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Biases in the endometriosis literature Illustrated by 20 years of endometriosis research in Leuven

Philippe R. Koninckx[a,b,*]

[a]*Department of Obstetrics and Gynaecology, Division of Endoscopic Surgery, University Hospital Gasthuisberg, and Center for Surgical Technologies, Catholic University Leuven (K.U.Leuven), B-3000 Leuven, Belgium*
[b]*Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, University of Oxford, Oxford, UK*

Abstract

Aim: To review the Leuven data on endometriosis to demonstrate the shifts that occurred over the years in diagnosis of endometriosis, classification of women with endometriosis and thus in interpretation of results. *Results*: The contributions to the LUF syndrome, to non-pigmented endometriosis, to cystic ovarian endometriosis, to deep endometriosis, to endometriosis as an immunologic disease and to the development of an animal model of endometriosis, illustrate the persistent interest in endometriosis over 20 years. Using these data it can be shown how progressively the recognition of endometriosis caused important shifts from women who in the beginning of this period were classified as normal, to women who later became classified as having minimal or mild endometriosis. This was caused initially by the active search for small typical lesions and later by the recognition of non-pigmented lesions as endometriosis. The second important shift was caused by the recognition that deep endometriosis is not only a frequent disease, but that these women are predominantly classified as having mild to moderate endometriosis and even as women without endometriosis. The third shift is still ongoing, since the deep lesions reported become progressively smaller, by the ''enthusiasm'' of the surgeons, and by the introduction of a menstrual clinical exam. A fourth bias in the literature concerns the diagnosis and treatment of cystic ovarian endometriosis. Together with these shifts in recognition and treatment of endometriosis, our understanding of the physiopathology of endometriosis has changed. This is illustrated by the new concepts which have emerged over this period. These are, the focal treatment of cystic ovarian endometriosis, the concept that mild endometriosis could be a normal physiological condition and the endometriotic disease theory. *Conclusion*: To interpret the data of the literature we should be aware of the shifts that have occurred in the classification of endometriosis over the past 20 years, and which still can hamper the comparison of results between research groups.

Keywords: Endometriosis literature; Endometriosis; Non-pigmented endometriosis; Cystic ovarian endometriosis; Deep endometriosis; LUF syndrome; Diagnosis; Classification; Interpretation of results

1. Introduction

Endometriosis, defined as endometrial glands and stroma outside the uterus, was introduced clinically at the turn of the century, as ovarian ''chocolate cysts'' [1], and as adenomyosis externa [2–7]. Already in 1899 smaller lesions of endometriosis were described by Russell [8] who wrote, ''On the microscopic study of the ovary, we were astonished to find areas which were an exact prototype of the uterine glands and interglandular connective tissue.'' In the following decades, endometriosis was described as a disorder causing pain and requiring surgery. In addition other localisations [9] were described and endometriosis was reported as an ''accidental'' finding during surgery for other gynecological disorders [10–13]. Only after the introduction of endoscopy in the late 1960s black-puckered endometriosis lesions were recognized to be a frequent observation in women with pain and/or infertility. When in the 1980s non-pigmented endometriotic lesions were described [14–17], the observed prevalence of the disease increased even further [18–27]. In the 1990s, the awareness grew that deep infiltrating endometriosis was more frequent than thought before especially since this type of endometriosis was not always recognized during laparoscopy or surgery.

*Corresponding address: Department Obstetrics and Gynaecology, Division of Endoscopic Surgery, University Hospital Gasthuisberg, Herestraat 49, Catholic University Leuven (K.U.Leuven), B-3000 Leuven, Belgium.

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Over the last 20 years gradual shifts in the recognition of the different stages of endometriosis thus occurred. The awareness of these shifts is important to understand and interpret the data reported in the literature. This is especially important when older data are compared with more recent observations since the progressive shifts in recognition of endometriosis by definition cause gradual shifts in the inclusion criteria of the different stages of endometriosis. These gradual shifts will be discussed and illustrated by a privileged observer of the Leuven data over the period 1978–1998, a period of constant interest in endometriosis, spanning three generations and three Ph.D. theses. This makes the Leuven data almost unique to illustrate these shifts, while paying tribute to Ivo Brosens, who started the interest in endometriosis in the department.

