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Original Article

Elasticity of adenomyosis is increased after GnRHa therapy and is associated with spontaneous pregnancy in infertile patents

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ABSTRACT

Objective: To explore the effects of GnRHa on adenomyosis by transvaginal elastography.
Methods: A prospective observational study included patients who were diagnosed as adenomyosis by conventional transvaginal ultrasound and infertility. The sonographic characters of elastography, the degree of dysmenorrhea and the values of serum CA125 before and following GnRHa (Triptorelin 3.75 mg were administered every 28 days) plus add-back therapy were reviewed and analyzed. Each case had a 6 months follow up and the information of pregnancy were recorded.
Results: 45 patients who completed the 6 months follow-up were included in the analysis. Twelve cases (group 1) were pregnancy during the follow-up and the other thirty-three cases (group 2) failed their attempts. The numerical rating scale and CA125 of all the cases were both significantly reduced 6 months after therapy. All of enlarged uterus decreased to accessible normal size. In group 1, the mean elasticity score was significantly higher for the uterine after therapy than before (3.6 ± 0.3 vs 2.3 ± 0.5, $p = 0.004$). In group 2, the mean elasticity score did not change for the uterine after therapy than before (2.2 ± 0.5 vs 2.5 ± 0.6, $p = 0.77$).
Conclusion: Elasticity of adenomyosis is increased after GnRHa therapy. And the higher elasticity of adenomyosis after GnRHa therapy is associated with spontaneous pregnancy in infertile patents.

Introduction

Adenomyosis always causes uterine enlargement, abnormal uterine bleeding, and dysmenorrheal in women in reproductive age. The histological analysis of uterine following hysterectomy was performed to make a definite diagnosis. However, it was a surgical intervention. 2D/3D transvaginal ultrasonography and MRI were applied to the evaluation of adenomyosis due to the development of imaging techniques. Recently, different forms of adenomyosis were discriminated by imaging detections Such as focal and diffuse forms of adenomyosis could be demonstrated by ultrasonogarphy and MRI [1].

However, there were several limitations of conventional ultrasound. The distribution of adenomyosis stiffness may be heterogeneous, especially for the diffuse form. Furthermore, changes of adenomyosis stiffness during medical therapy such as GnRH agonists (GnRHa) could not be evaluated. GnRHa has been used in the treatment of adenomyosis, in particular for the patients desiring fertility [2]. It was effective in decreased hypermenorrhea and relief of severe dysmenorrhoea. Moreover, it contributed to spontaneous pregnancy or down-regulation in IVT-ET [3–5].

As a new technique, transvaginal elastography ultrasound could assess stiffness changes and deformation of tissues in response to compression. The different colors express different elasticity degrees, usually varying from red (highly elastic tissue) to blue (barely elastic tissue) while the other colors represent intermediate degrees of stiffness. The method has been applied successfully in the prostate, breast, testes, liver, pancreas, lymph nodes, thyroid gland lesions and gynecology in recent years [6]. We have investigated the role of elastography in the conservative therapy of tubal pregnancy [7].

To our knowledge, a study of transvaginal elastography of the uterus in patients with adenomyosis before and following GnRHa therapy has not been reported previously in the medical literature. The aim of this study is to explore the effects of GnRHa on adenomyosis using transvaginal elastography.

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Methods

It was a prospective observational study. The study design and protocol were approved by our Institutional Review Board, and all patients gave written informed consent after the nature of the procedure was explained fully. The patients diagnosed with adenomyosis at the Gynecologic Oncology Department of Obstetrics and Gynecology Hospital of Fudan University were analyzed between June 2016 and December 2016.

All the enrolled patients were suspected with adenomyosis detected by conventional transvaginal ultrasound. And they had the symptoms of dysmenorrhoea with or without menorrhagia. All the patients did not receive medical therapy before the study and they refused surgery. The status of infertility was present for at least 1 year. The patients with endometriotic cysts of ovary and uterine fibroids detected by ultrasound were excluded. And women with the status of pregnancy, uterine infection, previous uterine surgery or specific hormonal therapy were excluded. The patients were asked to quantify their degree of dysmenorrhea. A numerical rating scale (NRS) was used to assess the degree of menstrual pain. It ranged from 0 to 10, where "0 "means "no pain "and "10 "means pain as "bad as it could be". It was shown to have adequate reliability and validity in the clinical research [8].

