Association of Endometriosis and Adenomyosis: Vast Literature but Scant Conclusive Data

Despite the presence of more than 15,000 articles with “endometriosis” or “adenomyosis” on their titles published in peer-reviewed journals, our understanding of these 2 entities remains limited and is thus subject to much controversy. As discussed previously in this journal, the elephant in the room is the number of publications and the quality control of the data [1]. The exponentially increasing flow of information also includes publications in journals that review poorly and on websites and social media. The information overload necessitates selective reading of properly reviewed good studies, often only of the abstract or conclusions. However, the huge volume of manuscripts submitted hampers the quality of peer review. This vicious circle is moreover fueled by the pressure to publish that stimulates slicing complex data into several partial reports. Slicing of data into simple questions multiplies the number of publications, accelerates publication, and facilitates reviewing. Slicing of data, moreover, becomes necessary when the length of publications is limited (e.g., to 2500 words), but this makes the understanding of more complex problems more difficult.

In the absence of an animal model to test a hypothesis, endometriosis and adenomyosis are limited to observational data with specific statistical pitfalls. First, the quality and completeness of data collection need a clear description of methods and definitions used. Second, it is obvious that a significant association of \( p = 0.05 \) also means a probability of 5% that the association is not true. Less obvious is the risk of 1 spurious or false-positive significant result when multiple comparisons are performed. When performing 10, 20, 40, or 60 comparisons, the risk of a false-positive result increases from 40% to 64%, 87%, and 95%, respectively [2,3]. To avoid this trap, it is important that the hypothesis or the aim of a study is clearly formulated before analysis, instead of analyzing data sets without a hypothesis, which some consider “torturing data until they confess” [2,4].

The article, “Anterior Focal Adenomyosis and Bladder Deep Infiltrative: Is There a Link?” [5], in the current issue of the journal provides good and clear data and suggests a common pathophysiologic mechanism. However, after reading the article several times in detail, the many emerging questions prompted us to comment to stimulate discussion on the association of endometriosis and adenomyosis, on their pathophysiology, and on the pitfalls of statistical evaluation of observational data.

Clinical Association of Adenomyosis and Endometriosis

Endometriosis and adenomyosis are widely believed to be associated, because both lesions fit the definition of endometrial glands and stroma outside the uterus. Hence, speculation about a common or similar pathophysiology becomes logical. However, a clear understanding of the association is hampered by the different phenotypes of endometriosis and of adenomyosis. Moreover, the accuracy of the diagnosis of both diseases varies with the diagnostic method.

Diagnosis of superficial endometriosis requires a laparoscopy. Without entering the debate of whether subtle lesions should be considered a pathology [6], we must be aware that in most studies it is not stated whether women with superficial endometriosis comprise women with typical lesions or those with subtle lesions. The latter would increase the prevalence of endometriosis from 50% to 80% in women with pain and/or infertility [7]. Diagnosis of cystic ovarian and of larger deep endometriotic lesions by imaging only, ultrasound, or magnetic resonance imaging (MRI) is highly accurate. However, the lower detection limit of deep endometriosis by imaging is not well established.

Adenomyosis was initially defined as the depth of invasion by microscopic examination. Later, 3 distinct groups were defined by MRI: a thickened junctional zone, diffuse adenomyosis, and a focal adenomyotic nodule that occasionally can become very large. Ultrasonic examination diagnoses adenomyotic nodules and diffuse adenomyosis of the myometrium with sensitivities and specificities of 60% to 80% [8]. Recently it was demonstrated that 3-dimensional ultrasound [9] permitted the visualization of the junctional zone.

Unfortunately, the exact relationship between endometriosis and adenomyosis as defined by pathologic examination and diagnosed by imaging only is not that well established because microscopic examination can be performed only in those in whom a laparoscopy with a biopsy or a hysterectomy [8] or a debulking of a large adenomyosis is performed.
The variability in phenotypes and limitations of diagnostic methods [10] illustrate the inadequacies of the available studies.

In contrast with the widely accepted belief, solid data demonstrating the association between endometriosis and adenomyosis are limited. In studies in which endometriosis was diagnosed by laparoscopy, the presence of focal adenomyotic nodules are reported to be more frequent in subjects with deep endometriosis [11,12]. Whether other forms of endometriosis, as subtle, typical, or cystic ovarian endometriosis, are associated with adenomyosis defined as a thickened junctional zone, as diffuse adenomyosis, or as focal adenomyotic nodules remains unclear. Studies without a laparoscopy (and thus limited to cystic ovarian endometriosis or larger deep endometriosis diagnosed by imaging) report a strong association with adenomyosis (either junctional zone thickening, diffuse adenomyosis, or a focal adenomyotic nodule) with prevalences of 80.6% endometriosis in adenomyosis and 91.1% of adenomyosis in endometriosis [13].

It is surprising that most studies on the association of endometriosis with adenomyosis are relatively small with no attempt to correlate comprehensively the different phenotypes and diagnostic methods used, such as laparoscopy, ultrasound, and MRI. This might be the consequence of slicing of data. However, we speculate that this might be due to the widely held belief that all phenotypes of adenomyosis and endometriosis are a single disease, which is a consequence of the Sampson theory.

A Common Pathophysiology?