Endometriosis has been considered for decades as the result of the implantation of retrogradely menstruated endometrial cells [1], or metaplasia [28,29] induced by this menstrual debris, or as implantation of cells after lymphatic [30,31] or hematologic spread. Over the last 20 years, simultaneously with the gradual shift in recognition of endometriosis and its different stages, new concepts of physiopathology have emerged such as the recognition that retrograde menstruation occurs in almost all women [32,33], and that this fluid contains viable cells [34] which can implant on the peritoneum [35]. Progression to cystic ovarian endometriosis and/or deep infiltrating endometriosis was assumed to be the natural history of the disease [36]. In recent years this concept of implantation and progression has been challenged by a new endometriotic disease hypothesis, which considers superficial endometriosis as a physiological condition occurring intermittently in all women, retaining only deep and cystic ovarian endometriosis as a true disease [37,38]. This endometriotic disease concept is moreover based upon, and incorporates the importance of immunology, genetics [39–44] and cellular mutations [45–48] for the understanding of the physiopathology of endometriosis.

2. The LUF syndrome and endometriosis [49]

In 1978 the luteinized unruptured follicle (LUF) syndrome was described to be associated with unexplained infertility and with endometriosis [50–52]. In the following years, it was shown that the LUF syndrome was associated with lower 17β-estradiol and progesterone concentrations in peritoneal fluid following ovulation [53–56] and with lower postovulatory follicle stimulating hormone (FSH) concentrations in plasma [57]. Simultaneously we had shown that retrograde menstruation was an almost universal phenomenon [32] in all women, and this led us already in 1979 at FIGO [58] to ask the question, ''why do not all women develop endometriosis?'' and to the hypothesis that endometriosis could be the consequence rather than the cause of the LUF syndrome [32]. The low steroid hormone concentrations in peritoneal fluid indeed could facilitate the implantation of regurgitated menstrual cells. (For reviews see Refs. [59,60])

The observation that the LUF syndrome was associated with endometriosis was initially confirmed [61–63] but questioned later (''The LUF syndrome was not a consistent change'' [64], ''these findings suggest that LUF occurs occasionally in association with mild endometriosis'' [65], ''incidence of anovulation and LUF in the endometriosis population was 9% and 34%'' [66], ''the incidence of luteinized unruptured follicle diagnosed by ultrasound was 2 of 27 and by estimation of steroid levels was 8 of 27'' [67], ''concludes that, in this series at least, there is a low frequency of LUF'' [68,69]. ''Ultrasonographic evaluations of follicular growth in luteal phase defect support the theory that luteal phase defect represents a spectrum of normal and abnormal ovarian cycle events'' [70], ''more data on the frequency of LUF in consecutive normal cycles compared to consecutive cycles in women with endometriosis would be beneficial'' [71], ''women with minimal to mild endometriosis only should be diagnosed as having unexplained infertility'' [72]). Not only the association of the LUF syndrome with endometriosis was questioned; also the validity of the laparoscopic inspection of the ovulation stigma was challenged, by raising the problem of the rate of reepithelialisation [73].

To interpret these data, it should be realized that in the literature, the groups of women defined as ''normal'' or as having minimal or mild endometriosis varied continuously from 1975 to the end of the 1980s. Indeed the scrutiny to look for endometriosis increased continuously. In the late 1970s, the diagnosis of endometriosis as judged from the number of women in the groups with and without endometriosis did not exceed 50% in Leuven (20% and 16% [50], and 17% and 20% [32], respectively). These figures can be considered as a valid estimate of the prevalence, since for these studies all women from consecutive laparoscopies were included. These prevalences were moreover comparable to those reported in the literature during this period. Increased scrutiny and awareness progressively increased the observed prevalences of endometriosis, especially after the recognition of subtle or non-pigmented endometriosis, to reach 80% at the end of the 1980s [27].

Thus over this period more and more women who initially would have been diagnosed as ''normal'' were later diagnosed as having endometriosis. The severity of the endometriosis in the group of women with endometriosis thus decreased progressively, by dilution with women with very minimal disease, previously classified as normal. This explains why the association of the LUF syndrome with endometriosis became weaker and was questioned later in the second half of the 1980s. Equally important is that the initial observations on the LUF syndrome and endometriosis were made before the association was established. Indeed all observations were made by one observer (I. Brosens) and the ovulation stigma was noted in the records as the signature of a

meticulous morphologist, making the observations absolutely unbiased. The actual interest was luteal phase insufficiency, LH peaks and onset of luteinization [51,74,75]. The association between endometriosis and LUF was found accidentally in the mid-1970s, and presented for the first time in 1976 at a local meeting in Pretoria, South Africa. During the period that the first observations on the LUF syndrome were made the quality of laparoscopy was less, whereas endometriosis was rather observed than looked for, making that the group of women with minimal endometriosis in this period probably had larger lesions than those with minimal endometriosis five years later. That the inspection and interpretation of an ovulation stigma was difficult and subjective was already expressed in 1980 [55] after the observation on low concentrations of steroids in peritoneal fluid by writing that ''these data at least show that the interpretation of the ovulation stigma was not too frequently erroneous''. Studies in the baboon model recently confirmed experimentally that endometriosis was associated with the LUF syndrome, that the LUF syndrome was recurrent and that the LUF syndrome diagnosed by inspection of the ovaries, correlated with the absence of ovulation [76].

