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Laparoscopy-guided myometrial biopsy in the definite diagnosis of diffuse adenomyosis

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BACKGROUND: The purpose of this study was to investigate the usefulness of laparoscopy-guided myometrial biopsy in the diagnosis of diffuse adenomyosis. METHODS: This prospective non-randomized study (Canadian Task Force classification II-1) was conducted in a tertiary medical center. One hundred patients who had clinical signs and symptoms strongly suggestive of adenomyosis were included as the study sample. Transvaginal sonography, serum CA-125 determination and laparoscopy-guided myometrial biopsy were performed. RESULTS: The mean largest myometrial thickness was 3.10 ± 0.56 cm (range 2.30–4.50). The mean serum CA-125 level was 49.64 ± 38.30 U/ml (range 10.90–205.28). Of these 100 patients, adenomyosis was pathologically proven in 92 patients, small leiomyoma in four patients and myometrial hypertrophy in four patients. The sensitivity of myometrial biopsy was 98% and the specificity 100%; the positive predictive value was 100% and the negative predictive value 80%, which were superior to those of transvaginal sonography, serum CA-125 determination or the combination of both. CONCLUSION: Laparoscopy-guided myometrial biopsy is a valuable tool for obtaining a definite diagnosis of diffuse adenomyosis with preservation of the uterus in infertility workup or in the evaluation of dysmenorrhea or chronic pelvic pain.

Keywords: adenomyosis; myometrial biopsy; laparoscopy

Introduction

Adenomyosis is a benign disease in which the myometrium is invaded by endometrial glands and stroma (Zaloudek and Norris, 1987). The definitive etiologic factors responsible for its development are at present undetermined. However, the histogenesis of adenomyosis has been explained as a deep proliferation of the normal endometrium. The frequency of adenomyosis reported in the literature varies widely from 5 to 70% (Azziz, 1998). The highest prevalence is in women 30–50 years old. Uterine enlargement, dysmenorrhea and menorrhagia are regarded as the cardinal clinical symptoms of adenomyosis (Kilkku *et al.*, 1984). However, these criteria predict the histologic diagnosis in only 22% of cases (Bird *et al.*, 1972).

At present, there is no reliable method to detect this condition. Although the classical signs and clinical symptoms may suggest the diagnosis , these signs and symptoms are, unfortunately, often misleading. Various diagnostic tools have been evaluated and are considered to be effective. However, histological diagnosis of adenomyosis is not practical or possible before conservative treatment in most cases. Hysterectomy remains the mainstay of treatment and is required in the case of a definite diagnosis. However, for many nulliparous patients in their fourth decade of life, it is impractical to perform a routine hysterectomy.

The purpose of this study is to investigate the usefulness of transvaginal sonography, measurement of serum CA-125 concentrations and laparoscopy-guided myometrial biopsy in the diagnosis of adenomyosis. To our knowledge, this is the first study to compare transvaginal ultrasonography, serum CA-125 and *in vivo* myometrial biopsy in the same series of patients.

Materials and Methods

For evaluating the feasibility and effectiveness of the sampling method, 10 myometrial biopsy specimens were taken for each patient with a Tru-cut needle from 20 surgically removed uteri, which were proved to be adenomyosis histologically. The sensitivity of this method was 100%. This confirmed that the diagnosis of adenomyosis can be made from the myometrial biopsy.

Each of the 100 patients in this prospective study were recruited from January 2004 to June 2006. They all signed the informed consent form, and the research protocol was approved by the IRB of the hospital.

In these 100 patients who had clinical signs and symptoms (i.e. uterine enlargement, severe dysmenorrhea and menorrhagia) strongly suggestive of adenomyosis, 10 myometrial biopsy specimens per patient were taken under laparoscopic guidance with a 14-gauze Tru-cut needle through abdominal wall from the location suspected to have adenomyosis, as determined by transvaginal sonographic and laparoscopic findings. The Tru-cut needle was inserted into the thickest myometrial wall as close as possible to the serosa for preventing endometrial biopsy. Prophylactic injection of pitressin solution (20 U of pitressin dissolved in 10 cc normal saline) into the biopsy sites was done to prevent myometrial bleeding. Laparoscopic diagnosis confirmed that there was no ovarian tumor, pelvic endometriosis or pelvic inflammatory disease in any of these 100 cases. In other words, patients with any of above conditions were all excluded from our study sample. Immediately after laparoscopic myometrial biopsy, laparoscopy assisted vaginal hysterectomy was performed.

