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New sonographic classification of adenomyosis: do type and degree of adenomyosis correlate to severity of symptoms?

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The different type and extension of adenomyosis detected by transvaginal ultrasound could be associated with clinical symptoms.

Abstract:

Study Objective: to correlate type and degree of adenomyosis, scored through a new system based on transvaginal sonographic (TVS) features, to patient's symptoms and fertility.

Design: This is a multicenter, observational prospective study**.**

Setting: two Endometriosis tertiary referral center (University of Tor Vergata Rome and University of Siena)

Patients: 108 patients with ultrasonographic signs of adenomyosis

Interventions: A new ultrasonographic scoring system designed to assess the severity and the extent of uterine adenomyosis was used to stage the disease in correlation with clinical symptoms. Menstrual uterine bleeding was assessed by a pictorial blood loss analysis chart (PBAC), painful symptoms were evaluated using a visual analogue scale (VAS) and infertility factors were considered.

Measurement and Main Results: 108 patients with ultrasonographic signs of adenomyosis (mean age 37.7±7.7 yrs) were classified according to the proposed scoring system. Women with ultrasound diagnosis of diffuse adenomyosis were older (p= 0.04) and had heavier menstrual bleeding (p=0.04) than women with focal disease, however no statistically significant differences were found regarding presence and severity of dyspareunia and dysmenorrhea. Higher values of menstrual bleeding were found for severe diffuse adenomyosis and the highest values found in those with adenomyomas. In those patients trying to conceive, the presence of ultrasound findings of focal disease was associated with a higher percentage of infertility compared to diffuse disease and the focal involvement of the junctional zone (JZ) showed a higher percentage of at least one miscarriage compared to those with diffuse adenomyosis.

Conclusion: The ultrasonographic evaluation of the type and extension of adenomyosis in the myometrium seems to be important in correlation to the severity of symptoms and infertility.

Key words: adenomyosis; transvaginal ultrasound; classification; heavy menstrual bleeding; pain

Introduction

Adenomyosis is a frequent benign gynecological disease, defined by the presence of endometrial glands and stroma within the myometrium, associated with hypertrophy of the smooth muscle. Adenomyosis may involve different sites of myometrium or most of the uterine wall, ranging from focal to diffuse adenomyosis. It can also present as a nodular lesion forming an adenomyoma (1).

The real prevalence of adenomyosis is difficult to accurately assess due to the necessary

histological confirmation following a clinical diagnosis based on symptoms and imaging. Its prevalence has been reported to range from 5 to 70 % in hysterectomy specimens (2-6). However, the study of prevalence through histological diagnosis presents a large selection bias since patients undergoing hysterectomy are in advanced age and with clinical symptoms. Moreover, a study highlighted the variability in the histological diagnosis of adenomyosis from center to center and between pathologists (7).

Certainly, it becomes more difficult to ascertain prevalence when various diagnostic criteria are used during imaging assessment in patients, with or without symptoms, not undergoing surgery.

Transvaginal sonography (TVS) has recently been used for the non-invasive diagnosis of adenomyosis and to study its prevalence (1,8-10). When TVS is performed by dedicated sonographers it shows high accuracy in detecting this pathology (11-13).

Adenomyosis seems to be associated with endometriosis (14,15). Surely both conditions share pathogenesis and symptoms such as dysmenorrhea, heavy menstrual bleeding, infertility, dyspareunia and chronic pelvic pain (14, 16-18).

Some authors suggest that the severity of symptoms and the clinical features correlate with the extent and depth of adenomyosis (18-21). So far, however, the only classification proposed for the extension of the disease is based on histological findings after surgery and not on imaging. Since adenomyosis often results in poorly defined lesions, possibly disseminated in different parts of the myometrium, it is difficult to express its severity in quantitative terms.

Through TVS it is possible to assess the characteristics of adenomyosis. Therefore, recently we have proposed a scoring system (22) that grades the type of adenomyosis and its extension inside the uterus.

To the best of our knowledge there are no prospective studies using non-invasive techniques to assess the link between type and degree of adenomyosis and severity of clinical symptoms.

The aim of this study is to correlate type and degree of adenomyosis to symptoms and fertility through a new scoring system (22) based on transvaginal sonographic (TVS) features.

Materials and Methods

This is a multicenter prospective observational study carried out in two tertiary referral university hospitals ("Tor Vergata" University Hospital, Department of Biomedicine and Prevention; "Santa Maria alle Scotte" University Hospital, Department of Molecular and Developmental Medicine) between January 2017 and March 2018. The study was approved by the local research ethics committee.