Elastography ultrasound was performed by a single radiologist (M.X.) with 10 years of experience in transvaginal sonography who had specialized in elastography for the last 3 years. All patients underwent imaging with an Hitachi ARIETTA 60 (Hitachi Medical, Tokoy,Japan) using a transvaginal 7-MHz probe.

First, conventional transvaginal (a vaginal probe of 7-MHz) was performed. The transvaginal probe was placed in the posterior fornix. After regular conventional B-mode scanning of the uterine, elastographic scanning (elastographic dual-mode scanning in real-time) was performed. The probe was focused on the lower uterine segment and moved against it with light compression. After 10 s, the region of acquisition in the elastogram was set to involve sufficient surrounding mass tissues when the image was stable. The elastographic sample box was placed in the same axis when movements were actualized along the axis of the transducer. All the data acquisition was administrated and recorded independently of uterine size and position. The tissue elasticity information showed in color. Blue indicated hard tissue, green indicated medium tissue and red indicated soft tissue. They were superimposed on B-mode images to permit better interpretation. An independent observer (R.Y.) was invited to access the elastography scores. For easy to image analysis, the elasticity images were evaluated by a 4-point scoring system that was used in a study of neck masses previously (Table 1) [9].

All the patients were treated with GnRHa (Triptorelin 3.75 mg were administered every 28 days) plus add-back therapy (combined with estradiol valerate 0.5 mg and dydrogesterone 5 mg daily, from the 3 cycles). And the values of serum CA125 before and 1 month following GnRHa therapy were recorded. Transvaginal ultrasound and elastography were repeated 1 month following GnRHa therapy.

All patients had a 6-months follow-up after the second elastographic detection. The information about the status of pregnancy was recorded. Cases lost to follow-up were excluded. Following 6 cycles GnRHa therapy, if the patients were not pregnant when resumption of menses, they were asked to quantify their degree of dysmenorrhea again.

The SPSS version 11.0 software package for Windows (IBM Corporation, Armonk, NY) was used for the statistical analysis. Data was expressed as mean standard deviation. The Mann-Whitney U test was performed to determine whether the elasticity scores were different before and following GnRHa therapy. $P < 0.05$ was considered statistically significant.

Results

A total of forty-five patients completed the treatment and the 6 months follow-up. Twelve cases (group 1) were pregnancy during the follow-up and the other thirty-three cases (group 2) failed their attempts. Before treated with GnRHa plus add-back therapy, NRS of menstrual pain of group 1 and 2 were 8.7 ± 1.2 and 8.3 ± 0.6 ($p = 0.72$), respectively. CA125 were 148.4 ± 36.7 and 170.1 ± 54.5 ($p = 0.51$), respectively. Initial uterine volume of group 1 and 2 measured by transvaginal ultrasound were $278.2 \pm 47.1 cm^3$ and $292.4 \pm 39.5 cm^3$ ($p = 0.80$), respectively. Pulsatility index (PI) of group 1 and 2 were 1.27 ± 0.41 and 1.22 ± 0.64 ($p = 0.88$), respectively. Resistance index (RI) of group 1 and 2 were 0.58 ± 0.26 and 0.62 ± 0.21($p = 0.68$), respectively.

Table 1
Elastography scoring system (ES 1–4) (The color which indicated stiffness was different in our study, red for soft and blue for hard) (Link page 6, line 119).

Elastographic score	Overall impression	Elastographic appearance
ES 1	soft	Predominantly purple, green or yellow with less than 10% displaying red. The node is indistinguishable from surrounding tissues.
ES 2	moderately soft	Predominantly yellow or green and with red areas comprising between 10% and 50%. The node is partially delineated from surrounding tissues.
ES 3	moderately stiff	Predominantly red and with yellow or green areas comprising between 10% and 50%. The node is partially delineated from surrounding tissues.
ES 4	stiff	Predominantly red and with less than 10% appearing yellow or green. The node is distinguishable from surrounding tissues.

