MINERVA OBSTETRICS and GYNECOLOGY

VOLUME 73 · No. 5 · OCTOBER 2021

EDIZIONI · MINERVA · MEDICA

PUBBLICAZIONE PERIODICA BIMESTRALE - POSTE ITALIANE S.P.A. - SPED. IN A.P.D.L. 353/2003 (CONV. IN L. 27/02/2004 N° 46) ART. 1, COMMA 1, DCB/CN - ISSN 2724-606X TAXE PERÇUE

© 2021 EDIZIONI MINERVA MEDICA
Online version at http://www.minervamedica.it

Minerva Obstetrics and Gynecology 2021 October;73:(5):588-605
DOI: 10.23736/S2724-606X.21.04864-8

REVIEW

ENDOMETRIOSIS AND PELVIC PAIN

Surgical management of endometriosis-associated pain

Philippe R. KONINCKX [1, 2] *, Anastasia USSIA [3, 4], Maria G. PORPORA [5], Mario MALZONI [6], Leila ADAMYAN [7, 8], Arnaud WATTIEZ [1, 9]

[1]Latifa Hospital, Dubai, United Arab Emirates; [2]Department of Obstetrics and Gynecology, KULeuven, Leuven, Belgium; [3]Sacred Heart Catholic University, Rome, Italy; [4]Villa Del Rosario Clinic, Rome, Italy; [5]Department of Maternal and Child Health and Urology, Sapienza University, Rome, Italy; [6]Endoscopica Malzoni, Center for Advanced Pelvic Surgery, Avellino, Italy; [7]Department of Operative Gynecology, V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology (FSBI), Ministry of Healthcare of the Russian Federation, Moscow, Russia; [8]Department of Reproductive Medicine and Surgery, Moscow State University of Medicine and Dentistry, Moscow, Russia; [9]Department of Obstetrics and Gynaecology, University of Strasbourg, Strasbourg, France

*Corresponding author: Philippe R. Koninckx, Department of Obstetrics and Gynecology, KULeuven, Vuilenbos 2, 3360 Bierbeek, Belgium. E-mail: pkoninckx@gmail.com

ABSTRACT

Endometriosis and pelvic pain are associated. However, only half of the subtle and typical, and not all cystic and deep lesions are painful. The mechanism of the pain is explained by cyclical trauma and repair, an inflammatory reaction, activation of nociceptors up to 2.7 cm distance, painful adhesions and neural infiltration. The relationship between the severity of lesions and pain is variable. Diagnosis of the many causes requires laparoscopy and expertise. Imaging cannot exclude endometriosis. Surgical removal is the treatment of choice. Medical therapy without a diagnosis risks missing pathology and chronification of pain if not 100% effective. Indications and techniques of surgery are described as expert opinion since randomised controlled trials were not performed for ethical reasons, since not suited for multimorbidity while a control group is poorly accepted. Subtle endometriosis needs destruction since some cause pain or progress to more severe disease. Typical lesions need excision or vaporisation since depth can be misjudged by inspection. Painful cystic ovarian endometriosis needs adhesiolysis and either destruction of the lining or excision of the cyst wall, taking care to avoid ovarian damage. Cysts larger than 6 cm need a two-step technique or an ovariectomy. Excision of deep endometriosis is difficult and complication prone surgery involving bladder, ureter, and bowel surgery varying from excision and suturing, disc excision with a circular stapler and resection anastomosis. Completeness of excision, prevention of postoperative adhesions and recurrences of endometriosis, and the indication to explore large somatic nerves will be discussed.

(*Cite this article as:* Koninckx PR, Ussia A, Porpora MG, Malzoni M, Adamyan L, Wattiez A. Surgical management of endometriosis-associated pain. Minerva Obstet Gynecol 2021;73:588-605. DOI: 10.23736/S2724-606X.21.04864-8)

KEY WORDS: Endometriosis; Operative surgical procedures; Ovarian cysts; Evidence-based medicine.

Endometriosis is an important cause of chronic pelvic pain, infertility and a decreased quality of life, with millions of women affected worldwide. The cost is a burden for the healthcare systems. Direct costs comprise medical therapy and surgery, endometriosis being the most important cause of surgery in women. Indirect costs relate to absence from work, decreased work efficiency, and relational aspects as sexuality and dyspareunia. Maybe the most visible aspect of the importance of endometriosis, are the many patient support groups for endometriosis.

The importance of endometriosis contrasts with our poor understanding of the initiation

and the growth of endometriosis lesions and the mechanism of the associated pain and infertility. Thus prevention and therapy of endometriosis remains discussed, especially in adolescent women.[1, 2] In the absence of a clear understanding of the pathophysiology of the initiation and the growth of endometriosis,[3, 4] it is not surprising that besides surgical and medical therapy, many alternative therapies such as acupuncture,[5] herbal medicine,[6] dietary changes,[7] physical medicine and anti-inflammatory and anti-oxidant[8] therapy have been formulated. Although beyond the scope of this review, they need to be known by the surgeon dealing with endometriosis and pain to discuss them with the patient when needed.

Pelvic endometriosis is a variable disease comprising tiny subtle lesions, typical black puckered gunshot lesions in a sclerotic area, small or large cystic ovarian endometriosis with pelvic adhesions and deep lesions which can invade ureters, bowels and sympathetic and somatic nerves. Endometriosis at distance in the lungs and many other organs will not be discussed.

A review on surgery for endometriosis-associated pain should discuss data, comparing indication, the technique of surgery, short and long term results and risks and complications. However, solid data are scanty because of the variability of the disease endometriosis and of the surgical skills and techniques, making comprehensive trials irrealistic since requiring prohibitively large numbers. Moreover, our understanding of the disease has evolved and histologic evaluation has been expanded with molecular biological, epigenetic and genetic aspects.

This review, therefore, will reflect the opinion of the authors of what they consider important for our understanding of today's surgery for endometriosis-associated pain. A historic overview should illustrate the changes over time. Our understanding of pathophysiology should explain why it is important for surgery whether endometriosis is composed of normal or genetic-epigenetically abnormal cells. The overview of surgery, unfortunately, will not discuss in detail the importance of chronification of pain, the important anatomical aspects of surgery, the physics of the energy used, and the postoperative complications.

What is endometriosis: problems of definitions

The history of histology

With better microscopes, lenses and histological staining in the mid-19th century, endometrium-like tissue was described in the uterine wall and the rectovaginal septum.[9, 10] They were called adeno-myoma's with the hypothesis of being Müllerian remnants or resulting from metaplasia.[11] With the observation of ruptured ovarian cystic cysts, containing endometrium-like tissue, and of retrograde menstruation, the implantation theory was born and Sampson coined the name 'endometriosis' to indicate these endometrium-like cells outside the uterus.[12, 13] Over the following decades, 70 to 100 reports described each year endometriosis lesions, found during surgery. By 1960, it was realised that endometriosis was the most important cause for surgery in women, even after menopause.[14] Since surgery could be difficult, alternative therapies as blocking splanchnic nerves were described.[15] With the introduction and widespread use of laparoscopy for pain and infertility in the 1970'ies,[16] it was realised that typical endometriosis lesions were found in almost half of the women with pelvic pain or infertility.[17] Later in 1986, also non pigmented lesions were recognised as endometriosis[18] and these tiny white and red vesicles, polypoid and flame-like lesions were called subtle lesions.[18, 19] Subsequently started the search for even smaller, microscopical lesions even in normal looking peritoneum by microscopy and scanning electron microscopy. This problem is not yet fully settled since very small lesions (<0.2 mm) were identified only on 35-mm films after surgery.[20] With the development of laparoscopic surgery, some lesions were found to invade much deeper under the peritoneum and they were given the name deep endometriosis,[21, 22] although similar to some adeno-myoma's described 100 years earlier.

The definition of endometriosis thus was and is histological, *i.e.* endometrium like tissue outside the uterus. This definition does not require clinical implications as pain, infertility or progression. With the oncologic concept that abnormal tissue in an abnormal location should be removed, surgical excision of endometriosis was

performed. With the introduction of radio-immuno-assays and the development of endocrinology and oral contraceptives in the 1970's, the medical therapy of endometriosis was developed by inducing a pseudo-pregnancy or giving oral contraceptives, progestagens only, and later ovarian suppression or aromatase inhibitors.

Fibrosis

Fibrosis is an inherent part of clinical endometriosis as reviewed recently.[23] Deep endometriosis is even predominantly composed of fibromuscular tissue with sparse glandular and stroma tissue. Many molecular biological pathways have been described, detailing the effects of innervation, platelets, immunology and endothelial mesenchymal and fibroblast to fibromuscular transition.[24, 25] Fibrosis has been linked to repetitive trauma and repair of the menstrual cycle. However, it remains unclear to what extend fibrosis is a prerequisite for pelvic endometriosis and pelvic pain. Unfortunately, some painful and fibrotic lesions, as some ovarian remnants and stromatosis, without endometrial cells by routine pathology do not fit the diagnosis of endometriosis although clinically similar.

Functional aspects

In the 1980's, it was realised that most subtle lesions looked histologically active, that typical lesions looked burnt-out, that cystic ovarian endometriosis contained little endometrium like cells on their surface, and that deep endometriosis looked rather active, at least in the deeper parts of the lesions.[22] Since peritoneal fluid contains high concentrations of progesterone even in the follicular phase[26] and given the high steroid hormone concentrations in the ovary, the burnt-out aspect of typical lesions and the scanty endometrium like cells in cystic ovarian endometriosis, and the activity in deeper endometriosis lesions, at distance from the peritoneal fluid, were considered to be explained by peritoneal fluid progesterone concentrations. However, the activity of the subtle lesions, bathing in a peritoneal fluid with high concentrations of progesterone has never been questioned. Even today an explanation for this apparent resistance to progesterone in most subtle lesions is not available.