A total group of 148 women aged between 29 and 46 years old referred to our center for pelvic pain were included in the study and divided in two groups based on the presence of sonographic signs of adenomyosis, according to previous studies (1,13,22). Inclusion criteria were: premenopausal status, availability to perform transvaginal ultrasound, and no hormonal therapy. An on-going pregnancy, a gynecological malignant disease and the presence of more than three uterine fibroids were considered as exclusion criteria. A total of 108 women with ultrasound diagnosis of adenomyosis were finally enrolled in the study and 40 patients without any sonographic signs of myometrial pathology were excluded from the analysis.

All patients underwent a detailed ultrasound evaluation of the uterus in which type and extension of adenomyosis were classified according to a previously published study (22).

Furthermore, demographic data and detailed medical history were recorded prior the TVS scan, as well as the presence of painful symptoms (including dysmenorrhea, dyspareunia, dyschezia and dysuria) of heavy menstrual bleeding and /or infertility were evaluated.

Historical information

A complete medical, surgical and obstetrical history including women's age, body mass index (kg/m2), age at menarche, gravidity and parity (number of all prior pregnancies: spontaneous pregnancy loss and/or live births) and the mode of delivery were recorded. Infertility was defined as no pregnancy after 12 months of unprotected intercourse.

Patients were also asked about any medication they were taking including the use of analgesics for the treatment of painful periods. The presence of the following painful symptoms was noted:

dysmenorrhea, dyspareunia, dysuria, dyschezia, and chronic pelvic pain. Symptom intensity was evaluated through the visual analogue scale (VAS) system, using a 10-cm line with the extreme points 0 and 10 corresponding to ‘‘no pain’’ and ‘‘maximum pain,’’ respectively. Severe symptoms were considered if VAS score was equal or more than 5. Furthermore, the presence of abnormal uterine bleeding (AUB) was investigated. Women were asked about frequency and duration of menstrual periods and about any episodes of intermenstrual bleeding. In order to obtain an objective evaluation regarding the amount of menstrual loss a pictorial blood loss analysis chart (PBAC) was used. The PBAC provides a score that depends on the number of tampons or sanitary towels used during the menstrual cycle and also on the degree to which each item is soiled. PBAC score has been shown to have a high specificity and sensitivity when used as a diagnostic test for objective menstrual bleeding (23) and the PBAC score more than 100 is consistent with menorrhagia.

Ultrasound Examination

All transvaginal ultrasound examinations were performed by two experienced sonographers (C.E. and L.L) and carried out using a 4–9-MHz probe with a three-dimensional (3D) capability (Voluson E6, GE Medical Systems, Zipf, Austria). The two sonographers were blinded to the patient's clinical symptoms and the clinical examination was performed after the ultrasound. Briefly a conventional two-dimensional (2D) ultrasound with grey scale and power Doppler for assessment of the pelvis was performed. Firstly, we carefully evaluated the uterus, the myometrium and the endometrium. The myometrium was systematically examined for the presence of any abnormalities. 2D examination was followed by acquisition of 3D volume of the uterus with and without power Doppler. Then the scan examined the adnexa, the pouch of Douglas and the other pelvic organs (bladder, rectum, rectosigmoid junction, ureters) and sites (posterior, lateral and anterior parametria, rectovaginal septum, vesicouterine pouch, uterosacral ligaments), looking for features of endometriosis according to a previous ultrasound mapping system (24). Women were considered affected by endometriosis if an ovarian endometrioma or deep endometriotic nodules were detected

at the ultrasound evaluation. Adhesions of the anterior and posterior compartment were suspected by the presence or absence of the ‘‘sliding sign’’ and the pain induced during the examination was recorded, carefully mapping all painful sites (‘‘tenderness-guided’’ ultrasonography) (25).

Images were stored as 2D still images, 2D video-clips and 3D volumes.

Sonographic diagnosis of adenomyosis was made when at least one of the following features of the disease was observed at the ultrasound examination:

- globally enlarged uterus: the fundus of the uterus appears enlarged
- asymmetrically enlarged uterus (one uterine wall thicker than others) unrelated to leiomyoma
- round cystic area within the myometrium surrounded by a hyperechoic halo
- inhomogeneous, irregular myometrial echotexture in an indistinctly defined myometrial area with decreased or increased echogenicity; hyper-echogenic islands, subendometrial lines and buds.
- myometrial hypoechoic linear striations seen as a radiating pattern of thin acoustic shadows not arising from echogenic foci or leiomyoma (fan shaped shadowing);
- Indistinct, fuzzy endometrial-myometrial border (ill-defined endometrial stripe)
- presence of diffuse minimal vascularity seen as diffuse spread of small vessels within the myometrium
- question mark sign [di donato] defined when the corpus uterus is flexed backwards, the fundus of uteri facing the posterior pelvic compartment with the cervix directed frontally towards the urinary bladder.

