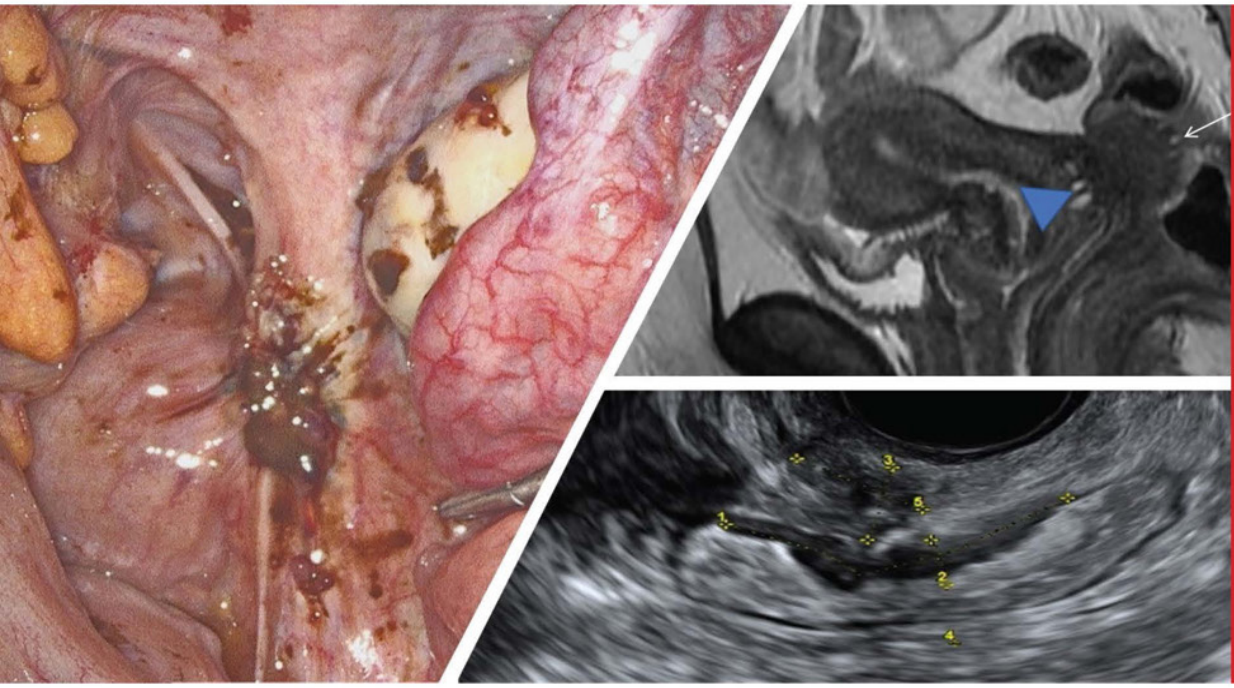
Endometriosis

Current Topics in Diagnosis and Management



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Preface

Endometriosis is one of the commonest causes of severe menstrual problems and pelvic pain, and is a major contributor to subfertility. It affects one in ten women, 176 million women worldwide. It takes a significant toll on sufferers' quality of life, leading to depression and breakdown in social relationships; affecting sufferers' employment and costing the UK economy up to £8.2 billion a year. Chronic pelvic pain also accounts for 10% of gynecological consultations. The conventional wisdom on the origin of the disease is based on a hypothesis from 100 years ago; its pathogenesis is poorly understood with significant crossover with other conditions. Its diagnosis as per current practice remains primarily surgical. As a result, women may suffer for a significant period of time before receiving diagnosis and treatment.

It is very clear that a major rethink is needed to shorten the time from a patient presenting with symptoms to diagnosis. In the UK, to help explore this step, two major specialist societies, the British Society for Gynaecological Endoscopy (BSGE) and the British Society for Gynaecological Imaging (BSGI), held a joint meeting in Surrey, UK, bringing together key opinion leaders in the field of imaging and endometriosis, to demystify the disease, chart a way forward and bring the management of endometriosis into the 21st century.

This book is dedicated to all those who suffer from endometriosis. It is aimed at healthcare professionals who work tirelessly to alleviate their patients' suffering by establishing a diagnosis and managing the problem to the highest professional standard. To achieve this, the authors propose new paradigms that will demystify the disease, speed up diagnosis and reduce the number of unnecessary procedures. The editors have brought together experts from across the specialties to provide the most up-to-date evidence-based approach, drawing upon their years of experience within the field of endometriosis.

This book addresses the challenges of endometriosis in three main domains. The first is dedicated to the origins of endometriosis and its prompt diagnosis. This requires a contemporary and radical understanding of disease evolution, the importance of history-taking and differential diagnosis and the pivotal role of imaging alongside the 'current' gold standard of surgical diagnosis. The second area is dedicated to medical and surgical challenges in the management of endometriosis. Finally, we address clinical service challenges, whether related to governance, standards and quality of service or training impacted by the COVID-19 pandemic. Special consideration is given to the need for a multidisciplinary approach to a multi-organ disease with complex management strategies. The overarching goal is to expedite diagnosis and offer the most appropriate evidence-based treatments.

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The editors acknowledge the attendees of the joint BSGI–BSGE meeting on endometriosis, who made it one of the best attended, and hope that those who did not attend will find this book a refreshing and illuminating read.

We would like to especially acknowledge the contributors to this book, who are recognized leaders in the field of endometriosis in their own subject areas.

The design of the cover was a joint effort of Nazar N. Amso and Saikat Banerjee.

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The Origins of Endometriosis

Jeremy Wright

Introduction

One of the axioms of medicine is that in order to successfully treat a disease, one needs to understand its etiology, epidemiology and demographics. A 2019 Google Scholar search on the etiology of endometriosis returned 27,000 results, while demographic prevalence returned 53,600 hits.

If one reviews treatment papers over the last ten years, the prevalence of endometriosis would seem to have slowly risen from 6% to around 10% (1, 2), but this probably represents greater diagnostic certainty with improved laparoscopic observation and biopsy confirmation, rather than an actual rise in the incidence of the disease. Most reports come from high-income countries suggesting that the rise in incidence as reported in case series is a feature of women recognizing that pelvic pain is not normal as much as the likelihood of the disease incidence rising possibly as a result of perinatal exposure to industrial toxins. As enthusiasm grows for laparoscopic intervention in middle-income countries, so the reports of endometriosis grow, but endometriosis remains largely ignored in low-income countries where facilities for diagnosis and treatment are lacking. There are, however, very few community studies of the prevalence of endometriosis (3, 4). These studies are ignored but do suggest that it is much less of a problem than the large number of case series being reported both in the literature and at conferences would suggest. Either way, the management of endometriosis has become predominantly surgical over the last decade, and as laparoscopic techniques have improved, surgery has become increasingly radical, especially since collaboration with colorectal surgeons has increased the complexity of the recommended surgery with bowel excision becoming increasingly common. There are, however, few long-term studies of the efficacy of this treatment that is increasingly based on the principles of extirpative cancer surgery.

