Introduction: Uterine adenomyosis, another enigmatic disease of our time

Jacques Donnez, M.D., Ph.D.,[a] Olivier Donnez, M.D., Ph.D.,[b] and Marie-Madeleine Dolmans, M.D., Ph.D.[c,d]

[a] Catholic University of Louvain, Société de Recherche pour l'Infertilité (SRI), Brussels, Belgium; [b] Institut du Sein et de Chirurgie Gynécologique d'Avignon, Polyclinique Urbain V (ELSAN Group), Avignon, France; [c] Pôle de Gynécologie Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium; and [d] Gynecology Department, Cliniques Universitaires Saint Luc, Brussels, Belgium

Like endometriosis, uterine adenomyosis is another enigmatic disease and remains a source of controversy. Uterine adenomyosis is characterized by the presence of endometrial glands in the myometrium. Two main theories may explain its pathogenesis: adenomyosis may arise from invagination of the myometrial basalis into the myometrium; or an alternative theory maintains that it may result from metaplasia of displaced embryonic pluripotent müllerian remants or differentiation of adult stem cells. Uterine adenomyosis is responsible for pelvic pain, abnormal bleeding, and infertility. Its diagnosis may be improved by high quality imaging. In this issue's Views and Reviews, authors stress the urgent need to establish some systematic classification. Medical and surgical strategies are discussed. It should be emphasized that treatment should be designed according to a patient's symptoms and an individual's needs. Surgical treatment remains a matter of debate. Indeed, the risk of uterine rupture during pregnancy after adenomyomectomy is a reality. Therefore, continued research into new molecules based on the pathogenic mechanisms is vital. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)

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Uterine adenomyosis, histologically characterized by the presence of endometrial glands in the myometrium, affects 20% of women of reproductive age and is responsible for pelvic pain, abnormal bleeding, and infertility (1, 2). However, high rates of comorbidity with other conditions like fibroids and endometriosis makes it difficult to attribute a specific pathognomonic symptom to adenomyosis (2). Neither its etiology (risk factors) nor the pathogenesis is yet fully understood, so information on its prevalence in adolescent girls remains limited.

This issue's Views and Reviews is devoted to uterine adenomyosis, from its pathogenesis to its classification, diagnosis, medical therapy, and surgical management.

Adenomyosis is a commonly encountered benign uterine disease characterized histopathologically by the presence of islands of ectopic endometrial tissue within the myometrium, typically found at different depths and often surrounded by hyperplastic and hypertrophic smooth muscle. It manifests as any of a spectrum of lesions, ranging from a slightly thickened functional zone to full-thickness uterine adenomyosis. Gross pathology usually reveals an enlarged and globular uterus with areas of hypertrophic myometrial smooth muscle. Histopathological examination allows direct vascularization of endometrial tissue within the myometrium, showing a variable degree of adjacent myometrial hyperplasia that causes globular and sometimes cystic enlargement of the myometrium. Some cysts are filled with hemolyzed red blood cells and siderophages. Two principal forms of the disease, focal and diffuse, are generally described but, as stressed by Gordts et al. (2), there is an urgent need for a more formal categorization and comprehensive classification of uterine adenomyosis. This should take into account its location in the myometrium, as well as different histological variants.

To date, two main theories have been proposed to explain the origin and pathogenesis of adenomyosis (1). The most common suggests involvement of the tissue injury and repair mechanism, claiming that adenomyosis arise from invagination of the endometrial basalis into the myometrium. An alternative theory maintains

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Correspondence: Jacques Donnez, M.D., Ph.D., Director, Société de Recherche pour l'Infertilité, Avenue Grandchamp 143, Brussels 1150, Belgium (E-mail: jacques.donnez@gmail.com).

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that adenomyotic lesions result from metaplasia of displaced embryonic pluripotent müllerian remnants or differentiation of adult stem cells. The epithelial-mesenchymal transition process occurring in the early stages of progression, as well as collective cell migration, may both be implicated in the later events of invasion.

Recent improvements in imaging techniques like transvaginal ultrasound and magnetic resonance imaging (MRI), as described by Bazot et al. (3), have led to major advances in the field, allowing new conservative treatments to be developed for adenomyosis. In their review, Bazot and Daraï also stress the need for uniform terminology and consensus classification. They clearly demonstrate the different morphology and locations of subtypes of the disease, including internal adenomyosis, adenomyoma and external adenomyosis. They draw our attention to possible pitfalls in the diagnosis of adenomyomas, such as confusion with leiomyomas and myometrial contractions. Myometrial contractions can be differentiated from leiomyomas or adenomyomas by sequential studies thanks to their transient nature (3). Visualization of physiological variations of the junctional zone on MRI images is dependent on the patient's age and hormonal status (contraceptive pills, gonadotropin-releasing hormone agonist [GnRHa], progestogens) as well as the menstrual cycle day.