It may be concluded from these data that the association between the LUF syndrome and non-pigmented endometriosis is weak or non-existent, between the LUF syndrome and typical and ovarian endometriosis remains valid, whereas the association between the LUF syndrome and deep endometriosis has not yet been addressed.

3. Subtle and non-pigmented endometriosis

Following the recognition of non-pigmented endometriosis [77], the race to find smaller and smaller implants led to a series of articles describing polypoid lesions [15–17,78,79], white and red vesicles, flame like lesions, and finally microscopic endometriosis [80–82], visible only under the microscope or by scanning electron microscopy [83,84]. This led to the suggestion that microscopic endometriosis could be present in all women, inducing techniques as peritoneal washings [85] or blood painting [86] to diagnose endometriosis. The interest in non-pigmented endometriosis was fueled, by the observation that these lesions were morphologically very active, leading to the speculation that this activity should be paralleled by secretion of ''active'' substances in peritoneal fluid [87], which could explain the infertility and pain. The activity of these lesions also made them prime candidates to be stimulated to grow and progress by substances in peritoneal fluid and to be inhibited by medical treatment [88–93]. This was indirectly expressed and emphasised when it was proposed to judge the severity of endometriosis by its degree of activity, rather than by its extent [94].

The data to support the concept of microscopical endometriosis have been rather anecdotal whereas in a systematic study in baboons the incidence is low [95]. Moreover, the prevalence of retrograde menstruation, being present in almost all women, together with the prevalence and remodeling of subtle endometriosis has led to the hypothesis that minimal endometriosis could be a physiological condition, occurring intermittently in all women, and that minimal endometriosis should not be considered a disease [38,96–100]. This controversy still persists and the same condition – minimal/subtle/non-pigmented endometriosis – can be regarded either as a very active disease, or as a normal physiologic condition. This controversy, however, is fundamental for our understanding of the pathophysiology of the disease and for our attitude towards treatment. Those who emphasize that subtle endometriosis is morphologically a very active disease assume implicitly that endometriosis, once established will ultimately grow and develop into a more severe condition [101–103], albeit that the rate of development may vary with local peritoneal factors such as angiogenic factors, growth hormones and cytokines. In this view, it is logical to scrutinize the pelvis for endometriosis, which should be treated to prevent progression and to treat the disease. Those emphasizing remodeling, assume that the remodeling observed in some women can be generalized and that minimal endometriosis will disappear completely in (some) women. The data supporting this concept are limited, and have to a large extent been generated during discussions on the baboon project. Revision of the data however, shows that the overall picture is mainly a progression of the number of the endometriotic implants, rather than a disappearance of all lesions in some animals.

In conclusion, the controversy still persists whether non-pigmented lesions should be considered as a pathologic or a physiologic condition. The future will tell whether attachment and implantation –the implantation/metaplasia theory – are the key features in the development of endometriosis or whether endometriosis should be regarded as a benign tumor – the endometriotic disease theory – making invasiveness and adhesion formation its most prominent features, or whether a more integrated picture should be used [104]. Indeed, recent data, demonstrating that the endometrium of women with endometriosis [105] is different from the endometrium of women without endometriosis, and data showing that endometriotic cells can be invasive [106] in vitro, can be interpreted in support of the implantation theory, e.g., attaching more readily, or in support of the endometriotic disease theory by being more invasive. Anyway, up to now, there are no data supporting the concept that treatment of non-pigmented endometriosis will prevent progression to a more severe condition.

4. Cystic ovarian endometriosis

The most important bias in the literature on cystic ovarian endometriosis is that clinically it can be very difficult to distinguish this condition from a cystic corpus