All these ultrasound features have been previously described and there is a wide consensus that they are reliable morphological markers of adenomyosis (1, 11-13, 22, 26-29).

The type of adenomyosis was divided into focal, diffuse, or adenomyomas according to the TVS features described in the previous paper (22). Focal adenomyosis is classified when typical ultrasonographic adenomyotic signs are circumscribed in aggregates and surrounded by normal

myometrium, while diffuse adenomyosis when typical alterations at TVS spread throughout the myometrium (30-33). Adenomyomas are a subgroup of focal adenomyosis surrounded by hypertrophic myometrium.

In our analysis we considered focal and diffuse adenomyosis of the outer and inner myometrium junctional zone (JZ) separately.

The ultrasound detection of each type of adenomyotic lesion in the external myometrium and in the junctional zone was classified in four grades according to the parameters published in the previous paper (22). Through the use of uterine drawings, the previously published adenomyosis extension score (using the same criteria) was simplified to help clarify it and make it easier to apply to all sonographers as shown in Figure 1. Briefly as previously described (22), we considered for 4 degrees of extension for each type of disease considered: diffuse and focal adenomyosis (of inner and outer myometrium) and adenomyoma. For diffuse adenomyosis of the outer myometrium degree is assigned according to the thickness of the uterine wall (>or <20 or 30mm) and number of the uterine walls affected (anterior, posterior lateral left/right). For diffuse adenomyosis of the inner myometrium thickness of the JZ and length of the infiltrated JZ tract was considered in the 4 degrees. Focal adenomyosis of the inner and outer myometrium was assigned a degree according the largest diameter of the focal lesion and the number of foci. Similarly, adenomyomas were divided in 4 degrees according size (largest diameter 20, 30, 40 >40) and number of adenomyomas. A score number of 1 to 4 was attributed to each degree of disease considered. Then, the ultrasound extent of the disease was calculated through the sum of the score numbers obtained and classified in three groups: mild (ranged between 1 to 3), moderate (4-6) and severe (>7) adenomyosis.

Patients' characteristics, severity of symptoms, and uterine menstrual bleeding were correlated to the type of adenomyosis and score. Finally, the extent of adenomyosis; classified as mild, moderate, or severe, was correlated to the severity of symptoms, uterine menstrual bleeding, presence of pelvic endometriosis (ovarian and deep infiltrating) and infertility.

Statistical analysis

Statistical analysis was undertaken using the Statistical Package for the Social Sciences (SPSS, version 15.0, Chicago, IL, USA). All continuous variables were expressed in terms of mean ± SD, while categorical variables were expressed in terms of frequency and percentage.

A PBAC score of ≥100 was estimated to be consistent with menorrhagia. Severe symptoms were considered if VAS score was equal or more than 5.

Prevalence of symptoms and percentage related to the single type and score of adenomyosis were calculated. Prevalence of pelvic endometriotic lesions at TVS evaluation was evaluated.

Two analyses were performed using predetermined combinations of predictor variables:

1. Correlation between single ultrasound types of adenomyosis and their extension inside the myometrium with patients' symptoms, infertility, miscarriage, and age;

2. Correlation between the total adenomyosis score and the patients' symptoms, infertility, miscarriage, and age.

The characteristics between adenomyosis groups were compared using chi-square tests for categorical variables and independent samples t tests or Mann-Whitney tests as appropriate for continuous data. Fisher's exact test was used to compare the prevalence and $p<0.05$ was considered statistically significant.

Results

The study included 108 women with an ultrasound evidence of adenomyosis.

Demographics, clinical characteristics, and symptoms are shown in Table 1. Deep endometriosis was detected in 40% of women with adenomyosis, while an ovarian endometriotic lesion was identified in 15% of cases. 55% of infertile patients had a history of at least one miscarriage in the previous two years. The correlation of each type of adenomyosis with patients' age, menstrual bleeding and painful symptoms is shown in Table 2. Each type of adenomyosis was also evaluated according the scoring system (Figure 1) and divided in 4 subgroups.