In order to plan effective treatment and consider preventative strategies, either to stop the condition or to try and prevent the severe manifestations and improve fertility in women with the condition, it is important to understand how the disease develops.

Etiology of Endometriosis

An embryologic theory of origin of endometriosis held sway from the early 19th century to the 1920s when the theory of spread by retrograde menstrual flow promulgated by Sampson (5) became the most favored. Sampson, as a result of many observational studies, proposed that retrograde menstruation was the major cause of endometriosis, and this view holds considerable sway to this day (6). In order to produce superficial endometriosis, the endometrial cells in the menstrual reflux would have to implant on, proliferate, and then invade the peritoneum while deep endometriosis would require an additional motive for invasion, inflammation, and fibromuscular metaplasia. There is no *in vivo* evidence that refluxed endometrial cells attach to and then proliferate and invade any pelvic surface to establish endometriosis.

Sampson's theory has been further modified and expanded by Brosens, who has suggested that reflux menstruation in neonates, as estrogen is withdrawn may cause endometriotic peritoneal implants, though with little experimental or observational evidence (7).

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Brosens has postulated this in a number of papers and has quoted histochemical and cluster of differentiation (CD) marker expression studies in support of his theory (7–9). Some studies have shown marked differences in behavior of eutopic endometrium between women with endometriosis and those without, suggesting that the endometrium from women with endometriosis have a greater tendency to adhere (10). Others have shown greater fibroblast progeny in endometrial mesenchymal stem/stromal cells (11); however, none of these studies has demonstrated implantation occurring. The objection to fetal reflux menstruation as the origin of endometriosis is identical to the objection to reflux menstruation in adults: without photomicrographic evidence of the steps of initial attachment and proliferation/invasion, it cannot be accepted as proven, even after 9 decades.

The retrograde menstruation theory, either in neonates or in adults, could not explain why endometriosis only develops in a minority of those who have retrograde menstruation, as presence of menstrual blood in the abdominal cavity has been demonstrated in more than 90% of healthy adult individuals (12) and up to 60% of neonates in occult form (13). Although refluxed endometrial cells or tissue have not been shown to attach to pelvic surfaces, endometrial autografts are possible. Indeed, the initial studies on endometrial changes throughout the menstrual cycle were studied by implanting portions of uterus into the anterior chamber of the eye of Macaque monkeys.

In 1988, David Redwine (14) demonstrated endometriosis in the posterior cul-de-sac of an infant who died of sudden infant death syndrome (SIDS) and subsequently both Fujii and Signorili demonstrated endometriotic tissue in fetal specimens, showing that endometriosis can exist prior to menstruation (15–17).

Embryology of the Genital Tract and the Origin of Endometriosis

Genes control embryonic development. If endometriosis has an embryonic origin, then genes must control expression of the disease. The protean and somewhat predictable manifestations of endometriosis in males and females are easily explained as the result of interactions of an expanding number of interacting genes which can be viewed together as the Mulleriotic Genetic Ensemble.

Initially there are two embryonic germ layers, the ectoderm, which is destined to form the brain, and the endoderm, which is destined to form the lining of the alimentary canal. Endometriosis is an abnormality of the mesoderm. All described locations of endometriosis are of mesodermal origin. Muscles are mesoderm wherever they occur, including in the walls of cerebral vessels, which explains a mesodermal disease in an ectodermal organ.

Gastrulation – so-called because the primitive groove appears to be ingesting ectoderm delivered to it by a process resembling opposing conveyor belts – is the process by which the swallowed ectoderm is converted to mesoderm after passing through the primitive groove. Mesodermal cells enter and physically advance within the space between the ectoderm and endoderm. Mesoderm forms all tissue other than the brain between the epidermis and intestinal mucosa.

It is during gastrulation that all genetic instructions begin to become manifest. Mesodermal cells have been tagged with genetic instructions to become everything in the body, including endometriosis. Everything seems connected in some way to everything else. This is a familiar thought to endometriosis surgeons: endometriosis is associated with a range of gynecological, urinary, and gastrointestinal problems including structural defects, such as Mullerian dysgenesis, cervical stenosis, absence of a kidney, and other closely related diseases, such as adenomyosis, fibroids, and other displaced Mullerian tissue. An endometriosis world view alone is too confining. The explanations which Sampson's theory could never give are given in full by expressivity of the human genome.

The fetal gonads do not differentiate to male or female until about the seventh week of development. The primordial germ cells develop from the endodermal cells in the wall of the yolk sac close to the allantois and then migrate along the dorsal ridge of the hind gut to then populate the genital ridge. They then form cords of cells and subsequently become clusters, each surrounding primitive germ cells, which subsequently develop into oogonia surrounded by follicular cells. The significance of this is that they have the potential to develop into endometrial epithelium that is hormone-responsive and thus has the potential to develop into an endometriotic ovarian cyst.

The genitalia, irrespective of genetic sex, develop from 2 pairs of genetic ducts, the mesonephric ducts and the paramesonephric ducts, which are an invagination of the coelomic epithelium on the antero-lateral side of the genital ridge, running initially laterally to the paramesonephric ridge but crossing ventrally to fuse in the midline, initially with a septum but then fusing to form the uterine canal. It is the failure of this fusion that may lead to uterine anomalies, such as uterus didelphys and, the more common variants, such as a uterine septum. Caudally, the tubes fuse to form the Mullerian tubercle and enter the urogenital sinus alongside the paramesonephric ducts.

The fused ducts are then covered by a broad transverse peritoneal fold, the broad ligament of the uterus in the upper border of which lies the fallopian tube; and on the posterior surface lies the ovary. The broad ligament further divides the pelvis into the uterovesical pouch anteriorly and the uterorectal pouch posteriorly. Underneath, the peritoneal fold is a layer of mesenchyme that develops to form the myometrium.

There is then a solid evagination from the paramesonephric ducts and this proliferates vigorously to become the sinovaginal bulb or Mullerian tubercle, the growth producing a greater distance from the Mullerian bulb to the urogenital sinus. By about the fifth month of intrauterine development, this vaginal outgrowth is completely canalized, with wing-like expansions of the vagina around the end of the uterus (i.e. the developing cervix) and become the vaginal fornices. A thin tissue plate, the hymen, marks the separation of the vagina from the urogenital sinus. All of this is largely under genetic control. The genome of each individual seems to preordain what they will be born with.

Historical Studies of Endometriosis

From the middle of the 19th century, when the laws on post-mortem examination were relaxed, there was an explosion of interest in normal and pathological anatomy at the same time as pathological examination of fetuses, and animal models. It is this combination of growing embryological and pathological knowledge that allowed various theories to be developed, helped in no small part by the better tissue preparation for histological assessment.

Medical journals were in their infancy, but published reports were being circulated with cases presented at meetings, causing much discussion and controversy – some of it quite bitter but allowing for theories to be tested, then modified, and accepted or rejected.