The day before laparoscopy assisted vaginal hysterectomy, all the women underwent transvaginal sonography using a vaginal probe of 5.0 MHz. The ultrasound instrument used was a Toshiba model SSA 260A. Longitudinal and transverse images were obtained and the thickest myometrial thickness was measured. Serum CA-125 levels during the proliferative phase of the menstrual cycle were measured with radioimmunosassay preoperatively in all 100 patients.

After hysterectomy, the surgical specimens were sent for pathological diagnosis. In each cases, the specimens were all sectioned. The pathologist diagnosed adenomyosis when the distance between the lower border of the endometrium and the affected areas was over one-half of a low-power field ($\sim$2.5 mm). The pathologist was not aware of the previous pathologic diagnosis from the myometrial biopsy.

The final pathological diagnoses were compared with the results of transvaginal sonography, serum CA-125 levels and pathological findings of laparoscopy-guided myometrial biopsy. The sensitivity, specificity and predictive value of a normal and abnormal test were calculated.

Results

The mean age of the patients who underwent hysterectomy was 39.96 ± 3.92 (range 30–49). The mean of the largest myometrial thickness was 3.10 ± 0.56 cm (range 2.30–4.50). The mean level of serum CA-125 was 49.64 ± 38.30 U/ml (range 10.90–205.28). In these patients, adenomyosis was pathologically proven in 92 patients, small leiomyomata in four patients and myometrial hypertrophy in four patients. The sensitivity, specificity and predictive value of transvaginal sonography, measurement of serum CA-125 concentration and laparoscopy-guided myometrial biopsy in the diagnosis of adenomyosis are listed in Table 1.

Laparoscopy-guided myometrial biopsies revealed adenomyotic foci in 90 among 92 patients with adenomyosis. Adenomyosis limited to the inner third of the myometrium was noted in those two false negative cases. No false positive cases were found. Among the 90 true positive cases, 8.6 (range 4–10) out of 10 biopsies were pathologically positive for adenomyosis. No intraoperative or post-operative complications were observed. The whole procedure usually took 15–30 min, and blood loss during laparoscopy was usually minimal. The sensitivity of myometrial biopsy was 98% and the specificity 100%; the positive predictive value was 100% and negative predictive value 80%, which were superior to those of transvaginal sonography, serum CA-125 determination or the combination of both (Table 1).

There was no any operation complication encountered in the whole study. No penetration into the endometrial cavity was noted.

Discussion

Numerous attempts have been made to find a reliable instrument to diagnose adenomyosis. Hysterosalpingography sometimes demonstrates multiple spiculations or true defects leading from the uterine cavity to the myometrial wall (Marshak and Aliasoph, 1994). However, such images of adenomyosis are not distinguishable from those produced by vascular or lymphatic extravasation. Because of its overall low accuracy, hysterosalpingography is no longer indicated for the evaluation of patients with suspected adenomyosis. The diagnostic capability of ultrasonography has been evaluated in various studies. Transvaginal sonography can diagnose adenomyosis with a sensitivity of 80–89%, a specificity of 50–96%, a positive predictive value of 50–81%, a negative predictive value of 73–94% and overall accuracy of 68–89% (Brosens *et al.*, 1995; Vercellini *et al.*, 1998; Tafazolo and Reinhold, 1999; Bazot *et al.*, 2001; Atri *et al.*, 2000; Dueholm, 2006). Transvaginal sonography seems to represent a real advance in the preoperative diagnosis of diffuse adenomyosis. Magnetic resonance imaging (MRI) has been shown to be highly accurate in diagnosing adenomyosis. Several investigations have reported sensitivity and specificity ranging from 38 to 100%, with an overall accuracy of 80–90% (Reinhold *et al.*, 1999; Tafazolo and Reinhold, 1999; Bazot *et al.*, 2001; Tamai *et al.*, 2005; Moghadam *et al.*, 2006). However, high cost and limited availability makes MRI an impractical tool for routine clinical use (Moghadam

Table 1: Diagnostic indices of various diagnostic modalities for adenomyosis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MT $\geq$2.5 cm	81	0	93	0
MT $\geq$3.0 cm	62	0	91	0
CA-125 $\geq$20 U/ml	85	100	100	30
CA-125 $\geq$35U/ml	66	100	100	16
MT $\geq$2.5 cm and CA-125 $\geq$20 U/ml	77	100	100	21
MT $\geq$3.0 cm CA-125 $\geq$20 U/ml	55	100	100	13
Myometrial biopsy	98	100	100	80

MT, myometrial thickness; PPV, positive predictive value; NPV, negative predictive value.

et al., 2006). Above all, all the diagnostic methods mentioned above only provide a suggestive, rather than definite, diagnosis.

