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JMIG The Journal of Minimally Invasive Gynecology

Review Article

Adenomyosis: What the Patient Needs

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ABSTRACT A panel of experts in the field of endometriosis expressed their opinions on management options in a 28-year-old patient, attempting pregnancy for 1 year, with severe cyclic pelvic pain and with clinical examination and imaging techniques suggestive of adenomyosis. Many questions this paradigmatic patient may pose to the clinician are addressed, and all clinical scenarios are discussed. A decision algorithm derived from this discussion is also proposed. Journal of Minimally Invasive Gynecology (2016) 23, 476–488 © 2016 AAGL. All rights reserved.

Keywords: Adenomyosis; Diagnosis; Pelvic pain; Pregnancy desire; Treatment

In 2013 a panel of Italian experts on endometriosis, adenomyosis, and pelvic pain disorders founded the Endometriosis Treatment Italian Club, or ETIC. ETIC has the primary scientific aim to identify any debatable issue in the management of endometriosis, offering the reader a complete review of the literature on that topic and trying to elucidate its controversies. Endometriosis and adenomyosis are considered as variants of the same disease and often-coexisting conditions. Both diseases are characterized by the

The authors declare that they have no conflict of interest.

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Submitted October 29, 2015. Accepted for publication December 31, 2015.
Available at www.sciencedirect.com and www.jmig.org

1553-4650/$ - see front matter
http://dx.doi.org/10.1016/j.jmig.2015.12.017

presence of endometrial glands and stroma outside their normal locations [1]. This article focuses on the management of a paradigmatic young patient, wishing to conceive, with the suspicion of uterine adenomyosis.

Clinical Case

A 28-year-old woman presented for a gynecologic consultation. Her family, past medical, and surgical histories were unremarkable. Menarche occurred at 12 years of age, and the patient had irregular and heavy menstrual periods. She had been trying to conceive for 1 year and complained of severe chronic pelvic pain (graded 90/100 on a 100-mm visual analog scale), severe dysmenorrhea (graded 95/100 on a 100-mm visual analog scale), and deep dyspareunia (graded 78/100 on a 100-mm visual analog scale) for 2 years. The patient had never used oral contraceptives or other hormonal therapies. Gynecologic examination, pelvic ultrasound, and magnetic resonance imaging (MRI) were suggestive of uterine adenomyosis. Given this background, the aim of the current study was to discuss all potential criticisms arising from this paradigmatic case of uterine adenomyosis to clarify the main issues potentially encountered during the management of this condition.

Uterine adenomyosis is defined as the presence of endometrial glands and stroma within the myometrium, and its reported prevalence in literature is extremely variable (14%–66%) because of the histologic criteria adopted for diagnosis and the technique used to obtain myometrial samples [2–6]. The definitive diagnosis of adenomyosis is based on histologic examination after hysterectomy. By tradition, a histologic diagnosis is made when endometrial glands and stroma are found at least 1 low-power field beneath the endomyometrial junction ($\geq$4 mm) [7], even if less restrictive criteria were proposed [8,9].

Uterine adenomyosis may be asymptomatic in about 35% of the cases [10], whereas 50% of women with symptoms have menorrhagia, 30% have dysmenorrhea, and 20% have metrorrhagia [11,12]. Around 20% of patients experience both menorrhagia and severe dysmenorrhea [13]. Dyspareunia and chronic pelvic pain are less common symptoms [14]. Because as many as 80% of women with uterine adenomyosis have coexisting pelvic disease, it is troublesome to distinguish which symptoms are caused only by adenomyosis [14]. Furthermore, the association of uterine adenomyosis with infertility is still debated. It was deemed that adenomyosis was a typical condition of parous women. However, adenomyosis has become more relevant in the setting of infertility and assisted reproductive technologies due to the improvement in imaging techniques and to the growing number of women delaying their first pregnancy until late thirties or early forties [15,16].

Pathogenesis

The pathogenesis of ectopic endometrial implants in the myometrium is still debated. Four principal theories were proposed. Recent studies suggest that estrogen-induced epithelial to mesenchymal transition of endometrial cells could play a role in the migration and invasion of endometrial cells. Higher expression of estrogen receptor-β in endometrium basalis and decreased expression of progesterone receptors A and B may be related to development or progression of adenomyosis [17]. Angiogenesis deriving from unbalanced proangiogenic and antiangiogenic factors could increase the survival of endometrial implants in the myometrium. Immune factors, such as cell surface antigens and adhesion molecules, have been shown to be altered in adenomyosis. According to the most widely accepted theory, the mechanical lesions to the endometrial–myometrial interface lead to disruption of the junctional zone (JZ) and invagination of the basal endometrium into myometrium, probably due to a defect of regeneration, healing, and re-epithelization of this site.

The incidence of adenomyosis is increased after uterine surgery, cesarean section, postpartum endometritis, pregnancy, uterine trauma, and surgery [18]. Thus, adenomyosis was initially thought to be a condition of parous women, with poor association with infertility [19]. On the contrary, in the last few years some authors linked this condition to subfertility, because more and more women are delaying childbearing due to social reasons and better imaging techniques have identified adenomyosis in women labeled as having “unexplained infertility” [15].

Histology

No universally accepted criteria exist to define the histologic presence of adenomyosis. Definitions such as “foci located deeper than 25% of the myometrial thickness” or “glandular extensions greater than 1 to 3 mm below the endometrial layer” are commonly used. Most studies use a cutoff of 2.5 mm below the basalis layer to define the minimal depth of invasion [5].

The main histologic feature of adenomyosis is represented by the presence of endometrial glands and stroma within the myometrium, and “ectopic” endometrium is generally associated with smooth muscle changes. These modifications of uterine structure may range from simple thickening of the JZ $>$ 12 mm to nodular or diffuse lesions involving the entire uterus. The JZ is the inner part of the myometrium involved in implantation and deep placentation that, similarly to the endometrium, is of Müllerian origin and from which the uterine peristaltic activity originates. The JZ shows cycle-dependent changes in response to hormonal stimulation, with usual thickness ranging from 5 to 8 mm in premenopausal women [20]. JZ hyperplasia (8–12 mm of thickness) indicating inordinate proliferation of smooth muscle cells (myosis) is not necessarily linked to the presence of heterotopic endometrium, even if many authors claims that the disruption of the architecture of this myometrial layer leads to adenomyosis development [21]. Adenomyosis can be defined as diffuse or focal. Focal