One of the earliest papers suggesting that ovarian cysts can develop from Pfluger's tubules within the ovaries was published in France in 1878. Pfluger's cords are the early development of the germinal epithelium and eventually differentiate in follicular cells. Waldeyer, in about 1892, proposed the embryological origin of endometriosis from these tubules, the original reference is lost in time but was referenced again by Pozzi in the book *Treatise in Gynaecology: Medical and Surgical*, William Wood & Company, 1892 (18).

Reports of uterine adenomyosis of embryological origin, adenomyosis of the round ligament which was argued arose from a Muller's duct, and rectovaginal endometriosis also followed. These case reports and others were presented at meetings across Europe at the time and subject to much discussion. Von Recklinghausen argued strongly for a metanephric (Wolffian) origin of these nodules in 1860, and this remained the thinking until work by Kossman Meyer and by Cullen (in the US). This discussion is well described by Cuthbert Lockyer, an English gynecologist in his book *Fibroids and Allied Tumours* (19).

Two world wars and the chaos in Europe brought most research to a standstill. It was the work of Cullen who supported a Mullerian theory that gained prominence as he reported 'adenomyosis' at surgery in all the anatomical areas that are now recognized as common sites of deep invasive endometriosis. This was eventually superseded by the advocacy of retrograde menstruation by Sampson.

David Redwine was one of the first gynecologists to start seriously challenging the accepted orthodoxy on the origins of endometriosis (20). His theory of origin, 'Mulleriosis', published in 1988, was based on fundamental surgical observations and pelvic mapping. It is worth examining in some detail, as it is the basis for understanding the embryological origins of the disease. Mulleriosis proposed a larger world view than just endometriosis and is an over-arching term for the genetically programmed and seemingly related developmental defects that are often associated with the disease. Redwine seemingly

demonstrated a case of ectopic endometrium and stroma in the cul-de-sac of an infant who died of SIDS, showing that endometriosis could exist in an infant. But Mulleriosis was more than embryologically misplaced endometrium. Endometriosis is simply the most common and most symptomatic of the entire family of gynecologic pathologies – including peritoneal pockets – which result from the Mulleriotic Genetic Ensemble's effect on the differentiation and migration of mesodermal cells during organogenesis. For endometriosis, this Mulleriosis results in tracts of tissue that are laid down in the pelvic and extra-pelvic locations that are so familiar to endometriosis surgeons, but which can occur literally anywhere there is tissue of mesodermal origin. These tissue tracts may contain islands of endometriosis but also carry the ability to undergo metaplasia into more visually obvious endometriosis as well as forming the fibromuscular metaplasia of deep disease. Female pelvic organs form as cells sweep down the posterior coelomic cavity, which explains the favored location of endometriosis in the posterior pelvis. These tracts may remain undifferentiated until stimulated by estrogen. The tracts seem to be most common on or near the surface of the peritoneum but can extend more deeply depending on embryonic development. If surgery removes a tract completely in three dimensions, endometriosis can be cured at that site. Incomplete excision of an undifferentiated tract may result in a small amount of superficial disease within or around the excision area. Tracts may extend onto the abdominal wall or perineum, with the formation of endometriosis by metaplasia of such tracts aided by the growth factors of wound healing.

In 1988, Mulleriosis had an obvious but as yet undefined genetic basis with resultant abnormal differentiation and migration of Mullerian cells. Genetics can now offer some explanation and the Mulleriotic Genetic Ensemble can accept as many genes as can be identified. The repetitive patterns of disease which are so familiar to the endometriosis surgeon are well-explained as the inevitable physical manifestations of genetic action.

In modern times, the results of gene mapping have now identified the genes responsible for embryological development, and these begin with the homeobox or Hox genes 9, 10, 11, and 13 (21).

The complex genetics of endometriosis, involving many interacting genes beneath the Hox genes, have been reviewed recently by Zondervan et al. (22).

Bulun, in a review in the *New England Journal of Medicine* (23), has speculated that either genetic or environmental factors may alter the function of these genes, specifically that changes in DNA methylation may cause epigenetic aberrations and pathological expression of critical genes. Examples would include steroidogenic factor (SF1) and estrogen receptor β (ER-β) in progenitor cells predisposing to the development of endometriosis. Interested readers are directed to the original article.

There is now embryological evidence as reported by Fujii (17) using specific tissue stains, such as Ca-125, which showed that, in addition to the normal Mullerian development, there can be secondary deranged Mullerian pathways developing in the coelomic epithelium and the surrounding mesenchymal cells. These cells, or cell rests, can lie dormant until exposed to estrogen and then have the capacity to show Mullerian development into the endometrial gland and the surrounding stroma to manifest themselves as endometriosis. This would explain why the majority of endometriotic lesions lie along the pathway of the developing genital tract, specifically the commonly found utero-sacral and upper recto-vaginal septal disease, originating from cell rests in the coelomic endothelium, as proposed in Redwine's Mulleriosis theory.

As stated earlier, the development of both the primordial germ cells originates in the yolk sac and migrates to the developing genital ridge alongside the hindgut, which itself develops in the yolk sac before undergoing dextro-rotation to return to the abdominal cavity; these two simultaneous embryological processes would offer an explanation for the relatively rare manifestations of appendiceal, caecal, and diaphragmatic endometriosis.

Redwine's demonstration of areas of endometrial glands and stroma in 1 of 9 infants dying of SIDS was strong evidence that endometriotic tissue exists before puberty and could well be of embryonic origin. In a subsequent and detailed study, Signorili and colleagues (15, 16) looked for evidence of endometriosis in 36 aborted female fetuses using a variety of staining techniques including Ca-125 and estrogen receptors. They were able to demonstrate evidence of endometriosis in 4 fetuses (11%), which is similar to the quoted prevalence rate of 10%. All these areas of endometriosis lay in the path of the Mullerian tract, suggesting secondary Mullerian tracts. More recently, a left-sided ovarian endometrioma was diagnosed in a 35-week fetus and subsequently removed in neonatal life (24).

The convergence of these papers now strongly points to an embryological explanation for endometriosis, but the absence of spontaneous endometriosis in animals makes the development of an experimental model very difficult and access to fetal material is increasingly difficult. So, although the circumstantial evidence of an embryological explanation is strong, there is no, and may never be, proof of this.

The theory, however, raises some interesting and difficult conundrums in treatment. Young women remain fairly intractable to surgical treatment, as the cell rests of endometriotic tissue have yet to manifest themselves. Due to insufficient exposure to estrogen in younger women (severe lesions are more common in older women), only snapshots of disease are available. There are no longitudinal studies with repeated laparoscopies in the absence of treatment. Little is known about the natural history of the disease and its progression if untreated. If early disease can be identified, will treatments that promote menstrual suppression delay the onset of severe disease and maintain normal anatomy and fertility? Can preclinical cell rests of endometriotic tissue be identified and excised, thus preventing severe fibrosis – particularly fibrotic septal disease – and reduce the need for mutilating and morbid surgery in young women? Can adenomyosis, a potent cause for uterine extirpation (hysterectomy for pelvic pain and uterine bleeding abnormalities) be identified and treated early to reduce this loss?