Table 2
The baseline characteristics of group 1 and 2 (Link page 8, line 161).

	group 1 (n = 12)			group 2 (n = 33)		
	before therapy	after therapy	p	before therapy	after therapy	p
Age	29.2 ± 3.5			30.7 ± 2.8		
NRS of menstrual pain	8.7 ± 1.2	2.4 ± 0.8	0.002	8.3 ± 0.6	2.8 ± 1.1	0.003
CA125	148.4 ± 36.7	46.7 ± 12.0	0.004	170.1 ± 54.5	42.1 ± 16.5	0.001
Initial uterine volume (cm3)	278.2 ± 47.1	$180.4. \pm 23.8$	0.008	292.4 ± 39.5	168.5 ± 17.7	0.006
PI	1.27 ± 0.41	1.31 ± 0.58	0.76	1.22 ± 0.64	1.20 ± 0.44	0.81
RI	0.58 ± 0.26	0.89 ± 0.24	0.032	0.62 ± 0.21	0.85 ± 0.33	0.043

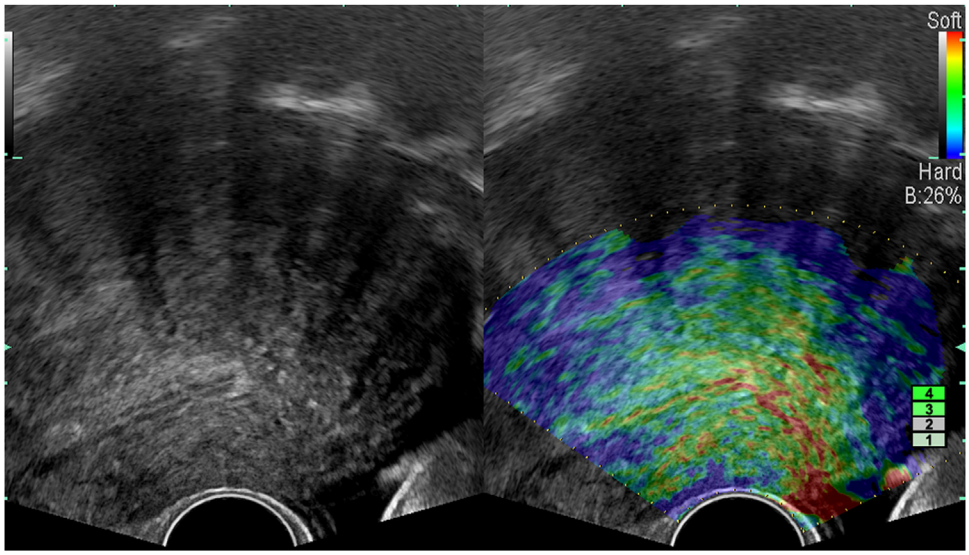

Fig. 1. Conventional ultrasound and ES of a patient in success group which appeared predominantly yellow or green and was clearly distinguishable before GnRHa therapy, scored as ES2.

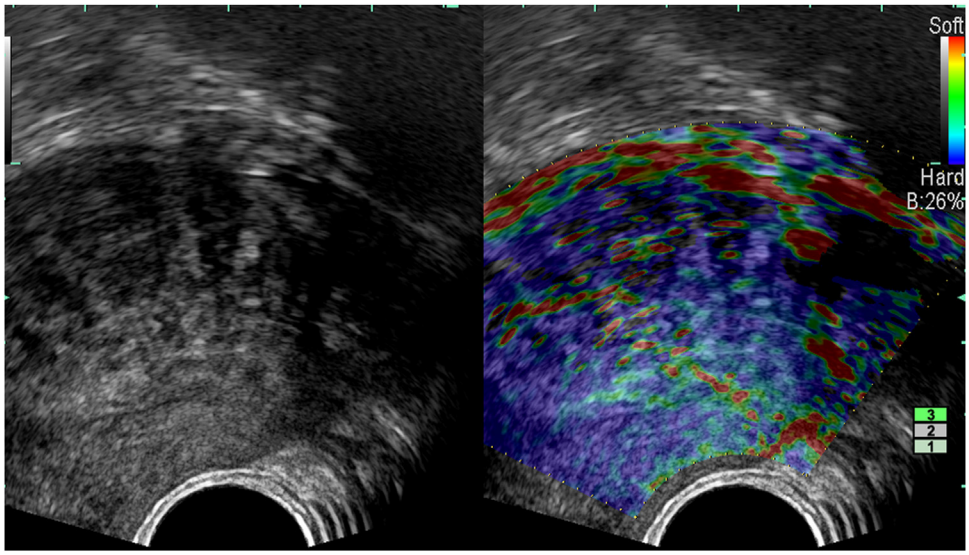

Fig. 2. The same patient of Fig. 1. Conventional ultrasound and ES following GnRHa therapy appeared predominantly blue, scored as ES 4.

