal transducer and activator of transcription-3.

Figure 3. Endometriosis models and mediators.

This schematic summarizes the known pathophysiological features of endometriosis. Hormone and cytokine mediators have been identified from animal studies and in vitro studies of primary cell and immortalized cell cultures. BDNF, brain-derived neurotrophic factor; C3', complement 3'; sICAM, soluble intercellular adhesion molecule; IGF-1, insulin-like growth factor-1; NK cell, natural killer cell; PDGF, platelet-derived growth factor; CCL5, CC-chemokine ligand 5; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor. Adapted from Ref [121]. **[PR: Permission has been applied for; check phrasing]**

Figure 4. Pelvic endometriosis.

Pelvic endometriosis is a heterogeneous condition with lesions presenting at different locations, with different sizes and colours and at various depths. 'Red' lesions are regarded as the most active and superficial endometriotic lesions, 'blue' or 'black' lesions are described as lying directly under the peritoneal surface with some blood deposits and 'white' lesions are mostly fibrotic and commonly involve deeper layers (that is, sub-peritoneal and subserosal layers) of the anatomy[169]. However, the course of disease progression remains unclear[248]. In addition, brown lesions have been described, as well as atypical or vesicular lesions, which occur more-frequently in adolescents. Endometrioma (ovarian endometriotic cysts) commonly have a fibrotic wall lined by a thin layer of stromal cells and, sometimes, glandular epithelial cells; these cysts often contain a thick brownish fluid of 'old' blood and dead cells, which is the origin of the term chocolate cysts that describes these lesions. Widespread superficial brown lesions (panel **a**). Vesicular or clear lesion (black arrow) and black lesion with some white fibrotic changes (white arrow; panel **b**). Left ovary with draining endometriotic (chocolate) cyst (white arrow; panel **c**). Superficial red lesions (black arrow) and black lesions (yellow arrow) are also present. A deep endometriotic white nodule (black arrow) close to the right utero-sacral ligament and mixed lesions in the Pouch of Douglas (white arrow; panel **d**).

Figure 5. Diagnosing endometriosis.

Transvaginal ultrasound with Doppler flow image of a left-sided endometrioma (panel **a**) with a typical unilocular ground-glass appearance and minimal vascularity. T1-weighted MRI scan of a female pelvis with bilateral endometrioma (arrows) behind the uterus (asterisk; panel **b**). Because of their close proximity this constellation is often called 'kissing ovaries'. MRI of the pelvis of another female patient with endometriosis (panel **c**). Surface posterior uterine haemosiderin (iron deposits, a blood breakdown product) is evident (yellow arrow) as is a fibrotic nodule (white arrow) extending through mesorectal fascia and fat with serosal tethering to the rectum (asterisk). Intra-operative photograph of a left-sided ovary (white arrow) with a ruptured endometrioma (panel **d**). The brown, thick fluid exiting the cyst is the origin of the common name 'chocolate cyst' for these structures. The uterus (asterisk) and normal right ovary (yellow arrow) are also shown. Haematoxylin and eosin-stained, paraffin embedded slide of an deep endometriosis lesion with glandular epithelial cells (black arrows) and stromal cells (yellow arrows; panel **e**); magnification ×200;

Figure 6. Simplified algorithm for management of endometriosis-associated infertility. According to guidelines of American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology[165,186,196], ovarian reserve, tubal function (by hysterosalpingography or hysterosalpingo contrast sonography) and partner semen should be first assessed in infertile women with suspected endometriosis. If all findings are normal and the woman is young, natural conception is possible and expectant management (watchful waiting) or superovulation and/or intrauterine insemination (SO/IUI) is recommended. Note that the UK National Institute for Health and Care Excellence (NICE) guideline does not recommend the routine use of IUI[195]. If the patient is of advanced reproductive age, or at least one parameter (ovarian reserve, tubal function and partner semen) is not normal, she should be scheduled for assisted reproductive technology (ART) unless she has severe pain, a large endometrioma (that might cause rupture or limit the oocyte retrieval) or suspected malignancy. Endometrioma can be detected and monitored by ultrasonography or MRI. Laparoscopy should be considered for patients in need of pain relief, cyst removal or histological diagnosis; however, adverse aspects of surgery (such as diminishing ovarian reserve) should be taken in account. Patients who failed to achieve natural conception after expectant management or SO/IUI for >6–12 months are also advised to receive ART. Prolonged hormonal downregulation prior to ART seems to benefit ART outcomes. As for all clinical guidelines, individual treatment decisions should always be made based on the patient's characteristics and desired outcomes.