Recently, it was demonstrated that endometriosis lesions were functionally variable and that deep endometriosis varies biochemically with lesions without and pronounced aromatase activity and without to severe progesterone resistance.[27]

Pathophysiology of endometriosis

Understanding the pathophysiology of endometriosis is important to discuss the completeness of surgery for endometriosis. Endometriosis was initially considered metaplasia, which is a histological concept that describes the transformation of a differentiated cell into another differentiated cell. Subsequently, the implantation theory[12, 13] postulated the implantation of endometrial cells from retrograde menstruation. Both theories thus describe normal cells with an abnormal behaviour explained by the environment of the peritoneal cavity and abnormal immunology. With this hypothesis, completeness of surgery was important since all endometriotic cells should be removed since otherwise, remaining cells would continue to proliferate. Moreover, new lesions would risk developing following each retrograde menstruation. Therefore endometriosis was considered a progressive and recurrent disease and surgery should be postponed as long as clinically reasonable eventually with medical therapy. This is especially important during puberty since early surgery carries the risk of recurrences and repeat surgery and more damage and adhesions. Surgery, when performed, therefore should be complete, even if a more radical approach by bowel resections is needed.

Recently the endometriotic disease theory or the genetic-epigenetic (G-E) theory (Figure 1)[3, 4] postulated that G-E incidents were needed to initiate more severe endometriosis, similar to most benign tumours and that the endometriosis cell thus is G-E different from a normal cell. During life, we accumulate G-E incidents, because of pollution or radiation or mistakes during cell division, but most of them remain clinically invisible because of the redundancy of molecular biological pathways. However, above a certain threshold of cumulative incidents, the disease endometriosis initiates. Heredity and predisposition are thus viewed as the inherited set of G-E incidents, increasing the risk that additional inci-

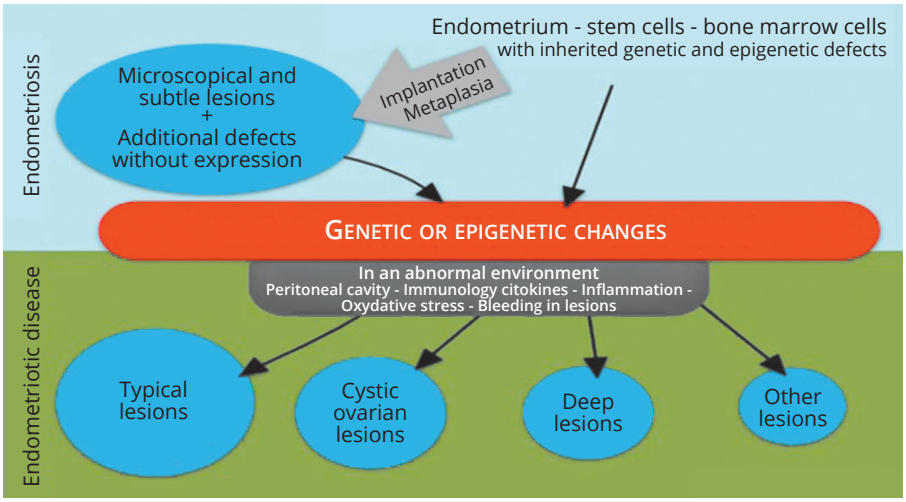

Figure 1.—The genetic epigenetic theory (from Koninckx *et al.*):[4] a set of G-E incident is required to start endometriosis lesions; growth varies with the set of lesions and with the environment.[3]

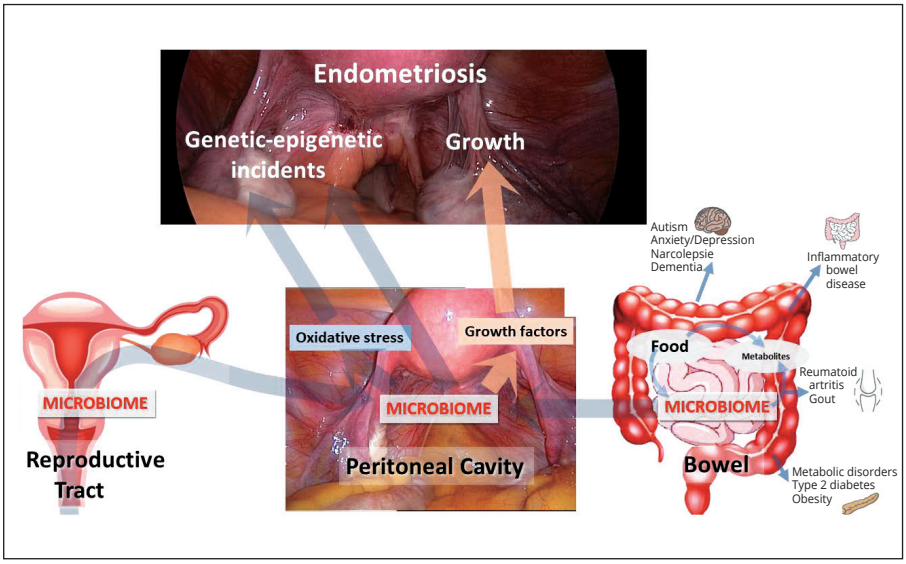

Figure 2.—Infection and the microbiota of the upper genital tract and the peritoneal cavity are cofactors in causing G-E lesions leading to endometriosis (from Koninckx *et al.*).[28]

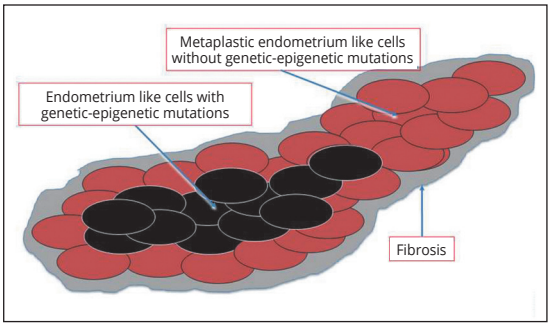

Figure 3.—The outer layer of deep endometriosis might be metaplastic cells without G-E changes since recurrence rates are similar after conservative surgery or short or large bowel resections (from Koninckx *et al.*).[30]

dents can initiate the disease. That endometriosis initiates after puberty seems logical because of the increased estrogen concentrations together with the increased oxidative stress of retrograde menstruation and infection when becoming sexually active (Figure 2).[28] Therefore the risk of initiating endometriosis will be is highest during adolescence and will decrease progressively with age. This concept is comparable with infertility where the most fertile women become rapidly pregnant and the fertility in the remaining group thus decreases. The most important consequences of the G-E theory are that preven-

tion of retrograde menstruation and infection should prevent the initiation of endometriosis, and that endometriosis is no longer a necessarily recurrent disease. The G-E theory also has consequences for the diagnostic accuracy of histology and the completeness of excision during surgery. Not all endometrium like cells are necessarily G-E abnormal. Clinical observation suggests that microscopical lesions in normal looking peritoneum, only found in research projects, or lymph nodes, found in bowel resection specimens, or in the bowel at distances of more than 5 cm from deep endometriosis nodules do not develop systematically into disease. Therefore large excisions of normal-looking peritoneum, or systematic lymphadenectomies or large margins when doing a bowel resection are not recommended. The fate of microscopic lesions is not known. They could disappear and return to normal as demonstrated for subtle lesions,[29] and this would not be surprising considering they are normal implanted endometrial cells. However, some could acquire more defects and start proliferating. The fibrosis around endometriosis does not need to be removed if viewed as a reaction of the body to the disease and thus as normal tissue. Since microscopic nests at distance from a deep endometriosis nodule, suggest induced (reversible) metaplasia, we moreover postulated that the peripheral cell layer of deep endometriosis nodules is also composed of G-E normal metaplastic cells, induced through cell-cell interaction by the central G-E abnormal deep endometriosis cells (Figure 3).[30] This is supported by the observation that recurrence rates after a conservative and at the cellular level incomplete resection of a deep endometriosis nodule from the bowel wall are not associated with a higher recurrence rate than a small or large bowel resection.[30]

Conclusion

Endometriosis is a heterogeneous disease with tiny superficial and cystic or larger lesions, which can be histologically inactive or active, with little or marked surrounding inflammation and fibrosis in and around the lesion. Also, immunology in women with endometriosis and the molecular biology of the individual clonal[31] lesions can be very different.

Histology is a crude instrument that cannot differentiate between G-E normal and G-E abnormal cells in endometrium like tissue. Genetically identical cells can look very different because of epigenetic differences, as illustrated by epithelial-mesenchymal plasticity.[32] Less clear is which epigenetic changes are irreversible and which are reversible, permitting the cell to return to normal after removal of the inducing stimulus. Therefore, the histological 'endometriotic metaplasia' can describe both a normal cell that can return to normal and an epigenetically irreversibly changed cell.

The (reversible) metaplasia and the implantation theories consider endometriosis as normal endometrium in an abnormal location, and endometriosis is thus a progressive and recurrent disease. This requires a radical and complete excision, and the unavoidable recurrence stimulate postponing surgery as long as clinically reasonable.

The G-E theory, with irreversible metaplasia, was formulated since the implantation and reversible metaplasia theories are incompatible with observations as clonality in endometriosis. Without identifying the important cellular incidents, irreversible, probably epigenetic, damage are postulated as the crucial trigger while the further growth of the lesions results from the set of G-E incidents and the environment. The clinically important consequences are that the risk of initiating endometriosis is higher in young women after puberty and that the risk decreases progressively with age. According to the G-E theory, not all 'endometrium like cells' are pathology. Unfortunately, by histology today we cannot distinguish between G-E normal and G-E abnormal (metaplastic) cells, only the latter requiring surgery.

Endometriosis and pelvic pain

The pain of individual lesions is variable. Although macroscopically and clinically indistinguishable, some endometriosis lesions cause pain while other lesions do not. This was demonstrated for subtle and typical lesions during conscious pain mapping.[33] Half of them are variably painful, but half of them are not. Most cystic ovarian endometriosis lesions are painful during a

clinical exam, but not all. Also, most deep rectovaginal endometriosis lesions are painful during the clinical exam.[34] However, occasional lesions, estimated at a few per cent, are not painful at all.