luteum. The persistence of a ''chocolate'' cyst is unreliable to diagnose cystic ovarian endometriosis since over the years several women with a ''chocolate cyst'' on ultrasound, persisting for more than four months even during treatment with LH-RH agonist or on oral contraception, have been found to have a cystic corpus luteum. We are fully aware that these clinical observations do not allow any conclusion about frequency of this problem, but the observations are consistent with the report that ovarian cysts can develop during ovarian down regulation [107]. Imaging, such as ultrasound and CAT scanning, has a sensitivity of 70% to 80% and a specificity of 90% to 95% [108–112]. This is a valuable method of diagnosis helping in the clinical management. It will, however, not prevent errors of judgment during surgery. Ovarian flow measurement does not seem to improve substantially specificity or sensitivity [108]. CA125 in chocolate fluid has been reported to have a sensitivity and a specificity of nearly 100% [113,114]. Unfortunately a rapid test, e.g., a stick assay is not available to make the diagnosis during surgery. A clinical rule of thumb is that, since cystic ovarian endometriosis is so strongly associated with adhesions [27], a ''chocolate cyst'' without adhesions has a high probability of being a cystic corpus luteum whereas the presence of severe adhesions especially in the fossa ovarica enhances the suspicion of an endometriotic cyst. This, together with the inspection of the inside of the cyst by ovarioscopy [115] or by inspection with the laparoscope [116], will help to make a correct judgment in the majority of women. ''Those with a flattened appearance and red or red and brown mottled ridges generally were endometriosis and those with a dark uniform base, an intracavitary clot, or a yellowish rim generally were corpus lutea or albicans'' [116].

A second bias is that the pathology report following surgery not infrequently will conclude that the cyst is ''compatible with endometriosis'', without a positive identification of endometrial glands and stroma. This problem is well known, but rarely addressed specifically in the literature, making it often difficult to judge how strictly the diagnosis of the reported endometriotic cysts was made.

Also treatment of endometriotic cysts can be biased. During the microsurgery period the cyst wall was excised and the ovary was repaired with suturing [117]. After the introduction of endoscopic surgery several techniques were developed. Aspiration and rinsing of cystic ovarian endometriosis has been attempted but the recurrence rate is high [118–120]. Ultrasound guided aspiration will moreover result the next day in chocolate in the pelvis (unpublished data), which might increase adhesion formation [121]. For smaller cysts, i.e., less than 5 cm diameter, the method of stripping the cyst from the ovary, as initially described by the Clermont Ferrand group, seems most attractive since it is rapid and technically relatively easy [122–124]. Closure of the ovary by tissucol when necessary, results in a ''normal ovary'' after surgery without denuded areas. The cyst wall can also be vaporized [125] or destroyed by unipolar or semi bipolar coagulation. The third option besides wall excision and wall destruction is focal treatment [126]. To understand the rationale of focal treatment, the rediscovery of the work of Hughesdon [127,128] was important, since he described by serial sections that an ovarian cyst could develop from adherence of the ovary to the side wall with the subsequent invagination and the stretching of the ovarian capsule over a pseudocyst formed by the hemorrhagic/chocolate fluid. When it is difficult to judge which areas are not involved, focal treatment is equivalent to vaporization of the wall. For larger cysts, the pragmatism of size practically excludes excision and/or vaporization. Whereas ultrasound guided puncture seems not to be a valid option, the method of making a large window in the cyst wall, followed by rinsing and focal treatment, is attractive and promising. It remains unclear, however, whether during this surgery it is important to do a full adhaesiolysis, if necessary, or whether the surgery should be kept to a strict minimum, i.e., marsupialisation combined with focal treatment to reduce the surgical trauma and possibly adhesion formation. It is also unclear whether postoperative medical therapy is helpful, albeit logical since it will prevent a corpus luteum to develop whereas a hypo-estrogenic milieu could reduce adhesion formation. It also remains unclear whether a second-look surgery should always be performed.

These different techniques of stripping or excision of the cyst wall, of vaporization of the cyst wall, or destruction with endothermia as was done in the late 1970s and early 1980s, or focal treatment, are often used simultaneously, making series using the same technique small and inconclusive. Larger series always comprise different techniques, with moreover systematic biases. Indeed, a small cyst will be vaporized, since it is easy and rapid whereas the remaining ovary is too rigid to permit closure. For the very large cysts, excision is technically impossible since little ovary would be left, whereas also extensive vaporization is unrealistic, making a primary surgery with opening of the cyst, rinsing and destruction of the most prominent endometriosis the only practical alternative. During a second procedure the cyst wall of a reformed (smaller) cyst is excised, or the remaining endometriotic spots on the ovarian surface are vaporized.

These considerations, describing the difficulty of diagnosis, and the different techniques used for treatment should be taken into account when interpreting results, which demonstrate that endoscopic and microsurgical treatments are comparable [129], ranging between 60% and 80% pain relief, a cumulative pregnancy rate of 60% to 70% after six months to one year and a recurrence rate of some 20% [130]. It can be concluded that the actual data do not permit a clear conclusion to designate any treatment technique as superior. It remains unclear whether preoperative or postoperative medical treatment or ovarian

down regulation significantly affect the results of surgery [131–135].

