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REVIEW

Adenomyosis: a life-cycle approach




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Giuseppe Benagiano has been Professor at 'la Sapienza', University, Rome, since 1980 and directed the First Institute of Obstetrics and Gynaecology and the Postgraduate School of Gynaecology and Obstetrics. Between 1993 and 1997, he acted as Director of the Special Programme of Research in Human Reproduction of the World Health Organization, and between 1997 and 2001 as Director General of the Italian National Institute of Health. Between 1997 and 2003 he was Secretary General of the International Federation of Gynaecology and Obstetrics. His postgraduate training was at Karolinska Institute, Stockholm and at Population Council, Rockefeller University, New York.

Abstract The life-cycle approach to endometriosis highlighted unexpected features of the condition; the same approach was therefore applied to gain insight into the clinical features of adenomyosis and to draw a comparison with endometriosis. This is possible today thanks to new imaging techniques enabling non-invasive diagnosis of adenomyosis. The specificity and sensitivity of magnetic resonance imaging and transvaginal ultrasound remain uncertain. Unlike endometriosis, little information is available on the presence of classic adenomyosis in adolescents, except for rare cystic forms that may not represent the true disease. Adenomyosis is most likely to affect adult women, although most reported incidences are still based on post-hysterectomy studies, and are affected by diligence in histopathologic diagnosis and the adopted cut-off point. The traditionally accepted associations of adult adenomyosis, such as multiparity, a link to infertility and its effect on pregnancy are uncertain. Active adenomyosis has been found in pre- and peri-menopausal women and in postmenopausal women receiving tamoxifen. In conclusion, major diagnostic limitations and the systematic bias of hysterectomy make it difficult to draw firm conclusions from existing evidence. In addition, no information is available on the natural history of adenomyosis and no study has systematically evaluated its existence in adolescents. 

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Introduction

Descriptions of 'mucosal invasions' of the peritoneal surface and organs were first published in the last part of the 19th century. With the exception of ovarian endometriosis, these structures were all considered to be adenomyomas (Benagiano

et al., 2014a). In the 1920s, two separate conditions were identified: endometriosis and adenomyosis, with different clinical profiles (Frankl, 1925; Sampson, 1925a, 1925b, 1927).

More recently, however, similarities between the two pathologies have led to a re-evaluation of the situation and to a theory that they may have a common origin (Benagiano and

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Brosens, 2011; Brosens et al., 2013a). In particular, evidence shows that endometriosis and adenomyosis have in common an endometrial dysfunction involving both eutopic and heterotopic endometrium (Benagiano et al., 2014b). Although anomalies are not identical, they share the common feature of leading to increased invasiveness. In both conditions, there is also a reaction of the inner myometrium that, although more pronounced in the case of adenomyosis, is nonetheless also present in endometriosis (Kunz et al., 2000).

Research on endometriosis has progressed rapidly owing to the introduction in the late 1960s and 1970s of endoscopic techniques; however, the study of adenomyosis continued to be limited to the evaluation of surgical specimen (i.e. to symptomatic disease requiring hysterectomy). Fortunately, over the past 2 decades, the availability of new diagnostic modalities, such as magnetic resonance imaging (MRI) and high resolution three-dimensional transvaginal ultrasound (3D-TVU), made it possible to study adenomyosis in women not requiring, or who cannot have, a hysterectomy and therefore to begin to reconstruct its natural history. In particular, the identification and evaluation of the inner myometrium or myometrial junctional zone by Hricak et al. (1983) provided new, non-invasive diagnostic criteria for adenomyosis (Luciano et al., 2013; Reinhold et al., 1996). This signalled the beginning of a new era, where comparative evaluation of the features of adenomyosis and endometriosis could be made, including both early and advanced stages. Also, the presence and frequency of the two conditions during the various stages of a woman's life can now be studied.

We have recently appraised endometriosis by applying a life-cycle approach (Brosens et al., 2013a). Here, we apply a similar approach to adenomyosis. Importantly, a life-cycle approach may allow the question of whether adenomyosis and endometriosis are linked to be re-visited, a concept that is not new and was proposed during the 1940s and 1950s (Javert, 1951; Novak and de Lima, 1948).