Conclusion

Although the embryology of the genital tract is better understood and we now have a better understanding of the epigenetics of endometriosis, we may at last be closer to offering early interventions that may stop or delay the development of fibrotic and destructive endometriotic plaques. What is missing, however, is the ability to offer early and noninvasive tests both to identify the presence of endometriosis and, equally, to detect where these plaques originate before they become overtly pathological so that they can be targeted and extirpated.

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2

Endometriosis: Clinical Manifestation and Differential Diagnosis

Oudai Ali and Nazar N. Amso

Introduction

Endometriosis is an enigmatic disease that affects around 10–15% of the population. The diagnosis is usually delayed by an average of 6.7 years (1). Often the symptoms are vague and nonspecific. The range of presentation in endometriosis includes pain, dysmenorrhea, midcycle pain, dyspareunia, bowel symptoms, bladder symptoms, fatigue and problems with subfertility (2). It is interesting to study the correlation between the severity of the disease and the severity of the symptoms and the correlation between the disease distribution and the pattern of symptoms and signs. The manifestation does tend to represent the structures, or organs, involved (3); so far, the best positive predictive value in clinical diagnosis is the tender nodularity in the uterosacral ligament together with severe dysmenorrhea 95% (4).

Endometriosis is a chronic benign 'infiltrative' disease; therefore, it is expected that the symptoms will acquire further significance as management will focus on improving the quality of life and restoring and maintaining function. Excluding other pathologies will be repeated throughout the patient diagnostic pathway, as understanding the differential diagnosis of signs and symptoms will provide a more precise approach and reduce the patient lag until a confirmed diagnosis is reached.

How does an endometriosis patient present to the clinician?

Generally, there are two possible scenarios:

1. **The symptomatic patient**: Due to the chronic and scarring nature of the disease, the patient may not necessarily recognize the meaning of their symptoms until noticing an increasing pattern that crosses the threshold from self-managing to referral. Usually there is no routine program of awareness. The symptoms get evaluated or treated for some time before it is referred for specialized input. As the currently accepted gold standard for confirming the diagnosis is by laparoscopy, there may be a further lag before the diagnosis is finally established. Symptoms are wide-ranging and not exactly specific but generally share features of being cyclic and improve upon reducing estrogen.
2. **The asymptomatic patient**: Some patients with endometriosis are self-managing and have not been to see a clinician. It is not uncommon for endometriosis symptoms to abate in postmenopausal women who had suffered it during their reproductive years; then the symptoms reappear with other medical conditions needing investigation, and endometriosis or endometrioma make the list of differential diagnoses. On other occasions, it may be suspected as an incidental finding during pelvic examination for other reasons, like colposcopy or infertility, thus necessitating a referral for second opinion. Endometrioid ovarian carcinoma is an ovarian neoplasm that arises in endometriomas, which carry the risk of malignancy (5).

In summary, there are no pathognomonic features of endometriosis. There can be few symptoms or a cluster of symptoms; manifestation can evolve over time and tends to settle with menopause; and the symptoms may overlap with coexisting pathologies (6).

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Epidemiology of Endometriosis

Endometriosis affects 10–15% of women (7). There are many variables to consider in order to accurately appreciate its epidemiology. One should consider that endometriosis is diagnosed by laparoscopy, hence access to health resources to allow this confirmed diagnosis can be very variable but are critical. In the same context, while publications about endometriosis are variable worldwide, they generally reflect a disproportionate representation of data from North America compared to other countries. The rate of publications also increased steadily over the last 4 decades, reflecting advances in minimal access surgery and disease recognition. It is also difficult to state confidently that there are geographical variations, but reports of trends in endometriosis observe differences between ethnic groups and other variables, such as socioeconomic and nutritional status. Figure 2.1 demonstrates the wide variation in publication trends on endometriosis (8).

The area of each country was scaled in proportion to its total number of publications (a). Different colors encode numbers of endometriosis publications. The red dotted line (b) indicates the steep increase in the number of publications after 1990.

Age, Hormonal Status, Infertility, and Parity

The median age of presentation of endometriosis is 33.2 years. Prevalence increases from the age of 15 years, and the highest is around 44 years (9). This increase reflects the cumulative scarring nature of

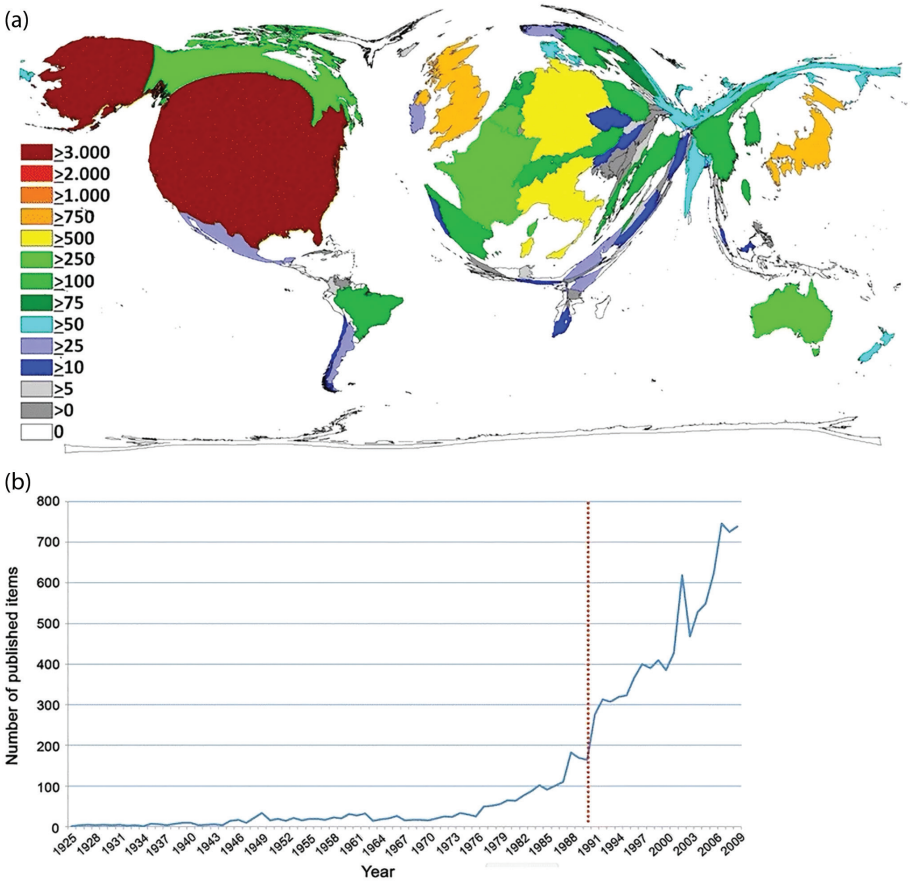

FIGURE 2.1 (a) Density-equalizing map of total endometriosis publications in each country. (b) Chronological evolution of endometriosis-related publications 1925–2009 (from ref 8 under Creative Commons license).

the disease that worsens over time and the delay in confirming the diagnosis because of the nonspecific symptoms. Prevalence of endometriosis in the general population increases from a nadir of under 1 per 1000 at ages 15–19; about 2 per 1000 at 20–24; 6 per 1000 at 25–29; just over 16 per 1000 at 35–39; and peaks at approximately 18 per 1000 at 40–44. It then declines (n = 6146) (9).