Pelvic pain and endometriosis are statistically associated: women with endometriosis often suffer from chronic pain, and women with chronic pelvic pain have more endometriosis.[35] However, this association does not permit the conclusion that the endometriosis found in a woman with chronic pain is the cause of her pain. Therefore women with chronic pelvic pain need to be investigated for all other known causes of chronic pelvic pain such as peritoneal pockets,[36, 37] varicose veins and pelvic congestion syndrome,[38] adenomyosis,[39] painful retroverted uterus,[40] rare diseases as Nutcracker syndrome[41] and ovarian remnants and pain caused by bowel, ureter, or bladder pathology.

The pathophysiology of endometriosis-associated pelvic pain is not clear. The many hypotheses for endometriosis to cause pain, comprise an inflammatory reaction around the lesions, the low-grade inflammation in the peritoneal cavity and the infiltration of endometriosis into the sympathetic and somatic nerves.[42] Less attention has been paid to the older observation that the peritoneum around endometriosis lesion is variably painful up to 3 cm.[33] Unidentified secretions by the endometriosis lesions have to be postulated to explain this neuroinflammation or activation of peritoneal nociceptors at distance. Without discussing the mechanism of neuroinflammation of sympathetic and somatic nerves at distance, it is important to realise that almost all somatic and sympathetic nerves in the sidewall of the pelvis are within a 3 cm range from the pelvic cavity.[37]

Endometriosis, especially cystic ovarian endometriosis is associated with adhesions and pelvic adhesions can cause pain.[43] By logistic regression, adhesions are a cause of pelvic pain in addition to cystic ovarian endometriosis.[44]

Clinically we should consider the brain effects of chronification of chronic pelvic pain,[45] together with the many mechanisms that modulate the pain perception of a pain stimulus.[46] The pathophysiology of the specific visceral pain nociceptors should be taken into account.[47] They are mainly stretch and pressure-sensitive, and the over 80% dormant nociceptors are rapidly recruited and sensitized by inflammation. This will increase their firing activity so much that during peritonitis even normal bowel movements cause severe pain.

Most women with endometriosis suffer from dysmenorrhoea in addition to chronic pelvic pain, and specific pain symptoms like dyspareunia, pain during micturition and bowel movements. Dysmenorrhoea is widely believed to be a consequence of bleeding in the endometriosis lesions. However, observations of bleeding in endometriosis lesions during menstruation are scanty. To the best of our knowledge active bleeding endometriosis lesions during menstruation has been observed only occasionally. Also bleeding in adenomyosis lesions during menstruation is not regularly observed. The only consistent observation is that deep endometriosis lesions are more painful and slightly larger during menstruation.[34]

Conclusion

Endometriosis is associated with pelvic pain but with a wide variability of pain caused by individual lesions. Also, the relationship between the severity of an individual lesion and the severity of pain is clinically unpredictable. Highly variable is the pain caused by touching a lesion, and the neuroinflammation up to 2.7 cm distance, and the pain caused by the associated adhesions. Since active menstrual bleeding in the lesions is rarely observed, we believe that the repetitive trauma and repair claimed as an important factor in the progression of endometriosis is rather the consequence of growth and involution of lesions rather than of active bleeding. The brain effects of chronic pain, suggest early treatment to avoid chronification.[45]

Diagnosis of endometriosis before surgery

Diagnosis of endometriosis is a catch 22 since surgery for endometriosis requires a diagnosis, and the diagnosis of superficial endometriosis and many deep endometriosis lesions requires a laparoscopy. Clinically important is when and which pain symptoms are an indication for laparoscopy,

which additional exams are useful before a laparoscopy and which expertise the surgeon should have to recognise the many causes of chronic pelvic pain. Also important is whether excisional surgery will be performed during the diagnostic laparoscopy, and when medical therapy should be given before or instead of surgery. The answers to these questions may vary. However, the indications used for surgery and medical therapy should be clear when discussing endometriosis, since both affect the findings during and the results of surgery. At KULeuven,[37, 48] from 1990 till 2011 (PK), the only indication for surgery was the severity and type of pain and the clinical exam, thus emphasising clinical experience. Medical therapy before a laparoscopy was given only in young women suspected of spastic dysmenorrhea. In all other women, we either did a laparoscopy based on symptoms, or no therapy was given. Additional exams as imaging were used to confirm the diagnosis and judge the severity of the disease. However, in the absence of pain, the imaging diagnosis of cystic ovarian or deep endometriosis was not used as an indication for surgery.

That our indication for surgery were only clinical exam and symptoms as infertility and the severity of pain may seem a blunt statement since most surgeons prefer to use also the results of imaging (ultrasound or MRI). However, it is rarely clearly explained in the literature to what extend imaging is also used as an indication for surgery, or whether imaging is mainly used to judge the severity of endometriosis and adhesions. This is important for discussing informed consent and for judging the duration of surgery and plan surgery. It moreover permits evaluating whether it is preferable to refer the patient. Today imaging before surgery is a useful routine to evaluate eventual bowel, ureter and bladder invasion before surgery. Bayesian analysis to investigate the added value of imaging when symptoms and clinical exam are known,[49] therefore is an intellectual exercise with little clinical relevance, provided imaging is not used as an indication for surgery in women without symptoms.

It is important to realise that only the predictive values (PV) of diagnostic exams are clinically relevant and that sensitivities and specificities describe the accuracy of a test. PV's vary with the prevalence of disease and PV's become poor when prevalences are below 5% (Figure 4)[50] even when sensitivities and specificities are over 95%.[51] This is important for the imaging diagnosis of deep endometriosis, cystic corpus luteum[52] and ovarian cancer in postmenopausal women.[53]

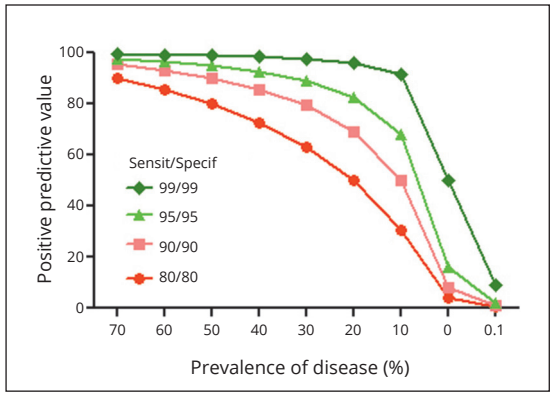

Figure 4.—The positive predictive value of imaging decreases rapidly when the prevalence of the disease is less than 5% (from Koninckx *et al.*).[50]

Although surgery for peritoneal pockets with eventually endometriotic spiders, varicose veins and pelvic congestion syndrome is beyond the scope of this manuscript, their diagnosis requires a laparoscopic inspection before the Trendelenburg position.

Conclusion

The indication for surgery of endometriosis should be based on clinical symptoms. Preoperative imaging is useful to confirm and evaluate the severity of the disease,[54] but the predictive value is low when the prevalence is low. We, therefore, should carefully consider decisions to perform a laparoscopy based on imaging only, *i.e.* either to do laparoscopy in women without symptoms or not to do laparoscopy in a woman with pain.

Surgery for endometriosis

History

The history of surgery for endometriosis paralleled the development of endoscopic surgery. Microsurgery introduced gentle tissue handling and demonstrated a higher fertility rate than achieved without.[55] The one surgeon, single

hand laparoscopic surgery was initially complementary to microsurgery, with coagulation with endothermia[56] and later CO_2 laser vaporization[57] of small cystic ovarian endometriosis and superficial pelvic endometriosis and minimal adhesiolysis.[58] When in the mid-eighties lightweight CCD camera's permitted video-laparoscopy and surgery with 2 surgeons, laparoscopic surgery progressively replaced microsurgery.[59] Unfortunately during this transition, the concepts of microsurgery were largely forgotten because of the idea that adhesion prevention no longer was an issue. This is illustrated by the replacement of Ringer's lactate as a rinsing fluid by saline, known already then and confirmed later, to be toxic for mesothelial cells. Only recently the importance of microsurgical principles was demonstrated and reintroduced in laparoscopic surgery, now called 'peritoneal conditioning'.[60] Deep endometriosis surgery required surgery of bowels and ureters and these interventions were pioneered by gynaecologists.[61] However, legal constraints introduced the concept of multidisciplinarity and recently the concept of the pelvic surgeon based on credentialling of the individual gynaecologist.

Evidence-based surgery

Diagnosis and therapy should be based on evidence, obtained without placebo effect and selection or patient or observer/believer/surgeon bias. Theoretically, this is best achieved with a randomised controlled trial (RCT). Practically, however, the RCT investigates only a single item and inclusion criteria limit group variability which reduces the number of women needed to reach significance. Therefore the RCT is poorly suited for rare events and multimorbidity or multifactorial events which require prohibitively large series. Also, ethical concerns limit surgical RCT's when the indirect evidence of the superiority of one type of surgery is already reasonably high, or when the expected benefit is too little to be clinically relevant.[62, 63] The surgeon also realises that a significant result is only the probability that an observed effect is not caused by chance. A probability of less than 5%, considered clinically significant, can hide that some 5% of significant results are obtained by chance only and thus wrong. Similarly, "not significant" does not equal 'not true' since the lack of significance can be due to a lack of power when the number of observations is low. To conclude that there is no difference requires non-inferiority trials[64] or a different type of statistical analysis needing a much larger sample size.

Therefore, the RCT is poorly suited to evaluate endometriosis surgery. The disease is variable and thus similar to multimorbidity and ethical concerns limit the inclusion of a control group without treatment or with a treatment perceived as inferior. Moreover, the results of most trials would be obsolete before being finished when large numbers are required. An authority based review,[65] with the consensus opinion of expert surgeons[66] is the best alternative to combine variability of disease with the many rapidly changing treatment alternatives.