5. Deeply infiltrating endometriosis

In the 1990s it was realized that deep endometriosis was a frequent disease, either recognized during laparoscopic surgery [27,136], or by clinical examination during menstruation [137]. What is reported as ''resection of deep endometriosis'' comprises techniques ranging from complete resection to debulking and resection–reanastomosis of the rectum, a difference that is rarely made clearly in the literature. The ''enthusiasm'' to recognize and to treat deep endometriosis is already producing and will continue to produce a progressive shift of the severity of the reported series of deep endometriosis, which will include increasing numbers of women with less severe deep endometriosis, which were previously diagnosed as having mild disease.

Rectovaginal endometriosis was known since the beginning of the century, but the high prevalence of deep endometriosis remained unsuspected until fairly recently. In the population these conditions, were considered relatively rare but actually estimates of prevalence of 3% to 10% seem appropriate. This estimation of some 10% to 20% deep endometriosis is derived from observations in Leuven from 1988 to 1991 [138], a period during which endoscopic surgery was not yet well developed, and in which deep endometriosis was not yet a well known entity. Referrals were thus only those for infertility and pain not for deep endometriosis. Assuming that laparoscopies for infertility are performed in some 10% to 15% of the population and taking into account that Leuven is a tertiary referral center, the prevalence of deep endometriosis can be estimated to be between 1% (the prevalence is 10% in younger age group with infertility which can be estimated at 15% of the population; in a tertiary center the prevalence is probably slightly overestimated) and 3% (prevalence of 20% of the older age group with infertility). Taking into account the observation that by menstrual clinical examination deep endometriosis is more frequent, prevalences between 3% and 10% seem a fair estimate.

The endoscopic excision of endometriosis has revealed that endometriosis invading deeper than 5–6 mm is associated with pain and infertility. Three subtypes were described [139]. Type I is characterised by a large pelvic area of typical and sometimes some subtle endometriotic lesions surrounded by white sclerotic tissue. Only during excision does it become obvious that the endometriotic lesions infiltrate deeper than 5 mm. Typically the endometriotic area becomes progressively smaller as it grows deeper, the lesion is thus cone shaped. Type II lesions are characterised by retraction of the bowel. Clinically they are recognised by the obvious bowel retraction around a small typical lesion. In some women, however, no endometriosis can be seen through the laparoscope, and the bowel retraction is the only clinical sign. Diagnosis is generally not too difficult since during laparoscopy the retraction under which an induration is felt, is obvious. In some women however the retraction is hardly seen and the induration can be hardly felt. Only during excision the endometriotic nodule becomes apparent, emphasising the need for a pre-operative diagnosis and training in recognising these lesions. Type III lesions are spherical endometriotic nodules in the rectovaginal septum. In their most typical manifestation these lesions are felt as painful nodularities in the recto-vaginal septum. At laparoscopy they generally present as a small typical lesion, and in some women a careful vaginal examination reveals some dark blue cysts (3–4 mm) in the fornix posterior. Type III lesions are the most severe lesions, and they often spread laterally up and around the uterine artery, sometimes causing sclerosis around the ureter. The spread along the uterine artery can be so obvious, that this can be considered as an indirect argument for the hypothesis that deep endometriosis has escaped from the inhibitory influence of peritoneal fluid and is mainly under peripheral circulation control. Whilst being prominent in most women these lesions are often missed unless a clinical examination during menstruation is performed. Sclerosing endometriosis, invading the sigmoid is similar to the rectal endometriosis, but is situated 10 cm above the rectovaginal septum. This is another form of deep endometriosis, which is fortunately a rare condition and which we proposed to classify as type IV. For type IV lesions a contrast enema and/or a rectoscopy are necessary to make the diagnosis. Although hard data of the prevalence are not available, we have clinical evidence that this diagnosis is easily missed, making prevalence higher than actually believed.

Surgery for deep endometriosis can be difficult and dangerous. Therefore a preoperative contrast enema and intravenous pyelography should be considered, whereas surgery itself requires a full bowel preparation in order to permit any kind of bowel surgery if necessary. This may require the collaboration of a colorectal surgeon, depending on the experience and training of the gynecologist. If gross distortion of the ureter is present, preoperative ureter stents are recommended. The surgical excision of deep endometriosis itself relies upon a combination of perfect visual inspection and tactile information. For types I, II and III, I prefer to use a CO_2 laser (80 Watt, Sharplan) together with a high-flow insufflator (Thermoflator, Storz) [140]. Guided by visual inspection together with tactile information of the softness of the tissue, the peritoneum is incised below the lesion at the border between the normal and soft tissue and the harder endometriosis, glowing yellowish under the CO_2 laser beam. First the lateral edges of the nodule are dissected to free the nodule if necessary from the ureter, the uterine artery, and from the spinosacral ligament. This is technically the most difficult part of the surgery. Subsequently, the posterior part of the nodule is dissected thus freeing the rectum: we feel it important that