Endometriosis was found to occur more in women with earlier menarche and shorter cycles (10) and less with high parity and current use of contraception. Moreover, women with endometriosis seeking infertility treatment had fewer prior pregnancies, compared to women without endometriosis seeking infertility treatment (10).

The associations between a history of tubal ligation and endometriosis remain unclear (11).

Ethnicity

There are recent studies that indicate a higher incidence in white women than Asian or Black women. However, there may be differences in the presentation of the disease. An interesting epidemiological study from France indicates that there is correlation with blue and green eye color as well as white skin, and an association with congenital nevi (12). It is difficult to explain the reason, and there is no plausible biological explanation for these observations (13).

Socioeconomic, Environmental and Nutritional Status

Evidence in the literature showed that endometriosis is reported more by urban residents and affluent people. There is some suggestion that endometriosis affects people who have higher professional performance. It is useful to know some positive and negative associations with endometriosis. While it has been associated with lower body mass index, the difficulty in assessing and diagnosing endometriosis in women with high body mass index must be accounted for. Consistently, there is a positive association of height with endometriosis (14). In a study from Sweden of 172 endometriosis subjects, it was noted that women with endometriosis consumed less alcohol, did fewer exercise and leisure activities and had less asthma. However, increased alcohol consumption was found to have a positive association with endometriosis (15). Increased caffeine consumption was found to be a risk factor in an old study (16), while smoking was found to have a negative association with endometriosis in many studies (10).

There are studies into some modifiable risk factors, and it seems that consuming more fish and omega 3 oil is associated with reducing the risk of endometriosis (17).

Association with Medical Diseases and Other Risk Factors

A positive association was reported with having irritable bowel syndrome and being on antidepressants. Also, thyroid receptor hormone antibodies were more elevated in endometriosis, suggesting a link with autoimmune disorders (18).

There is also an increased likelihood of association with cancer. There is a clear association between endometriosis and gastrointestinal and immunological diseases, ovarian and other gynecological cancers, and thyroid cancer (19). Endometriosis has been associated with other autoimmune diseases and allergies (20).

Family History

There is a tenfold increased risk of endometriosis between first-degree relatives (21). This may indicate a genetic predisposition to the disease. In a multivariate analysis with logistic regression of 148 patients, a positive family history of endometriosis was the only variable independently associated with endometrioma recurrence following laparoscopic removal (22).

Stronger evidence of heritability is provided by twin studies, which have shown higher concordance in monozygotic twins compared with dizygotic twins, a finding less likely to be affected by selection biases operating on diagnostic opportunity (23).

The largest twin study, among 3096 Australian female twins, estimated the heritable component of endometriosis at 51% (24). Women with endometriosis are more likely to present with a family history of cancer (10).

Clinical Presentation of Endometriosis

The most common complaints among patients with endometriosis are chronic pelvic pain for more than 6 months and infertility. It is important to assess how the disease impacts the quality of life and productivity by using standardized scoring systems, like the Endometriosis Health Profile, a Health Related Quality of Life patient self-report PRO (25). More likely indicators of successful diagnosis of endometriosis are positive family history, previous pelvic surgery, history of ovarian cysts and ovarian pain (26). Although the definitive diagnosis is made by laparoscopy there is usually a delay until surgical diagnosis. Despite surgery being increasingly simplified and standardized, it still carries some risk, and it is not easily and immediately accessible. Therefore, it is important to continuously improve the clinical and imaging diagnosis to reduce the delay. In that context, endometriosis centers created a role, the endometriosis specialist nurse.

Symptomatology

In assessing symptomatology, a risk assessment of the possibility of pregnancy or related conditions should always be exercised. It is crucially important to take a thorough and structured general as well as specific gynecology and obstetrics history, including that for sexually transmitted infections.

Pain

- Pain is a distressing feeling often caused by intense or damaging stimuli. The International Association for the Study of Pain's widely used definition of **pain** is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage' (27). In endometriosis, pain is the main cause of distress and the need for referral for assessment, medication, and intervention. Chronic pelvic pain in women is defined as persistent, noncyclic pain perceived to be in structures related to the pelvis and lasting more than six months (27). This pain is mostly chronic; but it is also occasionally acute as in a cyst rupture after years of self-managing chronic pelvic pain. In order to understand the differential diagnosis of pain in endometriosis, it is worth understanding the types of chronic pain in general:
  1. Chronic primary pain (chronic pain as a disease in itself)
  2. Chronic secondary pain (chronic pain syndromes, ICD 10)

Chronic secondary pain includes the following:

1. Chronic cancer-related pain
2. Chronic postsurgical or post-traumatic pain
3. Chronic neuropathic pain
4. Chronic secondary headache or orofacial pain
5. Chronic secondary visceral pain
6. Chronic secondary musculoskeletal pain

Chronic pelvic pain in females secondary to endometriosis is classified under Chronic Visceral Pain. So a clear understanding of this system will help to precisely define the pain symptom in endometriosis and clinically exclude other sources. Pain alone in endometriosis can be an insufficient indicator for diagnosis

and can be described as persistent, intermittent, cyclic, or progressive. It is usually described as severe, worse around periods and generally improves on the pill or suppressing the estrogen status. Interestingly, the response to nonsteroidal anti-inflammatory drugs (NSAIDs) tends to be better in patients without endometriosis; and, in those with endometriosis, NSAIDs become less effective over time (28). Studying the type of pain will add to the accuracy of the assessment as well as pain mapping (29).

Dysmenorrhea

Secondary dysmenorrhea refers to painful menses due to pelvic pathology or a recognized medical condition. Endometriosis is the leading cause of secondary dysmenorrhea in adolescents. Endometriosis should be considered in patients with persistent, clinically significant dysmenorrhea despite treatment with hormonal agents and NSAIDs. It is the most common symptom of endometriosis. A Swedish Study in 2017 (n = 26898) indicated that sensitivity of dysmenorrhea in endometriosis is moderately accurate with the diagnosis of endometriosis (30).

Dyspareunia

Dyspareunia is a complex and sensitive symptom to analyze and requires a skillful clinical approach and attention to the fact it can indeed be multifactorial.

Four types of deep dyspareunia are proposed in women with endometriosis by Yong et al. (2017) upon reviewing the penetrative disorder in endometriosis (31):

- Type I is directly due to endometriosis.
- Type II is related to a comorbid condition.
- Type III in which genito-pelvic pain penetration disorder is primary.
- Type IV that is secondary to a combination of types I to III.

Deep contact dyspareunia has low sensitivity but high specificity for endometriosis (31).