The different ultrasound types of adenomyosis are coexistent: diffuse adenomyosis of the outer

myometrium and of the junctional zone are associated in 51% (55/108) of cases. Focal adenomoysis of the JZ occurs together with focal adenomyosis of the outer myometrium in 31% (33/108) of cases. Diffuse adenomyosis of the junctional zone and adenomyomas are associated in 18/108 (17%) patients, while focal and diffuse adenomyosis coexist in only 6/108 (6%) women.

Women with diffuse adenomyosis (of the outer myometrium and JZ) compared to those with focal disease (of the outer myometrium and JZ) are significantly older, showed heavier menstrual bleeding (p=0.04), but no differences were seen regarding presence and severity of dyspareunia and dysmenorrhea. Moreover, women with adenomyomas were older and showed higher severity of heavy menstrual bleeding than women with focal disease, while the severity of dysmenorrhea was found lower than in women with focal disease of the outer myometrium.

Analysing the single ultrasonographic type of adenomyosis according to the score, which reflects the extension of the disease inside the uterus, we only observed a difference in age and PBCA mean score between scores 1 and 4 for diffuse adenomyosis of the outer myometrium and between score 1 and 3 for focal disease. Patients with low score for diffuse and focal adenomyosis showed a younger age. Mean dysmenorrhea VAS score was significantly higher in patients with a score of 4 for diffuse adenomyosis compared to a score of 1 for the same type and a score of 4 for adenomyoma.

In patients trying to conceive, the presence of ultrasound findings of focal disease was associated with a higher percentage of infertility compared to diffuse disease Table 3. In addition, women with focal disease affecting the junctional zone showed a higher rate of at least one miscarriage compared to women affected by diffuse adenomyosis. Concerning the association between adenomyosis and endometriosis, women with moderate and severe adenomyosis showed a statistically significant association with endometriosis compared to those with mild adenomyosis.

Tables 4 report patients' age, menstrual bleeding, pain symptoms, contemporary presence of and infertility based on the three degrees of uterine involvement by adenomyosis. The sum of the single score of each type of adenomyosis (i.e. adenomyosis total score) determined these three categories:

mild, moderate and severe. There was a statistically significant difference between severe and mild disease regarding age, but not for any other features. With regards to miscarriage, there is a tendency, although not significant, towards a higher percentage in patients with severe adenomyosis compared to mild.

Discussion

The aim of this study was to find a correlation between the TVS evaluation of type and severity of adenomyosis and painful symptoms, amount of uterine bleeding, and infertility.

The correlation between amount of histopathology features and clinical manifestations has been clarified in previous studies performed on uterine specimens obtained from hysterectomies. These studies showed no increase in number of adenomyotic foci in women with menorrhagia, but confirmed direct correlation of foci number with severe dysmenorrhea (5, 34, 35). Bird et al reported that dysmenorrhea was present in 4.3% of women whose uterus had histologically defined Grade I penetration, in 42.4 % and 83.3% with Grade II and Grade III penetration respectively (5). Furthermore, Levgur et al found that menorrhagia was also related to the depth of the adenomyotic foci within the myometrium (35).

Based on these findings there was the belief of a direct correlation between the extent of histopathological features and clinical manifestations with the consequent hypothesis of a causal relationship between the number and depth of the adenomyotic foci and specific symptoms.

However, several authors did not show significant differences in the prevalence of adenomyosis among women with or without a history of menorrhagia (4, 36-38). Unfortunately, all these studies showed a great bias, since they were conducted on the uteri of patients scheduled for hysterectomy for severe symptoms, were mostly of older age, and with no desire for pregnancy.

The TVS diagnosis of adenomyosis through specific features showed an accuracy up to 91% (22). TVS is a highly tolerable exam and due to its reduced invasiveness could be carried out in all

patients, including younger patients with fewer symptoms and a desire for pregnancy.

Therefore, TVS gave us the ability to evaluate the real impact of adenomyosis on specific symptoms. Previous papers have reported a correlation between the ultrasound features of adenomyosis and specific symptoms including infertility (18, 20, 21), however no correlation was ever demonstrated between the severity of symptoms and the type and extent of adenomyosis within the uterus.

We found that ultrasound features of diffuse adenomyosis were more frequent in older women with heavy menstrual bleeding compared to those with focal disease. We also observed a higher percentage of infertility and miscarriage in focal adenomyosis of the outer myometrium and the JZ respectively. These findings could lead us to believe that different types and depth of adenomyosis (in terms of localization in the outer or inner myometrium) have an impact on symptoms and fertility.