during this dissection, the nodule remains attached to the uterus and cervix or vagina thus elevating the nodule whereas the rectum progressively falls down by gravity. This dissection is continued as far as possible, at least until the rectum is completely liberated from the rectovaginal septum. Only after the completion of the dissection of the posterior part, the anterior side of the nodule is dissected from the cervix, and from the vagina. In some 20% of women part of the vaginal fornix has to be removed because of endometriotic invasion whereas we estimate that in some 20% of women the rectum has to be opened to permit a complete resection [141]. In the Leuven series it is noteworthy that resection of the rectum has not been necessary in any of these women.

A careful description of the excisional technique is necessary to understand pros and cons of the reported techniques. The advantages of the technique as described are the perfect visualization and the angle of access. Using CO_2 laser excision through the operating laparoscope, excisional surgery is performed with great magnification: excision can be performed with the laparoscope close in since the laparoscope carries the ''knife''; excision also has to be performed close in since the focal length of the CO_2 laser lens is some 2 cm from the laparoscope. A third advantage is that the direction of access of the rectovaginal septum, and especially the posterior side of the nodule is easier to reach through the laparoscope than through a secondary port. Obviously, this technique requires a high flow insufflator to maintain a clear picture throughout the excision, and to permit to use the laser continuously, without interruption. Three other techniques are used for the resection of deep endometriosis: sharp dissection together with electrosurgery through the laparoscope, sharp dissection together with electrosurgery through the secondary ports and a partial rectum resection followed by reanastomosis usually with a circular stapler. It is obvious that each surgeon performs best using the technique he is most familiar with, and that few endoscopic surgeons are familiar with all techniques. Most indeed have developed the technique which they started with generally for historical reasons. This however, should not prevent discussion of the relative advantages of the different approaches, as evaluated by expert surgeons performing surgical procedures often arranged on the basis of friendship. Sharp dissection together with electrosurgery through the laparoscope as developed by Redwine and co-workers [142–145] is technically almost identical to the CO_2 laser excision i.e., permitting a very posterior approach, working close in with great magnification in a bloodless operating field. The disadvantage is that this technique is physically demanding whereas less suited for video-endoscopic surgery thus reducing the possibility of help from an assistant. This technique, however, probably combines the advantage of an improved depth of vision (since not using a video screen) with enhanced tactile information (since also using sharp dissection). Sharp dissection together with electrosurgery through the secondary ports is the most widely used technique [123,146–155]. for several reasons. It is derived from the other endoscopic procedures; it does not require a CO_2 laser and possibly even more important a high flow insufflator that was not available during its development. Because the angle of access is much sharper, surgeons using this technique generally start dissection at the anterior site of the nodule, thus freeing nodule and rectum from the rectovaginal septum. Subsequently the rectum is dissected from the nodule, which has become freely mobile. Most of these procedures aim at debulking the endometriosis, rather than performing a complete resection. The word ''debulking'' is chosen when the surgeon prefers not to open the rectum, even if the resection is less complete. It is difficult to estimate whether this ''debulking'' attitude is a consequence of the technique used, or a consequence of the philosophy often dictated by local and medico–legal considerations. My experience was that resection of endometriosis using this technique is much more difficult than using the CO_2 laser approach, and that the best method to avoid bowel lesions was by avoiding traction and using gravity only. These same considerations could explain why some authors, probably in order to perform a complete resection and to avoid recurrences, perform a partial resection and anastomosis in women with larger nodules. At this moment it is not known whether those performing a complete resection, are overtreating their patients or whether those aiming at debulking the lesion, are undertreating the endometriosis.