Acute Pain

In the background of chronic pelvic pain (CPP), women may experience exacerbation usually around the menstrual phase or midcycle. Acute pain can be associated with complications of endometrioma (rupture, infection, and hemorrhage into a cyst). Another rare complication of endometriosis is acute bowel obstruction (32). In acute pain it is important to promptly initiate early diagnostic tests, e.g., blood and imaging, to exclude serious possibilities associated with acute abdomen issues, like ectopic pregnancy, ovarian torsion or pelvic inflammatory disease that may require early or urgent intervention.

Midcycle Pain

This symptom is not fully qualified in searching the recent literature and mostly is considered a normal phenomenon called ‘Mittelschmerz’. The pain is midcycle, acute, moderate, unilateral, and self-resolving. New symptoms or an increasing pattern of midcycle pain are noted in endometriosis. It is a trigger to exclude other pathologies, like pelvic inflammatory disease and pelvic scarring for any reason. A therapeutic trial with oral contraceptives is justified (33).

Bladder Symptoms, Dysuria, Cyclic Haematuria, Hydronephrosis

There is typically low incidence of urinary symptoms in endometriosis and tendency to overlap with urological comorbidities like chronic bladder pain or interstitial cystitis.

In 2017 Cavaco-Gomes et al. reviewed 327 studies including a total of 700 patients with ureteral endometriosis; preoperative evidence of significant hydroureter/hydronephrosis was found in 324 of 671

patients (48.3%). Ureteral endometriosis was more frequent on the left side (53.6%) and was bilateral in 10.6% of cases. Concomitant ureteral and bladder endometriosis was described in 19.8% of patients. Most patients presented with other pain symptoms but nonspecific to the urinary tract (34).

Endometriosis of the urinary tract needs a high index of suspicion especially if there is previous cesarean section or complex surgical history (35). The symptoms of cyclic haematuria are rarely reported in the literature. In a study published in 2017 (n = 473), dysuria was found in surgically confirmed endometriosis (22.6%) compared to 11.0% in a normal pelvis ($p < 0.03$) (29).

In summary, endometriosis of the urinary system is a silent disease and is not at the top of the list of the differential diagnoses in urology.

Bowel Symptoms, Dyschezia, Bloating, Diarrhea and Bowel Obstruction

Involvement of the posterior compartment is more frequent than the anterior compartment, and rectovaginal scarring is a severe manifestation of endometriosis. The rate of gastrointestinal involvement in endometriosis is quite variable in the literature (3.8–37%) (36). The sigmoid colon is the most common site, followed by the rectum, ileum, appendix, and caecum. The rectum and the sigmoid are the most common locations in 95% of the patients. Appendiceal endometriosis is found in 5–20% of patients (37). Small intestine lesions mostly involve the terminal ileum and account for up to 5–16% of gastrointestinal endometriosis cases. Extremely rare locations that have been reported include the gallbladder, the Meckel diverticulum, stomach, and endometriotic cysts of the pancreas and liver. Twenty-one cases of cystic liver masses were diagnosed as hepatic endometriomas. Gall bladder endometriosis is exceptionally rare (38). Very severe rectovaginal endometriosis can cause difficulty in bowel emptying and, rarely, can present as an obstruction.

Fuldeore and Soliman (2017), in a cross-sectional online survey (n = 48,020) of women already informed of an endometriosis diagnosis, reported that bowel symptoms, such as constipation, bloating and diarrhea were increased by OR, 1.9 (95% CI, 1.7–2.2) (39).

In summary, there is wide variability of bowel symptoms reflecting disease severity and distribution. It overlaps with a long list of differential diagnoses that include commonly irritable bowel syndrome and inflammatory bowel disease. Women are often directed to the endoscopy department to exclude bowel disease. In an analysis of 360 cases conducted in 2008, the severity of dyschezia in endometriosis does correlate with the degree of narrowing (40).

Fatigue

Fatigue is a lingering tiredness that is constant and limits normal activity. It results in unexplained, persistent, and relapsing exhaustion; systemic exertion intolerance disease (SEID). Chronic fatigue syndrome (CFS) is of long duration and causes a drop in functionality from pre-illness activities and unrefreshing sleep. The cause is unknown.

In a study of CFS and endometriosis including 36 women, it was found more than a third of women reported endometriosis as a comorbid condition (41).

A study published in 2018 on 1120 women, 560 of them with endometriosis, showed that frequent fatigue was experienced by most women diagnosed with endometriosis. Fatigue in endometriosis was associated with insomnia, depression, pain, and occupational stress but was independent of age, time since first diagnosis and stage of the disease (2).

Infertility

In the assessment of cases suspected of or confirmed with endometriosis, attention to fertility aspirations or difficulty is especially important, as it can modify the management.

In a study published in 2008 (n = 1285), it was noted that fertility issues were self-reported in 70.6% of cases with endometriosis, while in the general population, 25.2% ($p < 0.001$) reported these issues (42). In a 2008 national case-controlled study comprising women with endometriosis (n = 5540) and matched controls (n = 21,239) it was found that infertility/subfertility was six times higher; OR 6.2, confidence interval (5.4–7.1) (6).

Unusual Sites (Abdominal Wall, Thorax)

Endometriosis has been reported in unusual sites like abdominal wall scars, umbilicus, episiotomy scars (43), in the chest and pericardium, the brain and the eye (44). It was even reported in muscles and invading pelvic nerves, causing neurological symptoms (45). The only site where endometriosis was not reported is the spleen (43, 46).

The abdominal wall is the most common location of the extra-pelvic sites. This is mostly in association with cesarean section scars and causes diagnostic difficulty as the symptoms are not necessarily cyclic (47). Soft tissue high-frequency ultrasound helps in localization as well as MRI, but the confirmation is through histology after surgical excision and subsequent symptom improvement.

The presence of endometriotic nodules on the chest cavity can give cyclic symptoms (catamenial). These can be catamenial hemithorax, hemoptysis in endometriotic lung nodules and catamenial chest pain (48).

Abnormal Bleeding

Ballard and colleagues observed more reporting of menorrhagia in cases of endometriosis diagnosis over the non-endometrial population OR, 5.0 (95% CI, 4.6–5.5) (6).

In a recent cross-sectional survey of 50,000 women concluded in 2014, Heitmann et al. noted menstrual abnormalities were worse in cases with endometriosis than non-endometriosis, including heavy bleeding, irregular bleeding, passing clots, and irregular cycles. Premenstrual spotting also correlates with endometriosis in infertile women (49). Although these disorders are common in women with endometriosis, ironically, most women with endometriosis have regular cycles without abnormal bleeding (50). Menstrual irregularity is reported by only 10–20% of the patients. This symptom has a big list of differential diagnoses and could be mostly managed even improved through conservative measures like the Mirena coil.

The rare endometriosis presenting on the cervix can be a cause of postcoital bleeding (51).

Findings on Clinical Examination/Physical Signs

Understanding the range of presenting complaints and their significance will help make sense of the findings of the clinical examination as most of the cases with endometriosis could have a normal clinical examination (52). This starts with the general observation of the patient, checking for conditions like anemia, fatigue, depression, and low mood associated with chronic pain. Vital signs evaluation including temperature will be important in cases of suspected pelvic infections. Even observing the gait will provide important information, such as whether there is an indication of a musculoskeletal reason for pain rather than one referring to the pelvis.

