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PERSPECTIVE

An endometriosis classification, designed to be validated

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Abstract Several endometriosis classifications were proposed, based on the assumption that endometriosis is a progressive disease, and designed to score severity of visible lesions. In addition, several specific classifications, e.g., for deep endometriosis, were proposed. None of these classifications however, have been validated to be predictive for diagnosis, treatment prognosis, recurrence, progression or for the associated infertility or pain. The difficulties derive from the fact that pathophysiology and the natural history are still uncertain. A classification should avoid assumptions. It seems established beyond reasonable doubt that endometriosis presents as subtle, typical, cystic, and deep lesions and that severity of each lesion is related to size or volume. By pathology, these four lesions present as active, burnt-out, inactive, and active lesions, respectively. Besides this, there are many uncertainties. It is unclear whether endometriosis is one disease progressing ultimately into severe endometriosis or whether typical, cystic, and deep endometriosis represents three different diseases, each being an end stage. It is unclear whether endometriotic cells are different from endometrial cells or whether only the environment is different. It is unclear how adenomyosis, Müllerianosis, and peritoneal pockets should be considered. We therefore suggest a descriptive classification with the severity of Subtle, Typical, Cystic, Deep, Adenomyotic, and peritoneal pocket lesions, estimated by their area or volume. This classification should permit to evaluate the actual uncertainties in order to build subsequently a validated classification. The similarity of the classes for superficial and cystic lesions with the rAFS classification is considered an advantage. It is discussed why adhesions need not to be scored. In conclusion, a simple classification scoring separately severity of subtle, typical, cystic, deep, adenomyotic, and peritoneal pocket lesions is suggested. This will permit to confirm or reject statistically many of the actual uncertainties on endometriosis and to evaluate what the predictive power of the severity of each type of lesion is, both essential elements for a validated endometriosis classification.

Keywords Classification · Endometriosis · Adenomyosis · Peritoneal pockets · Müllerianosis

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Introduction

Endometriosis remains an enigmatic disease defined more than 100 years ago as endometrial glands and stroma outside the uterus. Yet we still do not have a solid understanding of the pathophysiology and natural history, which is not surprising in the absence of an appropriate animal model and of accurate non-invasive diagnostic methods. Also, the associated infertility and/or pain is poorly understood. Except for adhesions, we do not

understand the mechanisms of the associated infertility Also for pain, we do not understand why so many of the typical, cystic, and deep lesions do not cause pain.

With this 100-year-old microscopical definition, endometriosis presents clinically as subtle or non-pigmented lesions [1, 2], typical black puckered lesions in a white sclerotic area, cystic ovarian endometriosis, and deep endometriosis. Microscopically the glands and stroma of these lesions are active, burnt-out, inactive, and active, respectively. Other lesions as stromatosis, peritoneal pockets, endosalpingiosis [3–6], mullerianosis [7], and adenomyosis do not fit the strict definition

Historically, adenomyosis externa and cystic ovarian endometriosis were described more than 100 years ago [8–13]. In the 70's, with laparoscopy came the awareness of the high incidence of typical lesions in women with pain and infertility [14, 15]. In the mid-80's, subtle or non-pigmented lesions were recognized to contain endometrial glands and stroma [1], leading to the search for microscopical endometriosis, a concept that was neither substantiated nor refuted [16]. In the 90's, the prevalence of deep lesions increased rapidly probably as a consequence of awareness and improved diagnosis [17].

We do not have an adequate animal model for endometriosis. Rodents do not have spontaneous endometriosis which is not surprising since they do not have a menstrual cycle with a long luteal phase and menstruation. Transplanted human endometriotic tissue to immunocompromised mice or to the chicken allantoic membrane obviously has a different immunologic and endocrine environment. Also, primates are not an adequate model for endometriosis. The rhesus monkey only occasionally develops cystic ovarian endometriosis, possibly more after dioxin administration [18]. Also, in the baboon, we failed to induce the more severe cystic or deep endometriosis. Whether useful for superficial lesions also remains controversial since most results would have been negative if the points of the revised American Fertility Society (rAFS) classes would not have been multiplied by two.

A classification of endometriosis should permit to orient treatment based upon the prediction of pain, infertility, progression, and recurrence. Today, treatment remains empirical, either by medically inactivating the endometrial tissue, or by surgical removal, based upon the never proven assumption that all endometriotic tissue that can be visually identified should be removed.

The history of the endometriosis classifications

The variability in clinical expression and in severity prompted the development of a series of classifications, none of which today has been validated as a guidance to therapy nor as a predictor of endpoints as pain, infertility, progression, or recurrence.