These considerations do not exclude surgical biases. Surgical skills and quality of surgery are variable, but we do not know which aspects are important and how to evaluate them. Video registration[67] has been suggested as a tool to evaluate quality but is not yet widely accepted.

The technique of surgery and energy sources

Destruction of superficial lesions can be performed with one or two secondary ports. Severe disease requires dissection and three secondary ports. It is wise to use a high flow insufflator that permits coping laparoscopically with eventual severe bleedings. The principles of energy use for cutting and coagulating and cellular damage should be understood.[68] The focused CO_2 laser is an ideal cutting instrument since completely absorbed by water, resulting in superficial cell heating and vaporisation with less than 100µ tissue damage. For the same reason, coagulation properties are poor. Low power densities only heat tissue and the effect varies with the duration and diffusion of the heat. Electrosurgery is the most versatile energy source and the tissue effect varies with the voltage used. Below 200V (soft coagulation) the electro current only generates heat, decreasing exponentially with distance. Above 200 V sparks heat the air to more than 2000 °C resulting in an effect similar to the vaporising with a CO_2 laser. With higher voltages, sparks do not consume all energy and the resid-

ual energy heats the tissue with a coagulating effect. Electrosurgery is versatile since, the energy (watts) output being limited by the device, a large contact area increases the intensity and drops the voltage, changing cutting into coagulation. Since fat is a poor conductor, electrosurgery is less suited for fat tissue except when used as a sealing device controlling tissue temperature. Lasers have different wavelengths. The green argon laser is adsorbed specifically by the complementary red colour but is no longer used for endometriosis surgery.[69] The wavelengths of the recent diode lasers have the advantage of permitting the use of fibres but the penetration is deeper with more tissue damage. Plasma jet is a sophisticated use of sparks, but the penetration and tissue effect is to the best of our knowledge not well established. Ultrasonic energy has the advantage of being versatile with a limited lateral spread of heat and of being also suited for fat tissue but with the disadvantage of being less suited for point coagulation and dissection.

Subtle endometriosis

Subtle endometriosis lesions can be transient[29] lesions when composed of normal implanted endometrium or cells with reversible G-E changes. However, it seems wise to destroy them during surgery, since some of them could develop into more severe lesions when harbouring 'irreversible G-E changes' and since half of them are painful during conscious pain mapping.[33] Destruction by coagulation or laser vaporization is moreover fast with minimal surgical risk.

The clinical efficacy of treating subtle lesions has not been demonstrated. It is unclear whether the destruction decreases pain or increases fertility or decreases progression to more severe disease. Considering that many subtle lesions occur intermittently in most women[70] it is not surprising that surgical treatment is associated with high reoperation rates.

Typical endometriosis

Typical endometriosis lesions have to be excised or vaporised with a CO_2 laser since their depth becomes clear only during surgery. Although CO_2 laser vaporisation is the method of choice since faster and more precise than excision,[71] its use is disappearing. The optical quality of the new straight endoscopes is better than of the (older) operative endoscopes. However, the most important obstacle is the specific expertise required. The surgeon holds the laser and the camera and the assistant holds two instruments, including the bipolar for coagulation. This is different from laparoscopic surgery where the assistant holds the camera and a grasping forceps while the surgeon controls two instruments and cutting/coagulation. Historically endoscopic surgery started with a CO_2 laser for superficial endometriosis and dissection surgery came later and needed a second learning curve. Training today starts with dissection and excision, and the added benefit of a CO_2 laser is limited when compared with the extra learning curve of the surgeon and the assistant. As a result, the expertise in CO_2 laser surgery is slowly disappearing as illustrated by the observation that a CO_2 laser set-up was our standard in the 1990's while being used today only for women with extensive superficial endometriosis. The efficacy of fibre diode lasers used through a secondary port is not clear.

Excision or destruction of typical lesions decreases chronic pelvic pain,[72] but whether fertility is improved remains controversial.[73] The endocan trial was not blinded, and the 30% cumulative pregnancy rate in the treated group was as expected in women with unexplained infertility. The lower fertility in the untreated group could be explained by the psychological stress in women with high trait anxiety[74] being told still to have endometriosis, possibly secondary to the luteinized follicle syndrome.[75] Whether surgery of typical endometriosis affects recurrence rates has not been adequately investigated.

Cystic ovarian endometriosis

Ultrasound is the method of choice to diagnose cystic ovarian endometriosis, but the diagnostic accuracy to exclude a cystic corpus luteum and ovarian cancer in postmenopausal women is limited. Therefore, it is preferable to postpone surgery with ultrasound follow-up, when the onset of pain was acute and when the chocolate cyst has no adhesions. Inspection during surgery can be helpful, although erroneous in 27%.[76]

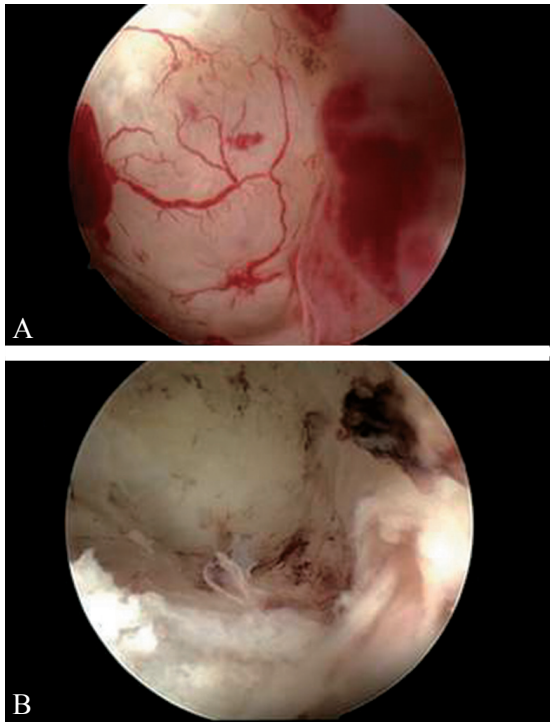

Figure 5.—A, B) THL and inspection of (smaller) cystic ovarian endometriosis followed by under-water bipolar coagulation, without causing postoperative adhesions (courtesy Prof S. Gordts, Belgium and from Koninckx *et al*.).[30]

There are no RCT's comparing superficial destruction of cystic ovarian endometriosis and excision of the cyst wall,[77, 78] the former and the latter technique being used for smaller and larger cysts respectively. Both techniques report some 60% cumulative pregnancy rates after 1 year[79] and a similar improvement of pain. Recurrence rates around 20% after superficial destruction, are believed to be higher than the 5% to 7% recurrence rate after excision. Excision was believed to be more harmful to the ovarian reserve,[80] although not confirmed in a recent review.[81]

The interpretation of these observations needs a common-sense evaluation. Irrespective of the techniques used, either a CO_2 laser or argon beam coagulator[82] or bipolar coagulation, the completeness and depth of superficial destruction are difficult to standardise and vary with the expertise of the surgeon. The excision of the wall can be technically difficult[83] with specific risks. An incorrect plane of cleavage results in more bleeding and coagulation. Bleeding and coagulation of the artery or vein from the hilus risks causing ischemia of the ovary. Normal ovarian tissue risks to be excised by errors in surgical judgment in ovaries with multiple endometrioma's. The excision of very large endometriomas leaves a thin rim of a poorly vascularized ovarian capsule. These technical considerations explain that surgery and results vary with the skill and the attitude of the surgeon.[84] The advantages and disadvantages of ultrasonic energy in cyst excision are not yet clear.

Since endometriosis infiltrates for only 2 mm[85] the fibrotic cyst capsule,[86] superficial destruction is logical. Chemical destruction with alcohol has the advantage of completeness,[87] and preliminary results are encouraging, although still poorly standardised.

Surgery for ovarian endometriotic cysts of less than 3 cm without pain is unclear. Especially in adolescents, the dilemma is recurrences and repeat surgery with early surgery versus growth and ovarian damage and more difficult surgery[1] with delayed surgery. When infertility is the only problem, the results of IVF are similar in women without and with a small cystic ovarian endometriosis.

In conclusion, for small cysts, especially in young women, transculdo-hydro-laparoscopy (THL) with underwater coagulation of small endometrioma's should be considered[88] since minimally invasive with less adhesion formation (Figure 5).[30, 77, 89] Superficial destruction is rather suited for small cysts, smaller than 2 cm, and excision for larger cysts. A cystic ovarian endometrioma of more than 6 cm when located centrally in the ovary, requires either an adnexectomy or a two-step approach, combining drainage and 3 months of GnRH treatment followed by a second intervention if needed. IVF without diagnostic laparoscopy risks missing other endometriosis lesions and other pathology in the pelvis that could be treated.

Deep endometriosis

Diagnosis of deep endometriosis can be challenging as discussed. Also, surgery can be challenging because of distorted anatomy, the involvement of bowels, ureters, bladder, the sympathetic nerves and occasionally larger somatic nerves.

The goal of surgery is the excision of the endo-

metriosis lesion, but the completeness of excision is less clear. Initially, completeness of excision was emphasised,[90] resulting in more and more extensive bowel resections, especially after bowel surgeons became involved. Gradually awareness did grow that less radical conservative excision was equally effective for pain with similar recurrence rates. Unfortunately, these opposing directions of radical versus conservative surgery are represented by surgeons using different techniques and with different backgrounds. The recent concepts of the pathophysiology of endometriosis rather point to less radical surgery. Another fundamental aspect of surgery is the balance between difficulty and completeness of excision and the prevention of complications. These considerations resulted in different technical choices, at least partially because of local privileges and preferences.[90] Over the last decades, however, many aspects have evolved into a consensus.