Assessing the general physical status will also add to the preoperative assessment, determining the need for surgical management and how issues like extreme body mass index, cardiovascular and respiratory system problems and hypertension, smoking, or asthma will impact the outcome.

It is important to maximize the information gained in that encounter with the patient and clinical examination has a positive impact on the doctor–patient relationship. Omitting or rushing the examination is a frequent root cause of missed, delayed or wrong diagnosis. It is important to follow the guidelines for intimate examination and be aware if there is a special need as in cases of learning disability and the noticeably young or frail patient. Colposcopy, office hysteroscopy, proctoscopy and urine testing are included here as they are considered examination adjuncts rather than specific investigations.

Abdominal Examination

The value of information gained from abdominal examination can be useful if assessing presence of tenderness, hernia, surgical scars and abdominopelvic masses. More often ultrasound, integrated with the clinical assessment, enhances the amount of information obtained.

Pelvic Examination

Care and patience must be taken during pelvic assessment as it may trigger pain in women with severe chronic pain. Scarring in the pouch of Douglas may also shorten the vagina and limit easy full opening of the speculum.

Assessment of the external genitalia does not particularly have any pathognomonic features of endometriosis except in the rare case reports of endometriosis at the perineum or the episiotomy scar. However, referred pain from pelvic endometriosis to the labia has been reported in the literature and thus, endometriosis should be considered in the differential diagnosis of perineal and vaginal pain (53). Abnormally heightened sensitivity to pain is another factor that should be considered during clinical examination (29). Visual assessment of the vaginal wall, particularly the posterior fornix, may reveal the presence of endometriosis, a pathognomonic finding. One should exclude congenital vaginal cysts which are less tender. Examination of the cervix may show the presence of rare cases of endometrioma of the cervix, but it will also be part of the diagnostic workup to eliminate other abnormalities or coexisting pathology, like pelvic inflammatory disease. The same is valid for noting any abnormal vaginal discharge.

Digital examination may demonstrate tenderness, fixation of pelvic structures, nodularity of the uterosacral ligaments or pelvic masses. Marasinghe et al. in 2014 found that in 110 patients with laparoscopically confirmed endometriosis, the vaginal examination has an 83% rate of accuracy (54).

Ultrasound in expert hands improves the accuracy of the vaginal examination (5). Ultrasound is not routinely available at primary care or even at the first consultation in the secondary care, then necessitating skilled pelvic examination. A completely normal examination may encourage more conservative measures, while significant findings will drive further investigations and interventions or even referral to a specialist center.

The Value of Swabs, Smears, and Specialized Cervical Assessment by Colposcopy in Endometriosis

So far, there are no reports in the literature demonstrating the value of routine use of colposcopy in endometriosis. It offers a magnified view with possibility of photo documentation and the ease of taking samples or biopsies. There is no recommendation to refer suspected cases of endometriosis for colposcopy unless there is a concern in the history about postcoital bleeding, abnormal cytology or abnormal-looking cervix on examination. Assessing the smear history is a routine part of the history taking. Taking swabs is a good practice in assessing the health of the lower genital tract and should be offered to exclude the possibility of sexually transmitted infections that can be an important part of the differential diagnosis.

The Value of Office or Outpatient Hysteroscopy and Endometrial Sampling

Increasingly, hysteroscopy is becoming more integrated as a one-stop diagnostic test. In the differential diagnosis of abnormal uterine bleeding, this diagnostic can immediately assess the quality of the endometrium, excluding focal lesions like fibroids or polyps. It will allow endometrial sampling. Although, routine endometrial sampling is not necessarily required in every case of suspected endometriosis.

The vaginoscopy technique can allow visualization of vaginal endometriotic nodules, however the office or outpatient hysteroscopy is not a routine recommendation in the clinical evaluation but rather a useful aid in selected cases, like in women with fertility issues or excluding endometrial cancer following the discovery of endometrial thickening on ultrasound (56).

The Value of Rectal Examination, Proctoscopy and Stool Studies

Rectal examination is usually the standard routine from the colorectal perspective if a woman with suspected endometriosis with dyschezia sees a surgeon first. In that regard, it may detect a low nodule of endometriosis that can mimic rectal carcinoma.

In general, digital rectal examination in primary care for palpable rectal tumor is an inaccurate procedure and a poor predictor for palpable rectal tumor (57).

From the gynecologist's perspective, most of the information will be gained by vaginal examination. Simultaneous vaginal and rectal examination would enable digital palpation and assessment of the high rectovaginal septum for nodularity and tenderness. Digital rectal examination may be the only way to assess the pelvis for endometriosis in *virgo intacta* with patient consent.

Doing rectovaginal examination on 140 cases under anesthesia before proceeding to laparoscopy or laparotomy, where the indication was masked, it was shown that rectovaginal examination has marked limitations despite the controlled circumstances of the operating room including general anesthesia, an empty bladder and ideal patient positioning. The specificity of the rectal examination is high, but the sensitivity of the rectovaginal examination is low (58).

The use of proctoscopy is rare in the gynecological setting. In a surgical setting it is rather routine and commonly used to assess for hemorrhoids, check the mucosa of the lower rectum and take a biopsy that may help in cases of inflammatory bowel disease. Endometriosis causes constricting scarring rather than affecting the mucosa, and it is usually at a higher level in the rectum and sigmoid colon.

Stool studies are not a routine request in the gynecology clinic, although they can be useful in checking for blood abnormalities, infection, and inflammation.

It is worth considering a referral for colonoscopy study in cases of suspected differential diagnosis of a bowel malignancy or inflammatory condition.

The Value of Urine Testing and Office Cystoscopy

There is no reported value for urine testing specific to endometriosis. It is good practice to do urine testing based on the history and examination in the presence of painful bladder or renal or suprapubic tenderness. Office cystoscopy is not a routine part of a generic gynecology clinic; in the urological department, cystoscopy can demonstrate bladder abnormalities without waiting for a procedure under anesthesia.

Nodules that partially affect the muscular layer have normal cystoscopy findings, thereby obviating the need for this procedure. Bladder endometriosis nodules are commonly associated with other forms of endometriosis and do not usually affect the ureteral meatus (59).

Differential Diagnosis of the Signs and Symptoms of Endometriosis

Although other gynecologic pathologies such as uterine fibroids can present with pain, it is noted that women with surgically proven endometriosis do have worse cyclic and chronic pain than women with normal pelvis or other pathology (29). Qualifying the pain further using the short-form McGill Pain Questionnaire can be helpful in the differential diagnosis. Droz, in a retrospective cohort study of women with chronic pelvic pain (n = 331), found that the most common diagnoses were endometriosis, interstitial cystitis and painful bladder syndrome and irritable bowel syndrome (Figure 2.2). Seventy-one percent of the patients had more than one diagnosis. Relative risks for pain descriptors as diagnostic tools for specific diagnoses were most significant, with 'cramping' for endometriosis, 'cramping' for interstitial cystitis and painful bladder syndrome, 'sickening' for irritable bowel syndrome and 'aching' for abdominal myofascial pain syndrome (60).