Many classifications were proposed highlighting the need and the difficulty. (for review [19]). As milestones, we consider Acosta [20] who suggested to distinguish between superficial lesions (class I) and cystic ovarian endometriosis including diameter, surgical difficulty, and adhesions (classes II and III). With this, the tone was set to distinguish superficial and cystic endometriosis. Subsequent attempts to be more complete with less ambiguity by Kistner and Buttram [21, 22] received no widespread acceptance or use; this prompted the American Fertility Society (AFS) to create a panel to design a classification system for endometriosis, published in 1979 and revised in 1985 [23, 24]. The AFS and the revised AFS classification became widely used. It was a point scoring system, attributing few points for superficial endometriosis according to the area involved, more points for cystic ovarian endometriosis increasing with size, and a lot of points for adhesions. Few attempts were made to evaluate the predictive value [23, 25] of these classifications while the clinical value was soon recognized as limited [26]. Analyzing the type of lesions found in each of the rAFS classes [24], it was shown that over 95% of women with rAFS class I and II had superficial lesions of less or more than 3 cm in diameter, respectively, while rAFS classes III and IV consisted of cystic ovarian endometriosis either small and unilateral or large and bilateral. The similarity between the Acosta and the rAFS classification thus is remarkable.

Since deep endometriosis is not scored in the rAFS classification, while varying widely in size and localization, several specific classifications were suggested by Koninckx [27], distinguishing between invading lesions and adenomyosis externa; by Adamyan [28], distinguishing between the degree of Douglas occlusion; and more recently, more surgically oriented classifications [29] and the ENZIAN score [30] specifying diameter and localization.

Elements to consider for an endometriosis classification

The pathophysiology is unclear

The first and most fundamental concept of a classification is whether the clinical presentations of subtle-typical-cystic-deep lesions results from progression to more severe forms [31], or whether each of these clinical forms constitute an endpoint of a different disease [32, 33].

The Sampson hypothesis [31], that endometrial cells regurgitated during menstruation could implant and develop into endometriotic lesions seems supported by the implantation and developmental potential of menstrual endome-

trium as demonstrated in women [34] and models as immuno-suppressed mice and the chicken allantoic membrane. Doubt came however, with the realization that retrograde menstruation occurred almost systematically in all women [35] and the question was asked why not all women developed endometriosis. It was even suggested that the lower steroid hormone concentrations in peritoneal fluid of women with a luteinized unruptured follicle syndrome might facilitate implantation [36]. Endometriosis thus would be a consequence of infertility instead of a cause. The observations that total body radiation and dioxin could increase the incidence of severe endometriosis, and that endometriosis was a hereditary disease moreover suggested a genomic alteration or predisposition. Also, the peritoneal fluid constituents did not bring an explanation for progression in some women only. More important is that progression—the key element of the Sampson hypothesis—have not been confirmed. Besides subtle lesions developing into typical lesions, there is no evidence of typical lesions developing into deep of cystic ovarian or of cystic lesions developing into deep lesions. Circumstantial evidence suggests, moreover, the opposite. In the late 70s, typical lesions were the focus of research at Leuven University. Two decades later, we realized that the women diagnosed with severe cystic or deep endometriosis were not specifically those diagnosed with typical lesions previously in this small community of the Leuven area. Also, the concept that endometriosis is a recurrent disease seems contradicted by the recurrence of cystic endometriosis which is only 5% following excision while the recurrence of deep endometriosis is even lower.

The endometriotic disease theory [32, 33] suggested that subtle endometriosis was a benign condition occurring intermittently in all women, whereas typical, cystic, and deep endometriosis would be the end points of three different diseases. It was postulated that implantation of regurgitated cells occasionally occurs in all women, but that the other types of lesions would require some genomic alteration similar as found in many benign tumors. According to the type of mutation, these cells would then develop into typical, cystic, or deep lesions. This hypothesis easily explains the effects of dioxin, of total body radiation, and the hereditary aspects. A strong argument is the findings that cystic and deep endometriosis is clonal in origin. Progression thus would be the consequence of a genomic mutation, and the altered peritoneal fluid environment would become a consequence instead of a cause.

In conclusion, it is unclear today whether the different clinical manifestations, typical-cystic-deep, are one disease and are the various forms of a progressive development of an implanted normal cell; or whether they represent three different diseases arising from three different types of mutations. It should, moreover, be realized that this not only applies to implanted menstrual cells, but also to the metaplasia theory, to development of embryological rests, and to implanted stem cells [37, 38]. Hematogenic and lymphogenic [39–42] spread probably variably consist of normal and abnormal cells.

Subtle endometriosis should be classified separately

The significance of subtle lesions is unclear. Subtle lesions are considered the first lesions after implantation of endometrial cells. It remains unclear however, whether subtle lesions are the initial phase of a progressive disease [31], or whether subtle lesions do occur intermittently in all women [43, 44] emerging, regressing, and re-emerging at other places of the pelvis.