For excision of deep endometriosis from the bladder wall, completeness prevails with a muscularis or a full-thickness resection if necessary, since suturing of the bladder in one or 2 layers and healing is uneventful. Technically the bladder should be entered ventrally, if needed, to avoid a lesion to the ureter and the absence of leakage after bladder suture needs to be confirmed. A large bladder catheter that permits evacuation of blood clots is left for at least 1 week, and it is wise to check the healing before removal. With a CO_2 laser, surgery started by dissecting the nodule from the uterus; today for larger nodules the paravesical space is dissected with identification of the ureters. When the trigonum is involved prudence requires two double-J stents and it is a surgical choice to balance completeness of excision with postoperative bladder instability.

Excision of deep endometriosis involving the ureter or requiring ureter dissection has become straightforward. Consensus exists that for deep endometriosis it is always wise to identify or dissect both ureters respecting the lateral vascularisation to avoid unexpected damage. A double J stent is indicated only in women with ureter stenosis and hydronephrosis. A double J does not protect the ureter, but lesions are more easily recognised and an eventual ureter resection or suture is facilitated.[91, 92] The resection and a 4-5 stitch anastomosis over a double J[93, 94] can be technically challenging but has become a standard procedure.[95] The treatment of severe ureter stenosis has evolved towards a more liberal use of resection-anastomosis, replacing a difficult and lengthy ureterolysis with the repair of an eventual trauma of a fibrotic ureter. It remains unclear, whether an epiploon flap to accelerate healing and to protect the ureter is helpful. When a larger segment of the ureter needs to be resected with traction on the anastomosis, and when the resection is close to the bladder wall, laparoscopic reimplantation with a psoas hitch should be considered.

The conservative excision of an endometriosis nodule from the sigmoid is feasible for nodules up to 2 cm in diameter. However, this is complication prone and technically difficult surgery since sigmoid nodules frequently require a transmural discoid resection, and since the mobility of the sigmoid and its cranial location makes suturing difficult. The sigmoid also is difficult to reach with a circular stapler. Since leakage rates of sigmoid resections and the early and late postoperative complications are low, liberal use of a short sigmoid resection is recommended (for review[30]).

For low rectovaginal nodules, it remains unclear which nodules can be excised conservatively and which need a bowel resection and anastomosis. Conservative excision of most low rectum and high rectovaginal nodules is feasible and the postoperative complication and recurrence rates are similar to those found after a resection anastomosis.[30] Low rectum and ultra-low rectum resections are associated with higher leakage rates and some 30% bowel and bladder instability and sexual disturbances because of nerve damage.[96] Resection anastomosis, on the other hand, has the advantage of being better standardised and faster surgery. The background and the expertise of the surgeon are also important since bowel surgeons start with dissection between the nodule and the uterus/vagina to mobilise the rectum, resulting in a mobile rectum making the resection of the nodule more difficult. Those who started with infertility surgery and a CO_2 laser left the nodule attached to the uterus/vagina to pull the nodule upwards and started dissection between the nodule and the rectum. Only after the rectum has

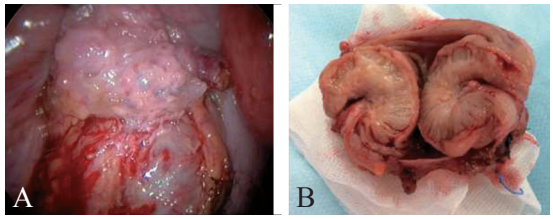

Figure 6.—Images of conservative excision of an endometriosis nodule from the bowel up to the mucosa (A) leaving a large muscularis defect to be sutured and of a short bowel resection (B) (from Koninckx *et al*.).[30]

been freed from the endometriosis, the nodule is dissected from the posterior wall of the uterus or vagina. The eventual large muscularis defects with large nodules can require large single or double-layer sutures, a procedure most gynaecologists and bowel surgeons are not familiar with. Over the last decades, the approach has become more conservative. Following a conservative debulking of the nodule from the rectum, the remaining endometriosis can be removed with a circular stapler,[97] which avoids opening the bowel while difficult and lengthy suturing is replaced with a circular stapler. Another important innovation is the short bowel resection (Figure 6)[30] limiting the resection to that part of the bowel containing the nodule, with minimal dissection and the reduction of the reservoir function of the rectum. Preliminary results suggest that complications are low and that recurrence rates are not increased (personal communication A. Wattiez). It is expected that this short resection will replace the larger bowel resection based on vascularisation. It is too early to discuss the advantages and disadvantages of a short bowel resection versus a more conservative approach, or to compare the results of suturing with a wedge resection using a circular stapler since the quality of suturing varies with the surgeon. Indocyanine green to check vascularisation of the rectum and thus the safety of sutures and anastomoses[98, 99] is expected to be proven to be useful.

Adenomyosis surgery

Adenomyosis is debulking surgery since cleaving planes between adenomyosis and the myometrium are absent. The radicality of the excision of adenomyotic nodules and the technique of suturing need surgical judgment.[100] Surgery can be challenging but postoperative pregnancy rates are encouraging.

Adolescent endometriosis

Adolescent endometriosis remains debated. New aspects are the arguments that the risk of developing endometriosis is highest after menarche because of the oxidative stress or retrograde menstruation and infections after becoming sexually active, and that the risk decreases progressively with age. After initiation, the growth of endometriosis is self-limiting and the severity and frequency of typical, cystic and deep endometriosis do not increase between 24 and 44 years of age.[48] The former would suggest early diagnosis and treatment, while the self-limiting aspect suggests that postponing surgery is not necessarily harmful. In conclusion, the jury is still out.

Prevention of recurrences of endometriosis after surgery

Unfortunately, we do not have data demonstrating the efficacy of prevention of recurrences of endometriosis after surgery. However, considering the G-E initiation of endometriosis it is expected that recurrences can be prevented by reducing oxidative stress and infection, especially in susceptible women. This could be achieved by abolishing menstruation by estro-progestins or progestins. This treatment would moreover also reduce the risk of upper genital tract infection by impairing transport of spermatozoa.

Prevention of postoperative adhesion formation

Prevention of postoperative adhesions is important because of the associated infertility, chronic pain and the occasional bowel occlusions. All suggestions formulated by microsurgery, have been investigated and confirmed recently. Before surgery, it is important to treat vaginal infections since they are associated with a less favourable peritoneal cavity microbiome. Surgery should be performed with gentle tissue handling, minimal duration of surgery, a low insufflation pressure and CO_2 pneumoperitoneum with the addition of some 10% of N_2O. Blood and fibrin deposits

should be avoided while saline as a rinsing liquid should be replaced with Ringers lactate. The pneumoperitoneum should be kept between 25 and 31 °C without desiccation. Dexamethasone at the end of surgery is probably beneficial. With the combined use of gentle tissue handling, 10% of N_2O, low insufflation pressure, lower temperature, adequate rinsing liquid, coined peritoneal conditioning, and a barrier at the end of the surgery, adhesion free surgery has become feasible.[60, 101]

Prevention of complications

The main long term complications of endometriosis surgery are postoperative adhesions and the decrease in ovarian reserve and recurrence after incomplete surgery or missed lesions. Adhesion prevention requires adequate surgery and peritoneal cavity conditioning.[101] The eventual decreased ovarian reserve is the cumulative effect of the damage caused by larger endometrioma's, and the surgical damage caused by the removal of tissue, coagulation, vascularisation damage and eventually hypoxia by the CO_2 pneumoperitoneum. It was suggested that careful surgery by a skilled surgeon is associated with minimal damage to the ovarian reserve.[83, 102]

Immediate postoperative complications are mainly associated with deep endometriosis surgery. It is complication prone surgery involving the bladder, the ureter and the bowel. The first aspect of prevention consists of a checklist at the end of surgery to judge eventual risks. This checklist will result in the decision to use a drain, a double J, postoperative antibiotics etc. The second and most important prevention of serious postoperative complications is an early diagnosis by checking the patient twice daily, by daily CRP (unpublished personal communication by the author P.K.) measurements and by the liberal use of a second look laparoscopy. The patient should always improve and CRP's should decrease from day 3 onwards, otherwise, something is wrong. An early repeat laparoscopy will be beneficial in case of bleeding, infection or ureter or bladder leak. This is mandatory for late bowel perforation that occurs after surgery since this pathology can be treated conservatively with suturing of the lesion and lavage if diagnosed within 24 hours.

Medical and IVF therapy of endometriosis

A full discussion of the pro and cons of medical therapy[103] being beyond the scope of this manuscript, only a few comments will be made. Progestins and the absence of estrogens reduce the proliferation of the endometrium and thus probably of endometriosis. However, endometriosis lesions are clonal and can thus individually differ, some being variably resistant to progesterone while others having an increased aromatase activity.[27] Lesions with strong progesterone resistance can grow when treated with estroprogestins,[104] progesterone being ineffective. Some lesions hardly require estrogens as demonstrated by deep endometriosis lesions that initiate and develop after menopause in the absence of estrogen treatment.[105]

Medical treatment before surgery is not recommended since there is no proven benefit while small lesions becoming inactive might be missed.[106] It is probable although not demonstrated, that medical treatment makes excision of deep endometriosis nodules less accurate when the borders are less clear. Medical treatment for many years without a diagnosis, especially in those with incomplete pain relief, should be avoided since women risk being treated for endometriosis without having endometriosis. Some lesions probably continue growing during medical treatment, as suggested by the repetitive observations by the authors (P.K., A.U., J.K., L.A., M.M., A.W.) of severe deep endometriosis nodules in women who had been taking medical therapy for more than 10 years. That adequate ultrasonographic follow-up can detect this is likely but not yet demonstrated. Also, the promotion of medical treatment to prevent the complications of surgery[107] is inappropriate since these reports review selectively the risks[108] without balancing the benefits of surgery. The risk that lesions might grow with more difficult surgery later has not been investigated.