Figure 7. Algorithm for management of endometriosis-associated pain. According to guidelines of American Society for Reproductive Medicine and European Society of Human Reproduction and

Embryology[165,184] and published expert opinions[102], women with endometriosis-associated pain should be asked for their desire to conceive. If this is immediate, patients are advised to try to conceive naturally, or to initiate fertility investigations and/or treatment (Fig. 6). If the desire to conceive is not immediate, medical therapy with combined oral contraceptives (COCs), progestin-only contraceptive pills (POPs) or progestins should commence as the first-line treatment. As second-line treatment, gonadotropin-releasing hormone (GnRH) agonists can also be used, ideally with 'add-back' therapy (addition of low levels of progestin and oestrogen) to reduce the hypo-oestrogenic adverse effects. If symptoms persist and/or adverse effects are experienced, conservative surgery that spares the ovaries and the uterus should be considered. Medication could be considered at the recurrence, or with the aim to prevent or delay symptom or disease recurrence. If the desire to conceive is no longer an issue and in case of symptom persistence and/or adverse effects from medical therapy, conservative or definitive surgery (hysterectomy and bilateral salpingo-oophorectomy) or GnRH agonists with add-back therapy could be attempted.

1952 **Table 1.** Genome-wide significant loci reported in genome-wide association studies of
1953 endometriosis.
1954

Chromosome	Locus[a]	Position (nearest gene)[b]	Risk/non-risk nucleotide	Effect size from largest study OR (95% CI); *P* value		Refs[c]
				All endometriosis	Stage III/IV	
1	rs12037376	22462111 (intronic, *WNT*)	A/G	1.16 (1.12–1.19); 8.9×10^{-17}	1.28 (1.18–1.36); 2.7×10^{-9}	51,56,250–252
2	rs11674184	11721535 (intronic, *GREB1*)	T/G	1.13 (1.10–1.15); 2.7×10^{-17}	1.18 (1.10–1.24); 1.9×10^{-6}	51,56
	rs77294520	11660955 (intronic, *GREB1*)	C/G	1.16 (1.11–1.21); 9.9×10^{-13}	1.29 (1.18–1.42); 1.5×10^{-8})	56
	rs6546324	67856490 (intronic, lincRNA AC007422.2)	A/C	1.08 (1.05–1.11); 3.0×10^{-8}	1.19 (1.11–1.26); 3.7×10^{-7}	51,56
	rs10167914	113563361 (regulatory region, 30Kb from *IL1A* and *IL1B*)	G/A	1.12 (1.08–1.15); 1.1×10^{-9}	1.15 (1.11–1.26); 7.6×10^{-5}	56
	rs1250241	216295312 (intronic, *FN1*)	T/A	1.06 (1.03–1.09); 6.2×10^{-5}	1.23 (1.15–1.30); 3.0×10^{-9}	56,251
	rs6757804	150779318 (intergenic, 2q23.3)	G/A	1.20 (1.13–1.29); 4.1×10^{-8}	Not tested	252e
4	rs1903068	56008477 (intergenic, 20Kb from *KDR*)	A/G	1.11 (1.07–1.13); 1.0×10^{-11}	1.33 (1.24–1.40); 2.6×10^{-15}	56,253
6	rs760794	19790560 (intronic, anti-sense RNA AL022068.1, 48Kb from *ID4*)	T/C	1.09 (1.06–1.12); 1.8×10^{-10}	1.17 (1.10–1.24); 8.7×10^{-7}	51,56
	rs1971256	151816011 (intronic, *CCDC170*)	C/T	1.09 (1.06–1.13); 3.7×10^{-8}	1.28 (1.19–1.36); 1.5×10^{-10}	56
	rs71575922	152554014 (intronic, *SYNE1*)	G/C	1.11 (1.07–1.15); 2.0×10^{-8}	1.35 (1.24–1.43); 2.9×10^{-12}	56
	rs2206949	152037556 (intronic, *ESR1*)	T/C	1.10 (1.06–1.14); 2.7×10^{-7}	1.09 (1.01–1.17); 0.025	56
	rs17803970	152553718 (intronic, *SYNE1*)	A/T	1.15 (1.09–1.21); 7.0×10^{-8}	1.35 (1.18–1.53); 4.8×10^{-6}	56
7	rs12700667	25901639 (intergenic, 7p15.2)	A/G	1.10 (1.07–1.13); 9.1×10^{-10}	1.28 (1.19–1.36); 6.7×10^{-11}	51,56
	rs74491657	46947633 (intronic, lincRNA AC004870.4)	G/A	1.08 (1.03–1.13); 1.2×10^{-3}	1.46 (1.28–1.59); 2.2×10^{-8}	56
9	rs1537377	22169700 (regulatory region, 48 Kb from *CDKN2B-AS1*)	C/T	1.09 (1.06–1.12); 1.3×10^{-10}	1.21 (1.13–1.27); 6.3×10^{-9}	51,56
	rs10757272	22088260 (intronic, *CDKN2B-AS1*)	C/T	1.07 (1.04–1.10); 2.6×10^{-7}	1.09 (1.02–1.16); 0.011	56
	rs1448792	22641633 (upstream, lincRNA1239)	G/A	1.08 (1.05–1.12); 1.8×10^{-7})	1.06 (0.98–1.14); 0.12	56
	rs10965235[d]	22115106 (intronic, *CDKN2B-AS1*)	T/C	1.44 (1.30–1.59); 5.6×10^{-12}	Not tested	250
	rs519664[e]	15246654 (intronic, *TTC39B*)	G/A	1.29 (1.19–1.39); 4.8×10^{-10}	1.47 (1.29–1.68); 1.4×10^{-8}	253
11	rs74485684	30242287 (intergenic, 25Kb from *FSHB*)	T/C	1.11 (1.07–1.15); 2.0×10^{-8}	1.26 (1.15–1.35); 7.8×10^{-7}	56
12	rs4762326	95668951 (intronic, *VEZT*)	T/C	1.08 (1.05–1.11); 2.2×10^{-9}	1.15 (1.08–1.21); 1.1×10^{-5}	51,56
14	rs10129516[e]	63133372 (intergenic, 10Kb from *PARP1P2*	T/C	3.10 (2.33–4.14); 1.4×10^{-10}	Not tested	254