Subtle lesions have not been demonstrated to be associated with pain or infertility. The luteinized unruptured follicle syndrome (LUF) [14, 36, 45, 46] was found to be associated with typical lesions but not with subtle lesions [47] the association of typical endometriosis and LUF disappearing after 1986 when women with subtle lesions were no longer considered normal but as having endometriosis.

Deep endometriosis should be classified separately

Deep endometriosis suffers from a lack of definition. It is suggested to add the pathologic appearance of adenomyosis externa to the initial definition of deeper than 5 mm under the peritoneum [27]. Indeed by pathology, some deep endometriosis lesions, generally smaller, are burnt-out lesions as typical lesions, while other lesions present with sparse glands and stroma in a fibromuscular nodule resembling adenomyosis (externa). If defined only as more than 5 mm under the peritoneum, we risk to include a variable number of larger typical lesions. Adding to the criterium of depth the pathologic aspect of adenomyosis externa, deep endometriosis nodules almost invariable are larger, rarely less than 1 cm in diameter, mostly unique, two nodules being rare, three or more exceptional.

Deep endometriosis is specific in being associated with metastasis in the regional lymp nodes [39–42] while being the strongest predictor of pelvic pain.

Adenomyosis, peritoneal pockets, and mullerianosis

The relationship between adenomyosis and endometriosis, pain and infertility remains unclear. Also the exact clinical significance of uterine junctional zone thickening and of adenomyotic nodules, which can become huge in size, remains debated [48].

Peritoneal pockets and Mullerianosis are debated since over two decades [49]. Peritoneal pockets almost invariably contain endometriotic lesions or mullerianosis. It is unclear whether these cells of embryological origin occasionally

progress or undergo mutations to develop into endometriotic lesions.

Suggestions for a classification designed to test statistically hypotheses in order to permit validation

Subtle, typical, cystic, and deep endometriosis should be scored separately together with the adenomyosis and peritoneal pockets, becoming a STCDAP classification. The severity of each lesion can be scored by the mean diameter of the pelvic area, or of the nodule. We however, suggest a scoring in classes (Table 1).

Subtle endometriosis (S) and typical lesions (T) can be scored according to a total area smaller or larger than 3 cm as S1 and S2 or as T1 and T2, respectively. This would correspond in over 95% of women to the actual rAFS classes I and II.

Cystic ovarian endometriosis (C) is suggested to be classified as: C1 being unilateral and less than 5 cm in diameter, C2 being bilateral or more than 5 cm in diameter, again because of the 95% similarity with the actual rAFS classes III and IV.

For deep endometriosis (D) we suggest to classify them as D1, D2, and D3 being the total volume corresponding to a nodule of less than 1 cm, between 1 and 3 cm and more than 3 cm in diameter. Since the importance for the associated pelvic pain, it is suggested to score in addition the localization, (rectovaginal, sigmoid, bladder) and the presence of hydronefrosis.

For adenomyosis (A), we should distinguish between a thickened junctional zone (A1) and a focal adenomyotic nodule of more than 1 cm (A2). For peritoneal pockets a diameter of less or more than 1 cm could be distinguished (P1 and P2, respectively).

It is strongly suggested to indicate explicitly the absence of lesions and the absence of information in order to avoid doubt during subsequent statistical analysis. A negative laparoscopy without an MRI or ultrasound of the uterus being performed, thus would become S0T0C0D0A.P0.

Discussion

A classification today should avoid unproven assumptions. It should preferably be descriptive containing the elements that will permit subsequent statistical analysis and hypothesis testing. Scoring each clinical type of endometriotic lesion independently as subtle, typical, cystic, and deep while adding adenomyosis, and pockets will permit to calculate the predictive value of each individual phenotype, to evaluate which variables behave as independent variables, and to test the hypothesis that the different phenotypes can be considered as progressive steps of severity. The VCUAM classification for congenital anomalies is an example of a similar approach [50].