That traditional statistical analyses are not suited for heterogeneous lesions is an additional problem. Homogeneity of a population indeed is a fundamental and necessary assumption for statistical analysis. This consideration cast doubt

on all published data of medical and surgical therapy including RCT's since the traditional statistical analyses can hide subgroups of women in whom medical therapy might be damaging.[104]

The many reports describing the results of IVF treatment in women with endometriosis deserve critical evaluation. The pregnancy rates of IVF treatment are not different in women with cystic ovarian endometriosis of less than 3 cm and women without endometriosis. However, these observations cannot exclude that the ultimate cumulative pregnancy rates of a combined treatment of surgery and IVF would not have been higher.[109] IVF also may be harmful since oocyte pick-up may induce pelvic adhesions, a risk that is possibly enhanced by the increased pelvic inflammation in endometriosis. Massive pelvic adhesions are a repetitive observation during surgery following several IVF attempts (P.K., A.U., J.K., L.A., M.M., A.W. unpublished data). Also, severe complications of untreated deep endometriosis nodules during pregnancy are well known.[110] Therefore, it seems unwise to proceed with IVF in women with untreated deep endometriosis nodules and possibly also those with cystic ovarian endometriosis.

Discussion

Endometriosis surgery needs to balance the diagnosis, the indication and the quality of surgery, postoperative care, and alternative treatments. Unfortunately, a comprehensive discussion including all aspects is difficult, since reviews rarely detail all aspects, and since they carry the bias of being written by specialists of imaging, medical treatment, infertility or surgery. Every specialist moreover tends to be biased since we tend not to cut the branch of a tree on which we are sitting. Also, this review risks carrying this bias since written exclusively by endometriosis surgeons.

The pitfalls of surgery for endometriosis begin with the diagnosis. The diagnosis of superficial endometriosis and most deep endometriosis can be suspected using age, background, symptoms, clinical exam and imaging, but need confirmation by a diagnostic laparoscopy in the majority of women. It is also important to decide what should be done when pathology or endometriosis is found. Preoperative imaging can help to discuss this with the patient before surgery and to have informed consent. Even in women with a clear diagnosis because of a big palpable and painful nodule or cystic ovarian endometriosis, it remains an art based on clinical experience, to comprehensively judge symptoms, duration of infertility, clinical exam and imaging. Bayesian analysis to estimate the added value of imaging besides symptoms and clinical exam might be scientifically important to understand. However, it seems clinically irrelevant since imaging is useful to estimate the severity and difficulty of surgery. When laparoscopy confirms the diagnosis of endometriosis, the decision to proceed with surgery or to refer the patient requires balancing the circumstances, the skills of the surgeon and the anticipated difficulty of surgery. The latter, unfortunately, often becomes clear only during the intervention. Surgery and postoperative care also require an experienced team. Although obvious, the importance of the team is uncommonly discussed and not transparent in the literature.

The quality of the surgical intervention remain poorly defined and opinions vary on how to balance personal skills, technique, choice of instruments and energy, duration of surgery and risks. However, during live surgery, there seems to be an overall agreement in recognising good surgery — "It is easier to recognise a miracle than to do a miracle."

Many aspects of endometriosis surgery for pelvic pain cannot be answered conclusively today. While it seems accepted that asymptomatic endometriosis does not require surgery, it remains unclear whether surgical excision of deep endometriosis is indicated before becoming pregnant. Although likely and useful it is not demonstrated that sequential ultrasound exams can adequately monitor the progression of lesions and thus add to the indication for surgery. The risk of progression and ovarian damage by growing small ovarian cysts is unclear and especially in puberty early or delayed surgery remains debated. The advantages and disadvantages of conservative excision, disk excision with a circular stapler, and small versus larger bowel resections remain to be established. Infertility treatment in endometriosis patients is not clear since solid data comparing the cumulative pregnancy rates of the sequential

use of surgery followed eventually by IVF versus IVF only are not available. It even becomes more difficult if the poorly predictable decline of fertility with age should be taken into account. The potential damages of early surgery with eventual recurrences versus the damage of lesions growing during medical therapy are unknown. It is unclear whether surgery should be postponed when medical therapy is effective in abolishing pain. It remains unclear whether monitoring the development and progression of the disease by ultrasound is clinically useful.[111] The efficacy of prevention of recurrences remains to be established. Prevention of chronification of pain is still poorly established in endometriosis. It is unclear when symptoms involving larger somatic nerves are due to neuroinflammation at distance or are due to endometriosis infiltration, and thus when exploration of larger somatic nerves is indicated or risks to be harmful. We do not know whether small subtle lesions only visible on film can cause this activation of nociceptors at distance.[20] We do not have data to balance the risks of surgery and the risks during pregnancy or the risk of progression in asymptomatic deep endometriosis.

"We only recognise what we know" certainly applies to endometriosis recognition. However, it also is important for the clinical application of research findings. Although observed in 1997[112] and 1998,[113] the up to 2.7 cm neuroinflammation at a distance from superficial endometriosis lesions, did not influence the surgery of the authors. Only last year, we realised the importance for peritoneal pockets causing neuroinflammation of larger somatic nerves[37] and only this year we realised that this concept had stimulated surgical excision with margins in the USA (Dan Martin, personal communication).

In conclusion, the diagnosis of superficial endometriosis needs a laparoscopy. The main indication for laparoscopy are symptoms and clinical exam while imaging is important for counselling and informed consent. Severe endometriosis with severe pain needs surgery in the absence of contraindications. During surgery, all endometriosis lesions should be removed although the arguments suggest that radicality of deep endometriosis excision might be less. If during the laparoscopic inspection the surgeon estimates not to have the appropriate skills matching the expected difficulty of surgery it is preferable not to proceed and to refer the patient. If the patient refuses surgery medical therapy can be discussed, knowing that medical therapy will not cure the disease and will not prevent progression in all women. However, we do not favour medical therapy for many years in the absence of a diagnosis, or when surgery has been incomplete. We expect, however, that medical therapy might become the method of choice to prevent recurrences by reducing the oxidative stress of menstruation and by preventing ascending infection.

References

1. Schindler L, Schindler S, Ussia A, Gordts S, Wattiez A, Koninckx PR. Cystic ovarian endometriosis and infertility: arguments for an early but less aggressive surgical treatment. Obs & Gyn Int J 2020;11:122–5.

2. Koninckx PR, Ussia A, Adamyan L, Keckstein J, Wattiez A, Gomel V, *et al*. The Genetic-Epigenetic Pathophysiology of Endometriosis: A Surgeon's View. In: Nezhat CH, editor. Endometriosis in Adolescents: Springer Cham; 2020. p. 173-93.

3. Koninckx PR, Martin DC, Donnez J. Do we need to separate initiation and growth to understand endometriosis? Fertil Steril 2020;114:766–7.

4. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Gomel V, Martin DC. Pathogenesis of endometriosis: the genetic/epigenetic theory. Fertil Steril 2019;111:327–40.

5. Mira TA, Buen MM, Borges MG, Yela DA, Benetti-Pinto CL. Systematic review and meta-analysis of complementary treatments for women with symptomatic endometriosis. Int J Gynaecol Obstet 2018;143:2–9.

6. Della Corte L, Noventa M, Ciebiera M, Magliarditi M, Sleiman Z, Karaman E, *et al.* Phytotherapy in endometriosis: an up-to-date review. J Complement Integr Med 2020;17.

7. Nirgianakis K, Egger K, Kalaitzopoulos DR, Lanz S, Bally L, Mueller MD. Effectiveness of Dietary Interventions in the Treatment of Endometriosis: a Systematic Review. Reprod Sci 2021. [Epub ahead of print]

8. Porpora MG, Brunelli R, Costa G, Imperiale L, Krasnowska EK, Lundeberg T, *et al.* A promise in the treatment of endometriosis: an observational cohort study on ovarian endometrioma reduction by N-acetylcysteine. Evid Based Complement Alternat Med 2013;2013:240702.

9. Rokitansky C. Über Uterusdrüsen-Neubildung in Uterus- und Ovarial-Sarcomen. (On the neoplasm of uterus glands on uterine and ovarian sarcomas). Zeitschr Ges Aerzte Wien 1860;16:577–81.

10. Cullen TS. Adeno-myoma of the round ligament. Johns Hopkins Hosp Bull 1896;7:112–4.

11. Russell WW. Aberrant portion of the Mullerian duct found in an ovary. Bull Johns Hopkins Hosp 1899;10:8–10.

12. Sampson JA. Perforating hemorrhagic (chocolate) cysts of the ovary. Their importance and especially their relation to pelvic adenomas of the endometrial type. Arch Surg 1921;3:245–323.

13. Sampson JA. Heterotopic or misplaced endometrial tissue. Am J Obstet Gynecol 1925;10:649–64.

14. Kempers RD, Dockerty MB, Hunt AB, Symmonds RE. Significant postmenopausal endometriosis. Surg Gynecol Obstet 1960;111:348–56.

15. De Sousa Pereira A. Blocking of the splan chnic nerves and the first lumbar sympathetic ganglion; technic, accidents and clinical indications. Arch Surg 1946;53:32–76.

16. Gomel V. Laparoscopy. Can Med Assoc J 1974;111:167–9.

17. Brosens IA, Koninckx PR, Corveleyn PA. A study of plasma progesterone, oestradiol-17beta, prolactin and LH levels, and of the luteal phase appearance of the ovaries in patients with endometriosis and infertility. Br J Obstet Gynaecol 1978;85:246–50.

18. Jansen RP, Russell P. Nonpigmented endometriosis: clinical, laparoscopic, and pathologic definition. Am J Obstet Gynecol 1986;155:1154–9.

19. Martin DC, Hubert GD, Vander Zwaag R, el-Zeky FA. Laparoscopic appearances of peritoneal endometriosis. Fertil Steril 1989;51:63–7.

20. Martin DC, Redwine D, Reich H, Kresh AJ. Laparoscopic appearance of endometriosis – Color atlas; 1990 [Internet]. Available from: https://www.danmartinmd.com/files/coloratlas1990 [cited 2021, Jul 9].

21. Koninckx PR, Martin DC. Deep endometriosis: a consequence of infiltration or retraction or possibly adenomyosis externa? Fertil Steril 1992;58:924–8.