Six months following therapy, NRS of menstrual pain of group 1 and 2 were 2.4 ± 0.8 and 2.8 ± 1.1 ($p = 0.68$), respectively. Five cases in group 1 were pregnant before menstruation return. CA125 were 46.7 ± 12.0 and 42.1 ± 16.5 ($p = 0.73$), respectively. Uterine volume of group 1 and 2 measured by transvaginal ultrasound were $180.4. \pm 23.8 cm^3$ and $168.5 \pm 17.7 cm^3$ ($p = 0.85$), respectively. NRS and CA125 of the group 1 and 2 were both significantly reduced 6 months following therapy than before. All the enlarged uterus decreased to accessible normal size. PI of group 1 and 2 were 1.31 ± 0.58 and 1.20 ± 0.44 ($p = 0.82$), respectively. RI of group 1 and 2 were 0.89 ± 0.24 and 0.85 ± 0.33 ($p = 0.74$), respectively. RI of the group 1 and 2 were both significantly higher 6 months following therapy than before (Table 2).

In group 1, the mean elasticity score was significantly higher for the uterine following therapy (3.6 ± 0.3) than before (2.3 ± 0.5) ($p = 0.004$). In group 2, the mean elasticity score did not change for the uterine following therapy (2.2 ± 0.5) than before (2.5 ± 0.6) ($p = 0.77$) (Fig. 1–4). The distributions of elasticity scores for group 1 and 2 were listed in Table 3.

Discussion

Several studies have concluded that transvaginal ultrasound provided relatively accurate in the diagnosis of adenomyosis. It was proved to be a noninvasive method for the diagnosis of clinically suspicious adenomyosis. The reported characteristics of adenomyosis on transvaginal ultrasound were similar, including a globular uterus with ill-defined adenomyotic lesions, myometrial cysts, linear striations of the myometrium, indistinct endomyometrial junction and asymmetric thickening of the myometrium [10–13]. However, all of the characteristics of image could only delineate the morphology of the adenomyosis. The stiffness of the uterus could not be demonstrated by conventional ultrasound.

In this study, we applied elastography in the evaluation of GnRHa therapy on adenomyosis. And our results suggested the change of stiffness of lesions were related with pregnancy following GnRHa therapy. The cases that were pregnant had

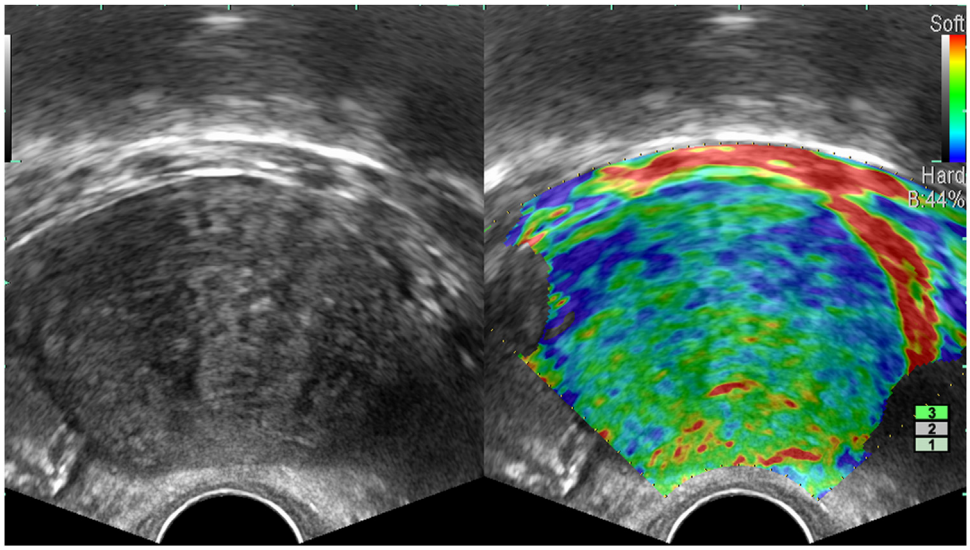

Fig. 3. Conventional ultrasound and ES of a patient in failure group which appears predominantly yellow or gree and was clearly distinguishable before GnRHa therapy, scored as ES2.