These technical differences in approach and technique should be kept in mind when evaluating results. Nehzat et al. [152] reported 25 pregnancies in 67 women following excision of deep endometriosis. We evaluated cumulative pregnancy rates (CPRs) in a consecutive series of 900 women with primary or secondary infertility without severe tubal damage and with a severe subfertile husband. Cumulative pregnancy rates were slightly lower in advanced stages of endometriosis according to the revised AFS classification being 62% and 44% in classes I and IV, respectively. When, however, the duration of infertility was taken into account – which was the strongest predictor of subsequent conception – the differences in CPR between classes I to IV disappeared, suggesting that the differences found between mild and severe endometriosis were mainly a consequence of differences in duration of infertility and possibly in age of the women [156,157]. The only single group with a significantly higher CPR following surgery were women with deep endometriosis. By Cox multivariate regression analysis the following model was established: pregnancy was predicted most strongly by a shorter duration of infertility and in addition by the surgical treatment of cystic ovarian endometriosis and/or of deep endometriosis. From these results it can be concluded that

aggressive and complete excision of deep endometriosis can be advocated, with subsequent spontaneous pregnancy rates up to 60% within one year. These results can be considered excellent taken into account the severity of disease and the large denuded area in the pelvis following excision of deep endometriosis. It remains unclear whether those women who did not conceive after one year, should be oriented towards in vitro fertilisation or to a second look laparoscopy. Medical treatment alone, as can be derived from indirect evidence, is probably not the treatment of choice for deep endometriosis and infertility. As has been pointed out, medical pretreatment seems to be useful to facilitate surgery as has been suggested for cystic ovarian endometriosis [158]. Both surgical and medical treatment were reported to be highly successful in treating pelvic pain. Candiani et al. [151] reported absence of dyspareunia and dysmenorrea in six and four women out of 10 after 40 months. Nezhat et al. [152] reported moderate to complete pain relief in 162 women out of 175 but in some two or more interventions had been necessary. Preliminary analysis of our results in 250 women in whom deep endometriosis has been excised with a CO_2 laser showed a cure rate of pelvic pain in 70% with a recurrence rate of less than 5% with a follow up period up to five years. These data should be interpreted carefully, since the completeness of excision has steadily increased. The results of recent years, strongly suggest an almost complete cure rate without recurrences; this however could be an overoptimistic clinical impression which will have to be proven by careful analysis of the data. In addition medical treatment of pelvic pain is highly efficient, and the effect of treatment often persists after treatment has been stopped [159].

In conclusion, for deep endometriosis the method of treatment and the philosophy of treatment should be considered. The future will tell whether debulking is undertreatment or whether complete resection is unnecessary while inducing enhanced the risks of complications of bowel lesions. A second consideration is the size of the lesions treated. Smaller lesions are found increasingly frequently, especially since a clinical examination is performed during menstruation. The concept of deep endometriosis is moreover the second revolution, causing important shifts in our classification of endometriosis. Firstly, deep endometriosis can be found in women with a normal pelvis, thus in women who previously were classified as normal. Secondly, most women with deep endometriosis are classified as stage I or II. Since deep endometriosis is such a prominent cause of both pelvic pain and infertility, it could be argued that in all series, the women with stage I or II disease harbour some 10% to 30% of deep endometriosis. This contamination could explain to a large extend the pain and infertility in these women as well as the improvement of pain following medical therapy.

6. Endometriosis is an immunological disease [160] and the baboon as a model for endometriosis [161]

A discussion of the Leuven data would be incomplete without the data on immunology and of the baboon model, since they contributed very much to the concepts discussed. They will only be mentioned briefly since they are beyond the scope of this manuscript.

Women with endometriosis have a reduced cellular immunity [162], later shown to be caused by a decreased natural killer (NK) cell activity in peripheral plasma and in peritoneal fluid [160,163–173]. Although attractive to postulate that this decreased immunity could explain the implantation and the progression and growth of endometriosis, it remains equally possible that this decrease in NK activity is rather the consequence than the cause of endometriosis. The data on immunology and endometriosis cannot be considered isolated from the data showing that in women with endometriosis, the endometrium is different from the endometrium in normal women. The observation that the endometrium of women with endometriosis was more resistant to lysis by NK cells indeed was the first observation pointing in this direction. This, together with the arguments that (invasive) endometriotic cells could be genetically [42,174] different and that endometriosis is an hereditary disease [42,174] was the basis to develop the endometriotic disease theory as opposed to the implantation theory.

Most of the concepts discussed, were reinvestigated in the baboon [76,95,175–190], showing that in this animal model endometriosis was found in some 20%, that endometriosis was associated with the LUF syndrome, that the corpus luteum was generally reepithelialized in the late luteal phase, that retrograde menstruation occurred in most animals, and that endometriosis could be induced by intrapelvic injection of endometrium.

New concepts, derived from the baboon model, were the observations that endometriosis was less prevalent in animals living in the wild, that intrapelvic injection with menstrual endometrium was more effective to induce endometriosis, and the concept of remodeling. Remodeling was the second trigger for the endometriotic disease concept.