[a]If multiple independent signals were observed at a single locus, the top associated SNP for each signal is provided. [b]Position from genome build GRCh37 (hg19); predicted consequence from http://www.ensembl.org. [c]Reported as genome-wide significant signals in following genome-wide association studies (GWAS): Japanese ancestry: 1,907 surgically and/or clinically diagnosed cases, 5,202 controls[250]; European ancestry: 3,194 surgically confirmed cases, 7,060 controls[251]; European and Japanese ancestry meta-analysis: 4,604 cases, 9,393 controls[51]; European ancestry: 2,019 surgically confirmed cases, 14,071 controls[252]; European ancestry in Iceland: 1,840 cases, 129,016 controls[253]; European and Japanese ancestry: 17,045 cases, 191,596 controls[56]; European ancestry: 171 surgically confirmed cases; 2,934 controls[254]. [d]Single-nucleotide polymorphism is polymorphic in Japanese, monomorphic in European ancestry populations; this locus has not been replicated in other GWAS studies. [e]Locus has not been replicated in other GWAS studies. lincRNA, long intergenic noncoding RNA; OR, odds ratio.

Table 2. Potential clinical applications for biomarkers in endometriosis.

Marker use	Application	Rule-out test[a]	Rule-in test[b]
Risk screening	Screening of either enriched (with increased risk, for example, family history) or general female population for risk of developing endometriosis	Unlikely feasible due to poor cost to benefit ratio	
Stratification of patients	Aiding decision making for further investigations and/or treatment	Negative test would avoid expensive and potentially harmful invasive tests and unnecessary treatment	Treatment could be initiated without further tests and decrease treatment delay
Treatment efficacy	Assessing efficacy of treatment of otherwise poorly accessible parameters (for example, lesion size)	Required by licensing authorities, would avoid costs and risks of second-look laparoscopies, would increase random assignment into trials and decrease drop-out rates	
Risk of recurrence (prognosis)	Estimating risk of recurrence after treatment or stratification of recurrently symptomatic patients	Negative test would give reassurance to patients and health care providers to minimize follow-up care	Positive test would increase awareness of potential for recurrence and reduce delay in investigation and treatment in symptomatic women
Assessment of best treatment option	Individualizing treatment	Not applicable	Would identify the best treatment option for women with highly suspected or proven endometriosis

[a]A reliable rule out test would need a high sensitivity; that is, a negative test would identify women without the disease.
[b]A consistent rule in test would need a high specificity; that is, if the test is positive a patient is highly likely to have endometriosis.

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