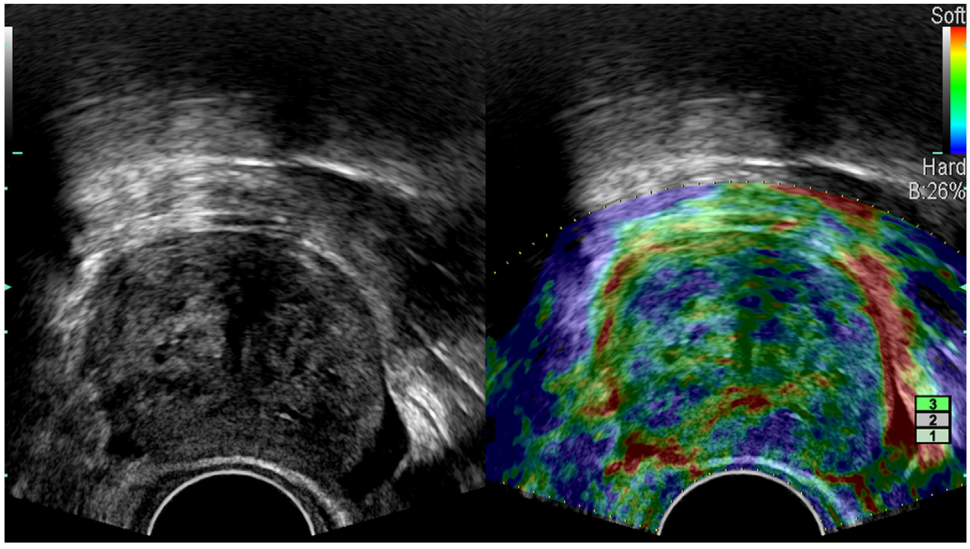

Fig. 4. The same patient of Fig. 3. Conventional ultrasound and ES following GnRHa therapy appeared predominantly yellow or green, scored as ES 2.

Table 3
Elasticity scores in group 1 and 2 before and 6 months after therapy (n = 45) (Link page 8, line 167).

Elasticity score	group 1 (n = 12)		group 2 (n = 33)	
	before therapy	after therapy	before therapy	after therapy
Score 1	1	0	2	2
Score 2	7	1	22	17
Score 3	4	3	9	11
Score 4	0	8	0	3
Total	12	12	33	33

higher elasticity score following GnRHa therapy than the non-pregnant cases. NRS of menstrual pain, CA125, initial uterine volume, PI and RI were similar between the two groups.

Macro et al indicated a new term “the cockrade-sign” to describe the elastographic image of adenomyosis [14]. It meant the adenomyotic area presented more softness compared with the surrounding uterine tissue.

And the borders of the adenomyotic area corresponded to the borders of the green area. In our study, we did not find typical “cockrade-sign”. However, the basal image characteristic of diffuse adenomyosis was similar with them. The borders of the soft area were irregular and poorly defined before GnRHa therapy. Following GnRHa therapy, the soft area in the uterus became harder in the pregnant women than the others.

Acar reported a significant increase of the myometrial stiffness estimated with shear wave elastography in patients with adenomyosis. In the study, values of Young’s modulus were used to quantitate the stiffness. They found the Emean was 72.7 kPa in adenomyosis and 28.3 kPa in non adenomyosis. The results were different from ours. The authors analyzed the main constraint was the operating depth was up to 3 cm due to the technical limitations of the technique [15].

Discrimination of adenomyosis and uterine fibroid was significant for the therapy. Frank revealed areas of adenomyosis had a spotted, irregular color appearance. And they showed softer than the adjacent normal myometrium. Lesions of adenomyosis

appeared a red center surrounded by a yellow and a green irregular border. However, uterine fibroid showed blue rounded areas. They seemed to be harder than the surrounding tissue and were often distinguished from the surrounding tissue by a regular green border. Significant differences of the maximum strain ratios were detected between the uterine fibroid and adenomyosis [16]. Stoelinga reported that fibroids and adenomyosis had different elastographic characteristics and different color patterns with elastography [17]. They certified fibroids were darker than adjacent myometrium. However, adenomyosis was brighter.