22. Cornillie FJ, Oosterlynck D, Lauweryns JM, Koninckx PR. Deeply infiltrating pelvic endometriosis: histology and clinical significance. Fertil Steril 1990;53:978–83.

23. Viganò P, Ottolina J, Bartiromo L, Bonavina G, Schimberni M, Villanacci R, *et al.* Cellular Components Contributing to Fibrosis in Endometriosis: A Literature Review. J Minim Invasive Gynecol 2020;27:287–95.

24. Guo X, Ding S, Li T, Wang J, Yu Q, Zhu L, *et al.* Macrophage-derived netrin-1 is critical for neuroangiogenesis in endometriosis. Int J Biol Macromol 2020;148:226–37.

25. Xiao F, Liu X, Guo SW. Platelets and Regulatory T Cells May Induce a Type 2 Immunity That Is Conducive to the Progression and Fibrogenesis of Endometriosis. Front Immunol 2020;11:610963.

26. Koninckx PR, Heyns W, Verhoeven G, Van Baelen H, Lissens WD, De Moor P, *et al.* Biochemical characterization of peritoneal fluid in women during the menstrual cycle. J Clin Endocrinol Metab 1980;51:1239–44.

27. Bulun SE, Yilmaz BD, Sison C, Miyazaki K, Bernardi L, Liu S, *et al.* Endometriosis. Endocr Rev 2019;40:1048–79.

28. Koninckx PR, Ussia A, Tahlak M, Adamyan L, Wattiez A, Martin DC, *et al.* Infection as a potential cofactor in the genetic-epigenetic pathophysiology of endometriosis: a systematic review. Facts Views Vis ObGyn 2019;11:209–16.

29. Wiegerinck MA, Van Dop PA, Brosens IA. The staging of peritoneal endometriosis by the type of active lesion in addition to the revised American Fertility Society classification. Fertil Steril 1993;60:461–4.

30. Koninckx PR, Ussia A, Adamian L, Alsuwaidi S, Amro B, Gharbi H, *et al.* Conservative Surgery of Deep Bowel Endometriosis. In: Ferrero S, Ceccaroni M, editors. Clinical Management of Bowel Endometriosis. Springer; 2020. p. 119-34.

31. Suda K, Nakaoka H, Yoshihara K, Ishiguro T, Tamura R, Mori Y, *et al.* Clonal Expansion and Diversification of Cancer-Associated Mutations in Endometriosis and Normal Endometrium. Cell Rep 2018;24:1777–89.

32. Kovacic B, Rosner M, Schipany K, Ionce L, Hengstschläger M. Clinical impact of studying epithelial-mesenchymal plasticity in pluripotent stem cells. Eur J Clin Invest 2015;45:415–22.

33. Demco L. Review of pain associated with minimal endometriosis. JSLS 2000;4:5–9.

34. Koninckx PR, Meuleman C, Oosterlynck D, Cornillie FJ. Diagnosis of deep endometriosis by clinical examination during menstruation and plasma CA-125 concentration. Fertil Steril 1996;65:280–7.

35. Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril 1991;55:759–65.

36. Carranco RC, Zomer MT, Berg CF, Smith AV, Koninckx P, Kondo W. Peritoneal Retraction Pocket Defects and Their Important Relationship with Pelvic Pain and Endometriosis. J Minim Invasive Gynecol 2021;28:168–9.

37. Koninckx PR, Ussia A, Keckstein J, Adamyan L, Wattiez A, Martin DC. Prevalence of endometriosis and peritoneal pockets in women with infertility and/or pelvic pain. J Obstet Gynaecol Can 2021;S1701-2163(21)00365-0. [Epub ahead of print]

38. Meissner MH, Gibson K. Clinical outcome after treatment of pelvic congestion syndrome: sense and nonsense. Phlebology 2015;30(Suppl):73–80.

39. Koninckx PR, Ussia A, Zupi E, Gomel V. Association of Endometriosis and Adenomyosis: Vast Literature but Scant Conclusive Data. J Minim Invasive Gynecol 2018;25:745–8.

40. Ott J, Nouri K, Demmel M, Zafraani S, Greilberger U, Huber JC, *et al.* Fourteen-year experience with laparoscopic ventrosuspension in patients with retroverted and retroflected uterus and pelvic pain syndromes. J Minim Invasive Gynecol 2010;17:749–53.

41. Hartung O, Grisoli D, Boufi M, Marani I, Hakam Z, Barthelemy P, *et al.* Endovascular stenting in the treatment of pelvic vein congestion caused by nutcracker syndrome: lessons learned from the first five cases. J Vasc Surg 2005;42:275–80.

42. Anaf V, Simon P, El Nakadi I, Fayt I, Buxant F, Simonart T, *et al.* Relationship between endometriotic foci and nerves in rectovaginal endometriotic nodules. Hum Reprod 2000;15:1744–50.

43. Demco L. Pain mapping of adhesions. J Am Assoc Gynecol Laparosc 2004;11:181–3.

44. Porpora MG, Koninckx PR, Piazze J, Natili M, Colagrande S, Cosmi EV. Correlation between endometriosis and pelvic pain. J Am Assoc Gynecol Laparosc 1999;6:429–34.

45. Sieberg CB, Lunde CE, Borsook D. Endometriosis and pain in the adolescent- striking early to limit suffering: A narrative review. Neurosci Biobehav Rev 2020;108:866–76.

46. Bhattacharjee Y. Scientists are unraveling the mysteries of pain; 2019 [Internet]. Available from: https://www.nationalgeographic.com/magazine/2020/01/scientists-are-unraveling-the-mysteries-of-pain-feature [cited 2021, July 9].

47. Cervero F. Visceral versus somatic pain: similarities and differences. Dig Dis 2009;27(Suppl 1):3–10.

48. Koninckx PR, Ussia A, Wattiez A, Adamian L, Martin DC, Gordts S. The severity of endometriosis lesions is not different between 24 and 44 years of age in women with or without a previous pregnancy. Facts Views Vision Obs Gyn 2021. [Epub ahead of print]

49. Chen Z, Hwang BS, Kim S. A correlated Bayesian rank likelihood approach to multiple ROC curves for endometriosis. Stat Med 2019;38:1374–85.

50. Koninckx PR, Deslandes A, Ussia A, Di Giovanni A, Hanan G, Tahlak M, *et al.* Preoperative imaging of deep endometriosis: pitfalls of a diagnostic test before surgery. Facts Views Vis ObGyn 2021;12:265–71.

51. Koninckx PR, Deslandes A, Ussia A, Di Giovanni A, Hanan G, Tahlak M, *et al.* Preoperative imaging of deep endometriosis: pitfalls of a diagnostic test before surgery. Facts Views Vis ObGyn 2021;12:265–71.

52. Kinkel K, Frei KA, Balleyguier C, Chapron C. Diagnosis of endometriosis with imaging: a review. Eur Radiol 2006;16:285–98.

53. Matsubara S, Kawahara N, Horie A, Murakami R, Horikawa N, Sumida D, *et al.* Magnetic resonance relaxometry improves the accuracy of conventional MRI in the diagnosis of endometriosis-associated ovarian cancer: A case report. Mol Clin Oncol 2019;11:296–300.

54. Malzoni M, Casarella L, Coppola M, Falcone F, Iuzzolino D, Rasile M, *et al.* Preoperative Ultrasound Indications Determine Excision Technique for Bowel Surgery for Deep Infiltrating Endometriosis: A Single, High-Volume Center. J Minim Invasive Gynecol 2020;27:1141–7.

55. Gomel V. The impact of microsurgery in gynecology. Clin Obstet Gynecol 1980;23:1301–10.

56. Semm K. Endocoagulation: a new filed of endoscopic surgery. J Reprod Med 1976;16:195–203.

57. Daniell J. Laser laparoscopy for endometriosis. Colposcopy Gynecol Laser Surg 1984;1:185–92.

58. Semm K. [Endoscopic intraabdominal surgery in gynecology]. Wien Klin Wochenschr 1983;95:353–67. [German]

59. Nezhat C. Videolaseroscopy: A new modality for the treatment of endometriosis and other diseases of reproductive organs. Colposcopy Gynecol Laser Surg 1986;2:221–4.

60. Koninckx PR, Gomel V, Ussia A, Adamyan L. Role of the peritoneal cavity in the prevention of postoperative adhesions, pain, and fatigue. Fertil Steril 2016;106:998–1010.

61. Penninckx F, Aerts R, Kerremans R, Koninckx PR. Laparoscopic cholecystectomy: some advantages or just an artifice of new technology? HPB Surg 1991;3:291–4, discussion 294–5.

62. Greenhalgh T, Howick J, Maskrey N; Evidence Based Medicine Renaissance Group. Evidence based medicine: a movement in crisis? BMJ 2014;348:g3725.

63. Jones DS, Podolsky SH. The history and fate of the gold standard. Lancet 2015;385:1502–3.

64. Gerlinger C, Schmelter T. Determining the non-inferiority margin for patient reported outcomes. Pharm Stat 2011;10:410–3.

65. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Donnez J. Deep endometriosis: definition, diagnosis, and treatment. Fertil Steril 2012;98:564–71.

66. Koninckx PR, Ussia A, Zupi E, Gomel V. Evidence-Based Medicine in Endometriosis Surgery: Double-Blind Randomized Controlled Trial Versus the Consensus Opinion of Experts. J Minim Invasive Gynecol 2017;24:692–4.

67. Koninckx PR. Videoregistration of surgery should be used as a quality control. J Minim Invasive Gynecol 2008;15:248–53.

68. Koninckx PR. Masterclass: Use of energy in laparoscopy; 2021 [Internet]. Available from: https://www.gynsurgery.org/wp-content/uploads//210218_electrosurgery.pdf [cited 2021, Jul 9].

69. Brosens IA, Puttemans PJ. Double-optic laparoscopy. Salpingoscopy, ovarian cystoscopy and endo-ovarian surgery with the argon laser. Baillieres Clin Obstet Gynaecol 1989;3:595–608.