To assess the importance of the severity of each type of lesion as a predictor of fertility, pain, recurrence, progression, etc., a measure of severity is required. The severity of each lesion could be indicated by the diameter or volume of the lesions, permitting for each lesion to assess the relationship between severity and prediction. This could become the basis of distinguishing clinical useful subclasses. It is anticipated however that this will require huge amounts of data for meaningful results. Whereas using the exact diameters obviously would be ideal, we however suggest a more simple classification of severity. First, the 95% similarity between the newly proposed classes T1, T2, C1 and C2, and the rAFS classes I, II, III, and IV, respectively, will maintain continuity with the actually used rAFS classification. Secondly, the clinical acceptance/usefulness of a classification increases with simplicity. Thirdly, in order to demonstrate the clinical impression that for subtle, typical, and cystic lesions, the area involved or

Table 1 A simple descriptive endometriosis classification with either the exact diameter of lesions or classes designed to permit statistical validation and analysis

Type of lesion	Localization	Mean diameter	Classes		
Subtle		mm	1=<3 cm	2=>3 cm	
Typical		mm	1=<3 cm	2=>3 cm	
Cystic		mm	1=<5 cm and unilateral	2=>5 cm and/or bilateral	
Deep	Rectovaginal	mm	1=<1 cm	2=2–3 cm	3=>3 cm
	Left/right		1=<1 cm	2=2–3 cm	3=>3 cm
	Sigmoid	mm	1=<1 cm	2=2–3 cm	3=>3 cm
	Bladder	mm	1=<1 cm	2=2–3 cm	3=>3 cm
	Ureter hydronefrosis	mm	1=<1 cm	2=2–3 cm	3=>3 cm
Adenomyosis			1=junctional zone	2=focal nodule	
Pockets			1=<1 cm	2=>1 cm	

the diameter of the cyst matters, simple 0/1/2 and absent/mild/severe classes should be sufficient to calculate for which types of lesions severity matters. Finally, using predefined classes instead of real diameters, will prevent future authors to use different cutoffs for classes making comparisons more difficult. For those entering data directly into a database, we suggest, however, that they enter mean diameters, although it is unclear whether an increased clinical predictive value will outbalance the increased complexity of using the exact diameters

Adhesions are not included and are suggested not to be scored. First, it was demonstrated that cystic ovarian endometriosis and adhesions are so strongly associated [8]; that statistically (logistic regression) they carry the same information and that identical rAFS classes can be obtained by increasing the points of either adhesions or cystic endometriosis and omitting the other. More importantly, adhesions are so variable in severity following previous surgery that it becomes difficult to distinguish between surgery-related and endometriosis-related adhesions. Finally, the occurrence of cystic ovarian endometriosis without adhesions is so rare that, anyway, a statistical evaluation of this potentially different group will be practically impossible by lack of numbers.

Subtle endometriosis is scored separately from typical lesions. By pathology, they are different, the former being active lesions, the latter being burnt-out lesions. Subtle lesions in contrast with typical lesions are not associated with the LUF syndrome while no data indicate today that subtle lesions cause pain or infertility. Another important argument to score subtle lesions separately is that typical lesions are readily recognized during laparoscopy, whereas the recognition of subtle lesions varies with the expertise and the scrutiny of the surgeon. A separate classification will permit to evaluate whether subtle lesions are clinically important for pain, infertility, progression, and most importantly whether subtle lesions predict more severe lesions in the future. For the patient, it indeed would be important to know whether subtle lesions herald the onset of more severe lesions or whether they should be considered less important.

Deep endometriosis also is scored separately, and to the definition of depth the, microscopical aspect of adenomyosis externa is added. Thus deep endometriosis would become a homogeneous group of active, larger, generally unique lesions while the definition of depth only risks to include the larger typical lesions. Since women with two or more larger nodules are rare, we suggest classifying the total volume since multiple nodules are so rare that the numbers required for meaningful statistics are expected to be prohibitively large. It is unclear whether other aspects as localization, lateral extension, and bowel or ureter infiltration or hydronephrosis should be included. Given the relationship with pain symptoms we however do consider it an advantage to add localization.

The classification as suggested is a descriptive classification aimed to investigate the relationship between type and severity of endometriosis and symptoms, progression, pathophysiology, and therapy. To do this obviously, other variables will have to be used as co-variables. For fertility factors as severity of adhesions, surgical aspects, age, and the duration of infertility will have to be used as co-factors [51]. To assess surgical difficulty and complications Douglas obliteration [28], depth of bowel invasion [30], degree of hydronephrosis, and number of previous surgeries are important. This points to the fundamental difference between the endometriosis classification proposed aimed to investigate the type and severity of endometriosis while controlling for other variables, and a (multivariate) prediction model as the fertility index [51]. Our main concern indeed is to limit the variables as much as possible, since otherwise the series required for multivariate statistical analysis would become unrealistically high.

Peritoneal pockets, mullerianosis, and uterine adenomyosis are suggested to be added to an endometriosis classification. After decades of discussion, little is known with certainty. The proposed classification will at least permit to evaluate whether peritoneal pockets are a pathology that should be treated and what the relationship with mullerianosis is. For adenomyosis the relationship with pain, infertility, and with endometriosis or more, specifically deep endometriosis, is unclear but is important to be investigated.

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