7. Conclusions and discussion

To interpret the data from the literature it is thus important to consider: (1) the awareness of minimal endometriosis, which is important to judge the ‘‘contamination’’ of the normal group with women having minimal endometriosis together with the overall severity of endometriosis in the group with minimal endometriosis; (2) the awareness of deep endometriosis will determine the incidence of ‘‘unrecognized’’ deep endometriosis in the

minimal-mild groups, whereas (3) only depth of penetration and volume will permit to evaluate the ''enthusiasm'' of the surgeon to include smaller spots infiltrating 4 to 5 to 6 mm; (4) the size of cystic ovarian endometriosis, the presence of adhesions, the pathological confirmation of the disease and the technique used, to compare reported series on cystic ovarian endometriosis.

To demonstrate this, the Leuven data of endometriosis, spanning 25 years of interest and three generations, have been reviewed, describing the contributions to the LUF syndrome, to non-pigmented endometriosis, to cystic ovarian endometriosis, to deep endometriosis, to endometriosis as an immunologic disease, and to the development of an animal model of endometriosis. These data were used to illustrate the important shifts that occurred in the data reported in the literature. During the seventies, the typical lesions, reported as endometriosis, became smaller and smaller, and this trend was boosted by the recognition of non-pigmented endometriosis followed by the ''witch hunt'' for the smallest lesion during the second half of the 1980s. It thus is obvious that over the years important shifts occurred from the group of women without endometriosis to the group of women with mild or moderate disease. These shifts are important to interpret the data on prevalence, immunology, results of treatment, etc. The second important shift is caused by the recognition that deep endometriosis is a frequent disease, and by the fact that women with deep endometriosis are generally staged as having stage I or II disease according to the revised AFS classification or even as women without endometriosis. The impact of this upon our understanding of endometriosis as a cause of pain and/or infertility has not yet been realized to its full extent, and today it still sounds as an hypothesis that mild and moderate endometriosis only rarely cause pelvic pain, whereas the pain symptoms reported in this group of women are generally caused by deep endometriosis. This would implicate that LHRH agonists are an effective treatment of pain only because of their effect upon deep endometriosis only. A shift occurring since a few years is that the deep lesions become progressively smaller, partly as a consequence of a menstrual clinical examination picking up smaller lesions, and partly because of the ''enthusiasm'' of the surgeons performing more easily surgery for deep lesions. Only a careful assessment of type of lesion and depth of infiltration will permit to evaluate the validity of this shift.

The diagnosis and the treatment of cystic endometriosis are still debated. The problem of misdiagnosis by removal of a cystic corpus luteum could be solved with a rapid – e.g., a dipstick – CA125 assay. The importance of emphasizing the physiopathology of cystic ovarian endometriosis is that focal treatment should no longer be considered as inadequate treatment by an inexperienced surgeon, but rather as the way to go, at least in women with larger cysts.

Understanding physiopathology has been in medicine our constant guide for diagnosis and therapy. The recognition of non-pigmented endometriosis was important to emphasize attachment of endometrial debris and early growth of endometriosis. The physiopathology of deep endometriosis is still unclear, especially whether type II – retraction – is a different entity. It remains obvious however, that type I and type III lesions are rarely associated with adhesions, whereas for type II lesions and cystic ovarian endometriosis, the presence of adhesions is the most prominent feature. That these concepts are important for the interpretation of the date can be illustrated with the NK data. The decrease in NK activity paralleled the severity of the disease by the revised AFS classification. When analyzed, however, by two-way analysis of variance (unpublished data) the decrease of NK activity was explained by endometriotic disease, deep endometriosis and cystic ovarian endometriosis, and not by mild and moderate endometriosis. This also illustrates the impact of deep endometriosis upon the stages I and II of the revised AFS classification.

The changes in our understanding of the pathophysiology are best illustrated in the endometriotic disease theory as opposed to the implantation theory. This thinking was initiated by the prevalence of minimal endometriosis, by the concept of remodeling, by the observations on deep endometriosis, and supported recently by the evidence that the endometrium in women with endometriosis is different from the endometrium of women without endometriosis. The similarity between endometriotic disease and a benign tumor is attractive, since it permits to incorporate easily observations on heredity, on immunology, and dioxin pollution, while not being contradictory to the classic implantation theory. It only emphasises that for endometriotic disease to develop implantation is not sufficient. Something else is needed, e.g., a mutation as has been shown to be the cause of many benign tumors, and this is more likely to happen in women who are genetically or immunologically predisposed, or in women who have a more ''toxic'' peritoneal fluid caused by the environment or by other factors such as LUF syndrome or retrograde menstruation. The type of genetic disorder will then determine whether this endometriotic disease is expressed as cystic ovarian or as deep endometriosis.

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