Gynecological Pathologies (or Conditions)

The gynecologist has the best perspective among other specialties in assessing and excluding other gynecological reasons in the differential diagnosis of endometriosis for the signs and symptoms, their associations and recruiting further diagnostic tests to the next steps in the management. In the diagnostic workup, exclusion of pregnancy and related problems will be always the priority.

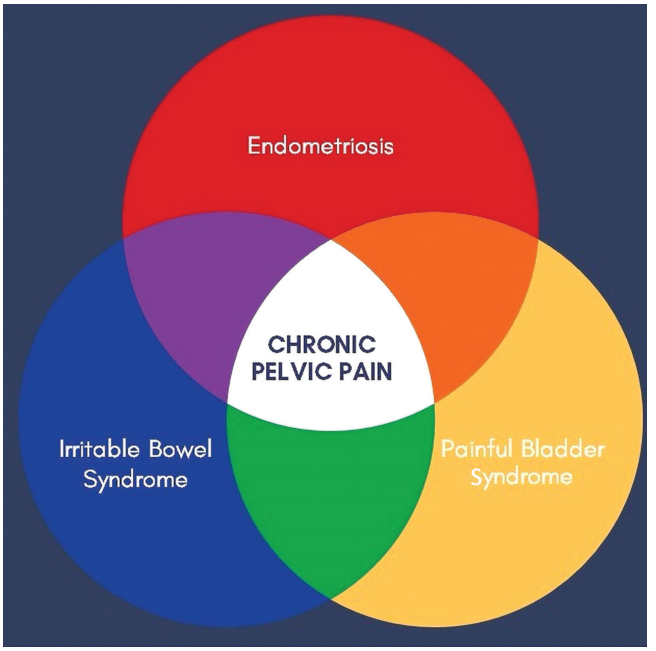

FIGURE 2.2 With chronic pelvis pain, there is an overlap of symptoms between interstitial cystitis, irritable bowel syndrome, and endometriosis.

Adenomyosis

It is important to regard adenomyosis as a separate entity from endometriosis even though it causes similar symptoms of pain, dysfunctional bleeding, dyspareunia and has a negative impact on fertility (61). It is difficult to attribute a specific pathognomonic symptom to adenomyosis due to overlap of symptoms with other conditions, like fibroids and endometriosis; and it is unclear in the literature how many are completely asymptomatic (62). Many patients with adenomyosis suffer *troublesome* heavy menstrual bleeding and dysmenorrhea with tender bulky uterus on examination. Ultrasound assessment including 3D is characteristically helpful in its classification as well as the MRI. It is important to note that sonographic features of adenomyosis are highly prevalent in women undergoing surgery for endometriosis (63).

Pelvic Congestion Syndrome

Pelvic Congestion Syndrome is frustratingly a difficult diagnosis due to controversial diagnostic methods and poor understanding of its etiology, and there are no specific diagnostic criteria. The symptoms of this condition can greatly overlap with many pelvic conditions, and the syndrome can be seen more in multiparous and overweight women, as well as present secondary to vascular anomalies and previous pelvic thrombotic events (55). Attention to the presence of varicosities and hemorrhoids can be a clue as well as worsening of premenstrual symptoms, after long standing, fatigue and after intercourse. Ultrasound assessment will show the diameter of the uterine vessels more than 8 mm, and Doppler studies will observe *slow* blood flow, reversed direction and the communicating pattern of the arcuate veins (64).

Pelvic Inflammatory Disease, Pelvic Adhesions

One of the main priorities in suspected endometriosis is to evaluate and exclude sexually transmitted infections. It is good practice to offer swabs and assess any abnormal discharge. Attention to sexual

history may raise the possibility of Chronic Pelvic Inflammatory Disease (PID) and presence of pelvic adhesions. Inflammatory markers and Ca125 normally settle down on resolution of the acute phase.

A retrospective cohort study of 141,460 women demonstrated that patients with PID had a three-fold increase in the risk of developing endometriosis (65). Dysbiosis and inflammation may be the underlying process in both PID and endometriosis contributing to adhesions and scarring.

Imaging helps in the diagnostic discrimination towards PID, rather than endometriosis, by indicating the presence of hydrosalpinx with cogwheel sign. Ovarian abscess has heterogeneous echogenicity on ultrasound and demonstrates different signal intensities on MRI. CT is helpful mostly in the acute phase particularly to exclude other surgical reasons for peritonitis (66).

Chronic Post-Surgical Pain Syndrome

Pain that lasts for more than three months after surgical intervention is a common unwanted adverse event which can cause functional limitation and psychological distress to patients (67). Post-surgical pain in gynecology is often seen after ablation, laparotomy or laparoscopy. In addition, endometriosis should be considered in the differential diagnosis when chronic pain persists for over 12 months in 11% of women following a cesarean section (68). Persistence and recurrence rates of endometriosis after surgery are reported to be 21.5% within 2 years, and 40–50% after 5 years (69). This should be a strong motive to not only rely on surgery to manage endometriosis but to adopt a multimodal strategy.

Fibroids

Fibroids and endometriosis often coexist, and each independently has a negative impact on fertility. In the fibroid group of one study, 19.6% had endometriosis, and in the endometriosis group of the study, 25.8% had fibroids (70). Another study concluded that an overwhelming majority of patients with symptomatic fibroids were also diagnosed with endometriosis. Overlooking the concomitant diagnosis of endometriosis in these women may lead to suboptimal treatment of the patients (71). In practical terms, this can be important if the management priorities are focused on one more than the other, as the therapeutic distinction to treat fibroids, such as with interventional radiology, does not improve endometriosis; and likewise, the combined pill or progestins often used in endometriosis do not help fibroid symptoms. Fibroids are more likely to cause pressure symptoms dependent on their location, number, and size.

Pelvic Mass Differential Diagnosis

The finding of a pelvic mass will raise alarm bells for the clinician and the patient. Ovarian endometriomas occur in 17–44% of patients with endometriosis and account for 35% of all benign ovarian cysts (72). One should notice the persistent nature of the cyst and the evolution of further symptoms. Endometriomas tend to be fixed and tender, and bimanual examination often reveals nodularity and fixation of pelvic structures. Pelvic ultrasound assessment is the mainstay for characterizing a pelvic mass. Pattern recognition and diagnostic models together with the Ca125 may help the differential diagnosis. In postmenopausal women, the priority is to exclude malignancy. Complex adnexal masses may require further imaging modalities and a multidisciplinary approach. The Royal College of Obstetricians and Gynecologists (RCOG) guidelines do not recommend doing Ca125 in endometriosis diagnosis or follow-up.

Non-Gynecological Pathologies (or Conditions)

It is unclear in the literature if the non-gynecologist would consider endometriosis first in the differential diagnosis when assessing symptoms of irritable bowel, painful bladder or chronic fatigue syndromes.