The pathophysiology of endometriosis and adenomyosis remains debated, with 2 opposing views [14]. The Sampson theory [15] considers endometriosis, and by extension adenomyosis resulting from the implantation of normal endometrial cells, either from retrograde menstruation, neonatal menstruation, or after metaplasia [16], of 1 of the following cell types: peritoneal mesenchymal cells, peritoneal or endometrial stem cells, or bone marrow or pale cells. The different phenotypes result from the different environment, and by definition a metaplastic cell returns to normal without this stimulus. However, the Sampson theory is a hypothesis, which is not compatible with the clonal origin of deep and cystic endometriosis. Also, the hereditary aspects of endometriosis and the effects of dioxin and radiation are difficult to explain using the Sampson theory.

The endometriotic disease theory therefore [14,17] postulates the necessity of a genetic and/or epigenetic incident and suggests that the type of incident will determine the further development into typical, cystic, and deep endometriosis (i.e., the different endometriotic phenotypes with clinical symptoms). A major difference with the Sampson theory is that the frequent subtle and microscopic endometriosis and the endometriosis found in the lymph nodes in women with deep endometriosis of the bowel are not (as yet) a disease. Another consequence is that endometriosis becomes a heterogeneous disease through a variable combination of genetic and/or epigenetic incidents. This heterogeneity can explain why during pregnancy most lesions will decrease in activity whereas others will progress, causing bowel perforations [18] or severe bleeding [19]. This may also explain the clinical observation of progression during the intake of progestagenic medical therapy. Applied to adenomyosis, the fundamental question is similar. Either these cells are “normal” or they have undergone a series of specific (epi)genetic changes.

The hypothesis of (epi)genetic incidents also changes our interpretation of the many reported differences in the endometrium of women with endometriosis. These changes can be considered as a first hit, explaining their predisposition or their vulnerability to a second hit. Numerous articles since 2014 describe similar alterations in endometriosis and in adenomyosis, such as apoptosis by endocannabinoids [20], matrix metalloproteinase promoter polymorphisms [21], genetic variation in COX-2-1195 [22], expression of DJ-1 and mTOR [23], differential proteomic analysis of endometriosis and adenomyosis by the iTRAQ technique [24], and COMT 158G/A and CYP1B1 432C/G polymorphisms [25]. Endometriosis and adenomyosis also were described to have similar comorbidities [26].

The questions if and how endometriosis and adenomyosis are associated is clinically important beyond research curiosity. The increasing focus on adenomyosis in the last decade and the observation that the prevalence and severity of deep endometriosis seems to be increasing over the last 20 years strongly suggest a causal relationship with our environment and with pollution [27]. Also the associations between endometriosis and adenomyosis and physiologic changes of spiral arteries in the junctional zone and pregnancy hypertension are important since they are detrimental to human reproduction [28].

Interpretation of Research Data and the Bias of Publications

The article by Marcellin et al [5] cited above describes that 50% of women with deep endometriosis of the bladder have focal adenomyosis of the anterior wall of the uterus, suggesting a common mechanism of infiltration of cells from retrograde menstruation in the vesicouterine fold. To explain the adenomyotic nodule in the myometrium, the mechanism of “outside-in” implantation had to be postulated. We suggest that the Sampson theory, which requires several additional hypotheses as metaplasia and now in this article “outside-in” implantation to remain compatible with clinical observations, must be viewed with suspicion.

A second issue with the article is that the conclusion is based on the negative association of focal anterior wall adenomyosis with deep endometriosis of the posterior compartment in women with deep endometriosis of the bladder. Their tables indicate that 59 analyses were made resulting in a risk of 95% to have at least 1 false-positive result [2,3].
Considering the low number of patients, this risk is even higher. Especially intriguing is the significantly shorter (p = .02) duration of infertility, a lower rAFS score (p < .01), less adhesions (p < .01), less deep endometriosis of the bowel (p = .01), and especially less focal adenomyosis of the posterior wall (p = .001) in women with focal adenomyosis of the anterior wall or the uterus in comparison with those without. The associations of focal adenomyosis of the posterior wall and deep endometriosis of the bowel and adhesions and infertility seem an equally valid and important conclusion. With this we want to congratulate the authors for being precise and complete in presenting all data even if this permits drawing different conclusions.

Also, their specific definition of deep endometriosis of the bladder as endometriosis infiltrating the muscularis makes it difficult to conclude whether the women included had a typical lesion or a deep endometriotic nodule. It also is surprising that junctional wall thickness, which must be visible on MRI, was not developed.

Conclusions

These comments illustrate several aspects of publishing. First, eventual different conclusions illustrate the importance of making the complete data available in supplementary tables as the authors did. Moreover, the electronic media today permit submission of the raw data together with the manuscript. This would be a major advantage, permitting subsequent analysis. Second, it is important to describe accurately definitions and methods, including the rationale as to why some aspects as the junctional zone were not included in the study. Third, these comments illustrate slicing of data. That focal adenomyosis of the anterior wall and deep endometriosis of the anterior compartment are associated, whereas focal adenomyosis of the posterior wall and deep endometriosis of the posterior compartment and cystic ovarian endometriosis and infertility are associated seem to be equally important observations. However, to understand the many associations, a multivariate analysis is necessary. This in turn requires a much larger data set while resulting in fewer but more comprehensive publications.

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