In another study, real-time elastography was performed to evaluate the response to magnetic resonance guided focused ultrasound surgery [18]. It was confirmed that the evaluation of the same myomas showed a significant increase of strain ratio and the treated fibroids had an increased stiffness within 2 h following treatment. The author presumed this response with a "reactive change" due to the coagulative necrosis and inflammatory of lesion. We agree with them. In our study, it was suggested that "reactive change" depended on the central downregulation with a deep suppression of gonadotropin secretion and a direct anti-proliferative action within the myometrium induced by GnRHa. Then the "reactive change" could be assessed by elastography.

Of course, there were some limitations in our study. First, it had a limited number of patients. And for all the cases of infertility, we did not exclude the factors such as blockage of fallopian tubes and ovulation abnormality. Moreover, we did not detect the value of hormone in the procedure of GnRHa therapy.

In conclusion, from this study, we revealed that elasticity of adenomyosis is increased after GnRHa therapy. And the higher elasticity of adenomyosis after GnRHa therapy is associated with spontaneous pregnancy in infertile patents.

Conflict of interest

We declare that we have no conflict of interest.

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References

[1] Champaneria R, Abedin P, Daniels J, Balogun M, Khan KS. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: systematic review comparing test accuracy. Acta Obstericia et Gynecol 2010;89:1374–84.
[2] Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. Hum Reprod Update 2012;18:374–92.
[3] Hirata JD, Moghissi KS, Ginsburg KA. Pregnancy after medical therapy of adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril 1993;59:444–5.
[4] Nelson JR, Corson SL. Long-term management of adenomyosis with a gonadotropin-releasing hormone agonist: a case report. Fertil Steril 1993;59:441–3.
[5] Lin J, Sun C, Zheng H. Gonadotropin-releasing hormone agonists and laparoscopy in the treatment of adenomyosis with infertility. Chin Med J (Engl) 2000;113:442–5.
[6] Shiina T, Nightingale KR, Palmeri ML, Hall TJ, Bamber JC, Barr RG, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: part 1: basic principles and terminology. Ultrasound Med Biol 2015;41:1126–47.
[7] Xie M, Zhang X, Wang W, Hua K. Evaluation of tubal pregnancy after treatment with methotrexate by ultrasound elastography. J Ultrasound Med 2018; 37:417–22.
[8] Naftalin J, Hoo W, Nunes N, Holland T, Mavrelos D, Jurkovic D. Association between ultrasound features of adenomyosis and severity of menstrual pain. Ultrasound Obstet Gynecol 2016;47:779–83.
[9] Lyshchik A, Higashi T, Asato R, Tanaka S, Ito J, Mai JJ, et al. Thyroid gland tumor diagnosis at US elastography. Radiology 2005;237:202–11.
[10] Meredith S, Sanchez-Ramos L, Kaunitz A. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metaanalysis. Am J Obstet Gynecol 2009;201(107):e1–6.
[11] Dueholm M. Transvaginal ultrasound for diagnosis of adenomyosis: a review. Best Prac Research Clin Obstet Gynaecol 2006;20:569–82.
[12] Tonni G, Ventura A. Adenomyosis: a novel approach using transvaginal power Doppler sonography. J Diag Med Sonography 2005;21:267–72.
[13] Dartmouth K. A systematic review with meta-analysis: the common sonographic characteristics of adenomyosis. Ultrasound 2014;22:148–57.
[14] Tessarolo M, Bonino L, Camanni M, Deltetto F. Elastosonography: a possible new tool for diagnosis of adenomyosis? Eur Radiol 2011;21:1546–52.
[15] Acar S, Millar E, Mitkova M, Mitkov V. Value of ultrasound shear wave elastography in the diagnosis of adenomyosis. Ultrasound 2016;24:205–13.
[16] Frank ML, Schäfer SD, Möllers M, Falkenberg MK, Braun J, Möllmann U. Importance of transvaginal elastography in the diagnosis of uterine fibroids and adenomyosis. Ultraschall Med 2016;37:373–8.
[17] Stoelinga B, Hehenkamp WJ, Brölmann HA, Huirne JA. Real-time elastography for assessment of uterine disorders. Ultrasound Obstet Gynecol 2014;43:218–26.
[18] Marigliano C, Panzironi G, Molisso L, Pizzuto A, Ciolina F, Napoli A. First experience of real-time Elastography with transvaginal approach in assessing response to MRgFUS treatment of uterine fibroids. Radiol Med 2016;121:926–34.