70. Koninckx PR. Is mild endometriosis a condition occurring intermittently in all women? Hum Reprod 1994;9:2202–5.

71. Mage G, Chapron C, Canis M, Wattiez A, Pouly JL, Manhes H, *et al.* [CO2 laser in operative laparoscopy. Techniques. Indications. Results]. J Gynecol Obstet Biol Reprod (Paris) 1990;19:657–65. [French]

72. Sutton CJ, Ewen SP, Whitelaw N, Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. Fertil Steril 1994;62:696–700.

73. Jacobson TZ, Duffy JM, Barlow DH, Farquhar C, Koninckx PR, Olive D. WITHDRAWN: laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database Syst Rev 2014;8:CD001398.

74. Demyttenaere K, Nijs P, Evers-Kiebooms G, Koninckx PR. Personality characteristics, psychoendocrinological stress and outcome of IVF depend upon the etiology of infertility. Gynecol Endocrinol 1994;8:233–40.

75. Koninckx PR, De Moor P, Brosens IA. Diagnosis of the luteinized unruptured follicle syndrome by steroid hormone assays on peritoneal fluid. Br J Obstet Gynaecol 1980;87:929–34.

76. Martin DC, Berry JD. Histology of chocolate cysts. J Gynecol Surg 1990;6:43–6.

77. Gordts S, Campo R. Modern approaches to surgical management of endometrioma. Best Pract Res Clin Obstet Gynaecol 2019;59:48–55.

78. Deckers P, Ribeiro SC, Simões RD, Miyahara CB, Baracat EC. Systematic review and meta-analysis of the effect of bipolar electrocoagulation during laparoscopic ovarian endometrioma stripping on ovarian reserve. Int J Gynaecol Obstet 2018;140:11–7.

79. Gordts S, Boeckx W, Brosens I. Microsurgery of endometriosis in infertile patients. Fertil Steril 1984;42:520–5.

80. Muzii L, Di Tucci C, Di Feliciantonio M, Galati G, Verrelli L, Donato VD, *et al.* Management of Endometriomas. Semin Reprod Med 2017;35:25–30.

81. Younis JS, Shapso N, Fleming R, Ben-Shlomo I, Izhaki I. Impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve: a systematic review and meta-analysis. Hum Reprod Update 2019;25:375–91.

82. Kulakov VI, Adamian LV, Kiselev SI, Yarotskaya EL, Golubev G. Argon Beam Coagulator in Laparoscopic Gynecologic Surgery. J Am Assoc Gynecol Laparosc 1996;3(Supplement):S23.

83. Canis M, Mage G, Wattiez A, Pouly JL, Bruhat MA. The ovarian endometrioma: why is it so poorly managed? Laparoscopic treatment of large ovarian endometrioma: why such a long learning curve? Hum Reprod 2003;18:5–7.

84. Muzii L, Miller CE. The singer, not the song. J Minim Invasive Gynecol 2011;18:666–7.

85. Muzii L, Marana R, Angioli R, Bianchi A, Cucinella G, Vignali M, *et al.* Histologic analysis of specimens from laparoscopic endometrioma excision performed by different surgeons: does the surgeon matter? Fertil Steril 2011;95:2116–9.

86. Guo SW. Fibrogenesis resulting from cyclic bleeding: the Holy Grail of the natural history of ectopic endometrium. Hum Reprod 2018;33:353–6.

87. De Cicco Nardone A, Carfagna P, De Cicco Nardone C, Scambia G, Marana R, De Cicco Nardone F. Laparoscopic Ethanol Sclerotherapy for Ovarian Endometriomas: preliminary Results. J Minim Invasive Gynecol 2020;27:1331–6.

88. Gordts S, Puttemans P, Gordts S, Brosens I. Ovarian en-

dometrioma in the adolescent: a plea for early-stage diagnosis and full surgical treatment. Gynecol Surg 2015;12:21–30.

89. Gordts S. 16 Transvaginal ovarian drilling. Reprod Biomed Online 2011;22:S100.

90. Keckstein J, Wiesinger H. Deep endometriosis, including intestinal involvement—the interdisciplinary approach. Minim Invasive Ther Allied Technol 2005;14:160–6.

91. Miranda-Mendoza I, Kovoor E, Nassif J, Ferreira H, Wattiez A. Laparoscopic surgery for severe ureteric endometriosis. Eur J Obstet Gynecol Reprod Biol 2012;165:275–9.

92. Wattiez A, Nasir R. Paraureteral Endometriosis with Bilateral Gross Hydroureters and Left Renal Compromise. J Minim Invasive Gynecol 2018;25:565.

93. De Cicco C, Schonman R, Craessaerts M, Van Cleynenbreugel B, Ussia A, Koninckx PR. Laparoscopic management of ureteral lesions in gynecology. Fertil Steril 2009;92:1424–7.

94. De Cicco C, Ussia A, Koninckx PR. Laparoscopic ureteral repair in gynaecological surgery. Curr Opin Obstet Gynecol 2011;23:296–300.

95. Frenna V, Santos L, Ohana E, Bailey C, Wattiez A. Laparoscopic management of ureteral endometriosis: our experience. J Minim Invasive Gynecol 2007;14:169–71.

96. De Cicco C, Corona R, Schonman R, Mailova K, Ussia A, Koninckx P. Bowel resection for deep endometriosis: a systematic review. BJOG 2011;118:285–91.

97. Kondo W, Ribeiro R, Zomer MT, Hayashi R, Ferreira LR, Martin RL. Double Discoid Resection in Deep Intestinal Endometriosis. J Minim Invasive Gynecol 2015;22(6S):S140.

98. Raimondo D, Maletta M, Borghese G, Mastronardi M, Arena A, Del Forno S, *et al.* Indocyanine Green Fluorescence Angiography after Full-thickness Bowel Resection for Rectosigmoid Endometriosis-A Feasibility Study. J Minim Invasive Gynecol 2021;28:1225–30.

99. Malzoni M, Iuzzolino D, Rasile M, Coppola M, Casarella L, Di Giovanni A, *et al.* Surgical Principles of Segmental Rectosigmoid Resection and Reanastomosis for Deep Infiltrating Endometriosis. J Minim Invasive Gynecol 2020;27:258.

100. Pistofidis G, Makrakis E, Koukoura O, Bardis N, Balinakos P, Anaf V. Distinct types of uterine adenomyosis based on laparoscopic and histopathologic criteria. Clin Exp Obstet Gynecol 2014;41:113–8.

101. Koninckx PR, Corona R, Timmerman D, Verguts J, Adamyan L. Peritoneal full-conditioning reduces postoperative adhesions and pain: a randomised controlled trial in deep endometriosis surgery. J Ovarian Res 2013;6:90.

102. Donnez J, Wyns C, Nisolle M. Does ovarian surgery for endometriomas impair the ovarian response to gonadotropin? Fertil Steril 2001;76:662–5.

103. Koninckx PR, Ussia A, Keckstein J, Adamyan LV, Zupi E, Wattiez A, *et al.* Evidence-Based Medicine: Pandora's Box of Medical and Surgical Treatment of Endometriosis. J Minim Invasive Gynecol 2018;25:360–5.

104. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Gomel V, Martin DC. Correction: heterogeneity of endometriosis lesions requires individualisation of diagnosis and treatment and a different approach to research and evidence based medicine. Facts Views Vis ObGyn 2020;11:263.

105. De Almeida Asencio F, Ribeiro HA, Ribeiro PA, Malzoni M, Adamyan L, Ussia A, *et al.* Symptomatic endometriosis developing several years after menopause in the absence of increased circulating estrogen concentrations: a systematic review and seven case reports. Gynecol Surg 2019;16:3.

106. Evers JL. The second-look laparoscopy for evaluation of the result of medical treatment of endometriosis should not be performed during ovarian suppression. Fertil Steril 1987;47:502–4.

107. Streuli I, de Ziegler D, Santulli P, Marcellin L, Borghese B, Batteux F, *et al.* An update on the pharmacological management of endometriosis. Expert Opin Pharmacother 2013;14:291–305.

108. Vercellini P, Viganò P, Buggio L, Somigliana E. "We Can Work It Out:" The Hundred Years' War between Experts of Surgical and Medical Treatment for Symptomatic Deep Endometriosis. J Minim Invasive Gynecol 2018;25:356–9.

109. Koninckx PR, Ussia A, Adamyan L, Gomel V. Reproductive surgery in the 21st century. Glob Reprod Health 2018;3:e12.

110. Setúbal A, Sidiropoulou Z, Torgal M, Casal E, Lourenço C, Koninckx P. Bowel complications of deep endometriosis during pregnancy or in vitro fertilization. Fertil Steril 2014;101:442–6.

111. Abrao MS, Andres MP, da Cunha Vieira M, Borrelli GM, Neto JS. Clinical and Sonographic Progression of Bowel Endometriosis: 3-Year Follow-up. Reprod Sci 2021;28:675–82.

112. Koninckx PR, Renaer M. Pain sensitivity of and pain radiation from the internal female genital organs. Hum Reprod 1997;12:1785–8.

113. Demco L. Mapping the source and character of pain due to endometriosis by patient-assisted laparoscopy. J Am Assoc Gynecol Laparosc 1998;5:241–5.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—All authors read and approved the final version of the manuscript.

Acknowledgements.—The authors thank Victor Gomel (Canada), and Dan Martin (USA) for their critical reviews. They are also grateful to Jörg Keckstein, Austria, Paulo Ribeiro, Marco Bassi and William Kondo and Rodrigo Fernandes from Brazil, and Muna Tahlak, Shaima Alsuwaidi, Bedaya Amro, and Hanan Gharbi from the United Arab Emirates, for the many discussions on endometriosis surgery they have taken part in.

History.—Article first published online: May 12, 2021. - Manuscript accepted: April 23, 2021. - Manuscript received: April 18, 2021.

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.