The elevated serum concentrations of CA-125 are a well-documented marker of epithelial ovarian tumors. Elevated serum CA-125 levels have, however, also been observed in women with no ovarian cancers but with advanced endometriosis, pelvic inflammatory disease or adenomyosis, as well as in women during menses (Patton *et al.*, 1986; Takahashi *et al.*, 1990a,b). Takahashi *et al.* (1990a,b) reported that considerably higher levels of serum CA-125 were observed in patients with adenomyosis and they suggested that serum CA-125 could serve as a good marker to differentiate adenomyosis from uterine myoma. In an earlier report, they also confirmed that CA-125 was present on the normal endometrial glandular epithelium and glandular epithelium localized in muscle adenomyosis (Kijima *et al.*, 1987). Our data supports the findings of Kijima *et al.* (1987). However, because it is non-specific, the CA-125 level is only suggestive rather than definite in the diagnosis of adenomyosis.

McCausland (1992) evaluated the hysteroscopic myometrial biopsy and Walker (2003) evaluated transvaginal ultrasound-guided myometrial biopsy for diagnosing adenomyosis, and both concluded that a myometrial biopsy specimen can be used to diagnose adenomyosis (McCausaland, 1992). However, Darwish *et al.* (1999) found hysteroscopic myometrial biopsy is inadequate and is not recommended. In a German study, the sensitivity of a single myometrial biopsy was as low as 8–18.7% (Popp *et al.*, 1993). Even 10 specimens from a uterus resulted in a sensitivity of only roughly 40–70%. They considered that the small number of positive findings in their series of myometrial biopsies from uteri *in situ* was not only due to the low sensitivity of this method but also to the poor correlation of clinical signs with the histologic diagnosis. Similarly, Vercellini *et al.* (1998) found that a single uterine needle biopsy for removed uterus in diagnosing adenomyosis led to a sensitivity of 44.8% a specificity of 95.9%, a positive predictive value of 81.2% and a negative predictive value of 81.4%. They concluded that uterine needle biopsy was a suboptimal test. However, in a study of *in vitro* myometrial needle biopsies in the diagnosis of adenomyosis, Brosens *et al.* found the sensitivity of eight biopsy specimens was 100% compared with 79% for four specimens and 56% for two specimens (Brosens and Barker, 1995). They concluded that myometrial needle biopsy was a highly specific technique for the diagnosis of adenomyosis, but the sensitivity was low and dependent on the number of biopsies and the depth of adenomyosis. Similarly, in our study the two false negative cases were grade I adenomyosis according to the classification by Brosens and Barker (1995), and the adenomyosis was limited to the inner third of the myometrium. A low severity of disease may decrease the sensitivity of this technique.

Vercellini *et al.* (1998) thought that the results of *in vivo* biopsy may be even less satisfactory because of technical difficulty during the sampling procedure. So they concluded that further studies are needed to standardize the correct histological threshold limit for the diagnosis of adenomyosis. In our study, there was no false positive cases fortunately, but it could possibly happen if the biopsy orientation is not perfectly perpendicular to uterine serosa. The 10 biopsies were done routinely without any difficulty, and our study revealed that laparoscopy-guided myometrial biopsy is a valid diagnostic tool in the group of women with clinical signs and symptoms suggestive of adenomyosis. We suggest that laparoscopy-guided myometrial biopsy from the thickest wall of the uteri may achieve better results. Also, the method described can be carried out with minimal risk. Prophylactic injection of a small amount of pitressin solution into the biopsy sites may prevent myometrial bleeding. There were no immediate or long-term complications related to the myometrial biopsies in our study.

Ovarian suppression with GnRH agonist has been suggested to be useful as a surgical adjuvant in adenomyosis since the early 1990s (Grow and Filer, 1991; Hirata *et al.*, 1993; Farquhar and Brosens, 2006). It also may be useful in the temporary management of adenomyosis for the patient with a strong desire for fertility preservation. The application of laparoscopy-guided myometrial biopsy may help direct the medical treatment. In deed, diagnostic laparoscopy has been considered to be the final examination of infertility workup for many years.

In conclusion, the sensitivity and specificity of laparoscopy-guided myometrial biopsy in identifying adenomyosis are very good. It may become a valuable tool for obtaining a definite diagnosis of diffuse adenomyosis with preservation of the uterus. We suggest that this new technique can be applied as a final step of infertility workup for ruling out pelvic endometriosis and confirming the diagnosis of adenomyosis. This technique may also be used in the evaluation of patients with dysmenorrhea or chronic pelvic pain. Further morphological and immunohistochemical examinations of myometrial specimens may be the basis for developing more specific means of medical treatment.

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