Although we have recently reviewed the pathophysiology of uterine adenomyosis (Benagiano et al., 2012), we wanted to assess whether further insight into its pathogenesis can be gained through understanding the disease in women not undergoing hysterectomy and by comparing features in different stages of life. This can now be done by applying the new, early, non-invasive diagnostic criteria for adenomyosis (Champaneria et al., 2010; Dueholm, 2006; Meredith et al., 2009; Novellas et al., 2011; Tamai et al., 2006).

Materials and methods

In order to identify features of adenomyosis at different stages of a woman's life, and attempt a comparison between adenomyosis and endometriosis, areas in which differences and similarities had already been evaluated were selected (e.g. incidence, imaging diagnosis, infertility, parity and pregnancy).

Critical evaluation and comparison was only possible for adult women. Therefore, for this group of patients, we searched for all articles published over the past 20 years on adenomyosis using Scopus and PubMed searches. The cut-off point for our search was March 2014. For adenomyosis, 143 articles were identified on histopathologic features and incidence, 160 on imaging diagnosis, 18 on issues relating to

parity, 69 on infertility and 81 on pregnancy-related issues. At this stage, analysis of publications was restricted to studies reporting findings in relation to age groups or a comparison with adenomyosis. Because of the variation in diagnostic criteria and in research methods, these studies do not lend themselves to meta-analysis and, although existing recent meta-analyses were used, a critical narrative review of published literature was opted for.

Given the paucity of data, all articles dealing with young or menopausal women were summarized, including early studies. All articles on adult women dealing with the above-mentioned topics were systematically identified, and relevant articles selected.

Imaging diagnosis

The specificity of a preoperative diagnosis of adenomyosis based on clinical findings is poor (Bird et al., 1972), ranging from 2–26% (Azziz, 1989; Molitor, 1971; Sammour et al., 2002). Meredith et al. (2009) analysed data from 14 selected published hysterectomy studies and found that adenomyosis was more common in women with heavy bleeding (31.9%), compared with all other hysterectomies (25.9%). The probability of adenomyosis in a woman with heavy bleeding and positive ultrasound features was 68.1%, compared with 65.1% probability in a woman with positive ultrasound if undergoing hysterectomy for any symptom. The investigators reported that the value of transvaginal ultrasound is weakened by the lack of uniform histopathologic and ultrasound criteria. Therefore, before a life-cycle approach can be applied to the natural history of adenomyosis, it is necessary to critically evaluate the accuracy of the new non-invasive diagnostic procedures.

In a systematic review and meta-analysis of the diagnostic accuracy of transvaginal ultrasound and MRI compared with histological standards (Champaneria et al., 2010), only three studies using MRI (Bazot et al., 2001; Dueholm et al., 2001; Reinhold et al., 1996) and six comparing transvaginal ultrasound (Bazot et al., 2001, 2002; Dueholm et al., 2001; Kepke et al., 2007; Reinhold et al., 1996; Vercellini et al., 1998), fulfilled quality criteria. Agreement was reached on three of the transvaginal ultrasound diagnostic features: the presence of myometrial cysts, a heterogeneous myometrium and focal abnormal echo-texture (Figures 1 and 2). All studies except Dueholm et al. (2001) and Reinhold et al. (1996) included the presence of globular or asymmetrical uterus. Two studies (Bazot et al., 2002; Kepke et al., 2007) emphasized the diagnostic value of sub-endometrial linear striations; only one study used colour Doppler (Bazot et al., 2002). The study by Bazot et al. (2002) reported on the diagnostic value of individual features examined, but some features had a higher sensitivity than the overall assessment, which appears contradictory. The reported sensitivity, specificity, positive and negative predictive value for transvaginal ultrasound in the study by Kepke et al. (2007) are the same as those reported for the sonographic feature of 'heterogeneous myometrium'. Thus, the relative weight of individual features remains unclear. Sonography concurred with histopathology in assessing the depth of invasion in only 57% cases and in assessing the degree of involvement and lesion density in only 23% (Bazot et al., 2001). Reinhold et al. (1996) on the other hand, reported good agreement between transvaginal

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