We also demonstrated that severe diffuse adenomyosis is correlated to severe dysmenorrhea and heavy menstrual bleeding. However, we were not able to find any other correlation to symptoms when classifying the extension of the diseases inside the uterus in mild, moderate and severe.

This is in contrast with the results previously reported by Naftalin at al., in which there was a correlation between ultrasound severity of adenomyosis, menstrual pain, and heavy bleeding (21, 39). Nevertheless, in these studies adenomyosis was not distinguished in types (focal and diffuse) or in regards to its extension inside the myometrial layers, but only according to the number of ultrasound features to evaluate the severity of the disease. Assessing the severity of adenomyosis based only on the number of sonographic characteristics could lead to false results: in some cases a small focal lesion could show multiple ultrasound features of adenomyosis and vice versa.

The absence of a direct correlation between the ultrasound extension of adenomyosis within the uterus and the severity of symptoms was also observed in this study, this could be partially explained by the presence of other coexisting conditions such as endometriosis, rather than the adenomyosis per se. Otherwise we could hypothesize that this condition is very similar to pelvic

endometriosis, where often the severity of the disease is not related to the severity of symptoms. In fact, small endometriotic lesions may cause a lot of pain, whereas sometimes, deep nodules are completely asymptomatic.

A possible limitation of the present study could be that only two expert sonographers were recruited from specialized endometriosis centers.

Although not uniformly accepted as standard of care, a strength of this study is the use of a sonographic diagnosis for adenomyosis, avoiding the need for histologic diagnosis, to assess the correlation with the symptomatology. Furthermore, this study investigates several important new issues. Firstly, it attempts to provide a description differentiating the three types of the disease (diffuse, focal and adenomyomas) using TVS. Secondly, these three types are divided according to the depth of involvement in the myometrial layers (external and internal myometrium) and thirdly the extension of the disease inside the whole uterus is assessed through a detailed schematic scoring system. In addition, we attempted to correlate these characteristics to the severity of symptoms. In our study the evaluation of symptoms was not limited to investigating their presence or absence but was obtained using the VAS score and the PBAC score, allowing a quantitative assessment. Another major strength of the study was its prospective nature.

To conclude, we feel that transvaginal sonography is able to assess type and severity of adenomyosis inside the uterus. Our preliminary data showed differences between focal and diffuse adenomyosis regarding age, menstrual bleeding, infertility, and miscarriage, however, we were not able to demonstrate a correlation between severity of symptoms and the ultrasound extension of the disease (mild, moderate and severe) within the uterus.

Further studies on larger population could be useful to confirm our findings and to determine if this new TVS assessment scheme may be helpful in selecting and evaluating the effectiveness of medical and surgical management, as well as the possible relationship between adenomyosis and infertility.

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Legend of Figures and Tables