From Vannuccin and colleagues (4), messages on existing medical therapy are very clear: medical management is still controversial; no drug is specifically labeled for use in case of uterine adenomyosis at present; and there are no particular guidelines to follow for optimal management.

These authors do, however, provide an exhaustive review of all drugs available to treat the symptoms of this disease. From non-hormonal (nonsteroidal anti-inflammatory drugs) and hormonal agents (progestins -delivered orally or locally, contraceptive pills, GnRHa) to new drugs under development, such as selective progesterone receptor modulators, aromatase inhibitors, valproic acid, anti-platelet therapy, and GnRH antagonist, medical therapy offers numerous possibilities, despite most of these drugs being off-label for this indication. Vannuccini et al. (4) provide a very interesting account in a dedicated section on medical treatment in women with uterine adenomyosis suffering from infertility. Summarizing existing evidence on the effect of adenomyosis on fertility and clinical in vitro fertilization outcomes, they show that long-term GnRHa therapy prior to in vitro fertilization increases clinical pregnancy rates, in both symptomatic and asymptomatic patients.

There is no doubt that the great majority (almost 90%) of cases of adenomyomectomy documented in the literature today are from Japan, so it is entirely logical that Osada (5) contributes a review on conservative surgical treatment of adenomyosis in young women, first reported in 1952. Subsequently, partial excision of adenomyotic nodules as cytoreductive surgery became widespread after the introduction of wedge resection, in which the uterine wall is excised in a V-shape. Thanks to the development of more homologous and less reactive suture materials provoking less severe tissue responses, as well as novel powered devices like electric, ultrasonic and high-frequency scalpels that minimize bleeding, complication rates fell to significantly lower levels than those seen before the 1970s.

Surgical treatment of adenomyosis remains a matter of debate, not only in terms of indications, but also the technical aspects of surgery. Since 1990, instead of the classic V-shaped resection approach, various forms of surgical management have been attempted. These include the uterine muscle flap method involving asymmetric dissection, and a number of modified procedures allowing fertility preservation and widely used in Japan, where 2,123 cases have been reported since 1990.

The triple-flap method, which involves reconstructing the uterine wall defect using normal uterine muscle, is carefully described by Osada (5). This technique is not only effective for diffuse uterine adenomyosis, but also for nodular adenomyosis, and can potentially to contribute to preventing uterine rupture during postoperative pregnancy.

Out of Osada's 2,123 surgical cases, a total of 397 postprocedural pregnancies were reported, 337 of which yielded live births and 23 that ended in uterine rupture. A higher incidence of placenta accretae and percreta was noted compared to cesarean section and myomectomy (5).

Factors causing uterine rupture during pregnancy are clearly detailed. They include the surgical technique applied, the extent and volume of the uterine defect, the method of repair of the uterine wall (and sometimes the uterine cavity), postoperative wound infection and hematoma formation, and finally, as stressed by Osada (5), the skill and experience of the surgeon.

In conclusion, like endometriosis, uterine adenomyosis remains a contentious entity from pathogenesis to therapy. Moreover, there is an urgent need to establish some systematic classification, taking into account not only histological findings but also results from the latest imaging techniques, such as transvaginal ultrasound and MRI. Continued research into new molecules based on the pathogenic mechanisms of uterine adenomyosis is vital.

REFERENCES

1. García-Solares J, Donnez J, Donnez O, Dolmans MM. Pathogenesis of uterine adenomyosis: invagination or metaplasia? Fertil Steril 2018;109, XX-XX.
2. Gordts S, Grimbizis I, Campo R. Symptoms and classification of uterine adenomyosis. Fertil Steril 2018;109, XX-XX.
3. Bazot M, Daraï E. The place of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertil Steril 2018; 109, XX-XX.
4. Vannuccini S, Luisi S, Tosti C, Sorbi F, Petraglia F. The place of medical therapy in the management of uterine adenomyosis. Fertil Steril 2018;109, XX-XX.
5. Osada H. Uterine adenomyosis and adenomyoma: the surgical approach. Fertil Steril 2018;109, XX-XX.