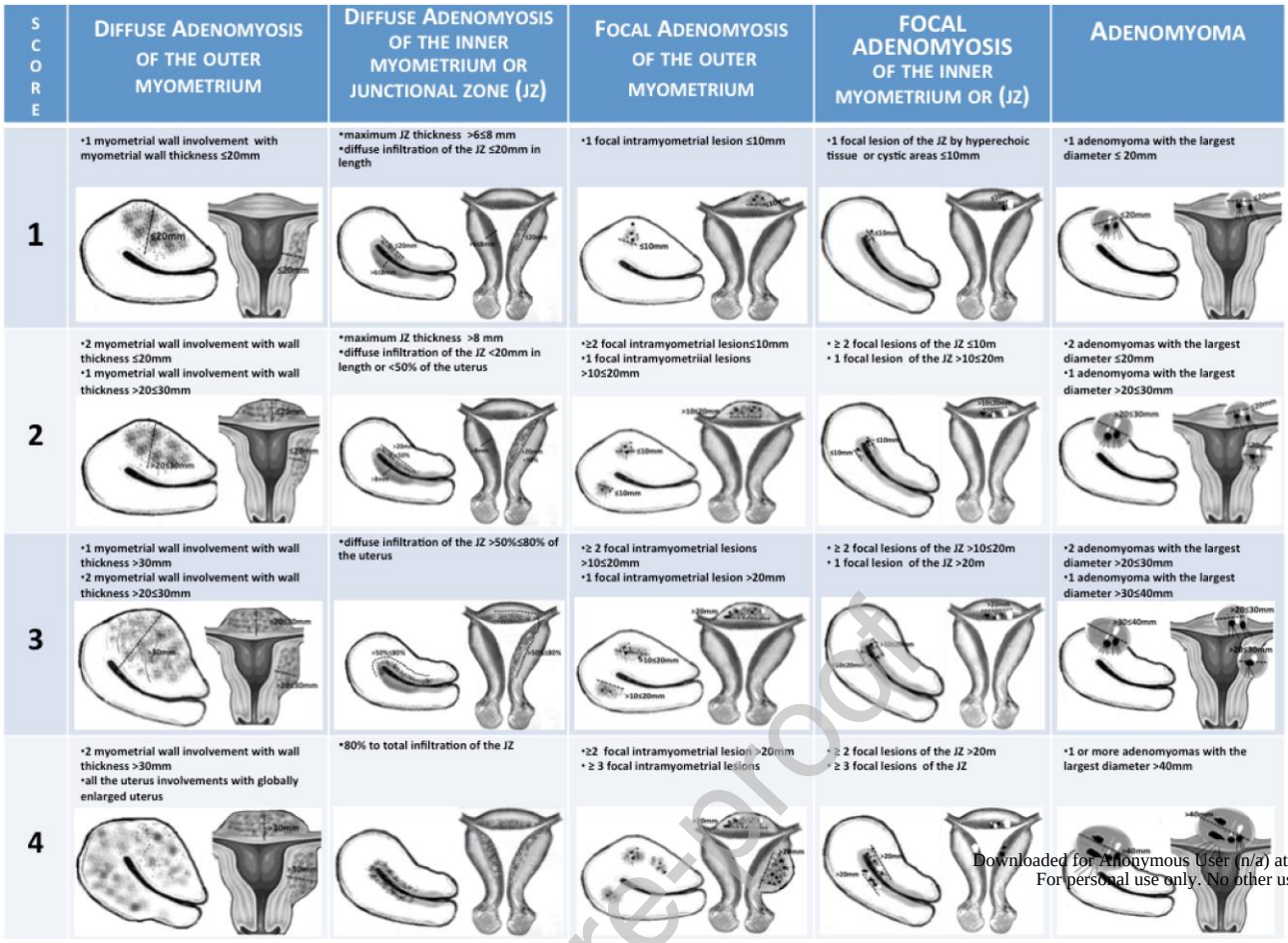

Figure 1 Ultrasound score system used to classify the severity of adenomyosis (20).

Table 1: Patients characteristics and symptoms of the study population

	Study group n= 108
Age *(mean±SD)*	37.7±7.7
BMI *(mean±SD)*	22.4±4.3
gravidity *(mean±SD)*	0.43±0.8
parity *(mean±SD)*	0.21±0.5
Amount of menstrual bleeding with PBCA *(mean±SD)*	248.3±201.8

Heavy menstrual bleeding PBCA ≥ 100 ***(N pts (%)***	91(84.2)
Dysmenorrhea VAS score ***(mean±SD)***	6.0±3.6
Severe dysmenorrhea VAS score ≥5 ***(N pts (%))***	78(72.2)
Dyspareunia VAS score ***(mean±SD)***	3.2±3.7
Severe dyspareunia VAS score ≥ 5 ***(N pts (%))***	43 (39.8)
Infertility ***(N pts (%))/ try to conceive***	39/70 (55.7)
Miscarriage ***(N pts (%))/ try to conceive***	24/70 (34.3)
Endometrioma ***(N pts (%)***	17(15.7)
Deep Endometriosis ***(N pts (%))***	43(39.8)

Table 2: Correlation of adenomyosis classified in different forms (diffuse, focal and adenomyoma), location inside the myometrium (outer and JZ) and extension inside the uterus scored in 4 points according to symptoms;

Adenomyosis n=108	**Age** mean ±SD	**Menstrual Bleeding PBCA** mean ±SD	**Dysmenorrhea VAS score** mean ±SD	**Dyspareunia VAS score** mean ±SD
Diffuse Outer Myometrium (n=60)	**38.8±7.2***	**279.2±233***	**5.6±3.8**	**3.0±3.7**
Score 1 (n=16)	**34.8±7.3^**	**200.7±128.2^**	**5.3±2.3^**	**5.3±2.3**
Score 2 (n=19)	**38.7±7.5**	**190.6±94.5**	**4.4±4.2**	**2.3±3.6**
Score 3 (n=9)	**42.1±5.2**	**283.7±140.8**	**5.9±3.0**	**3.0±4.1**
Score 4 (n=16)	**41.1±6.4^**	**427.2±338.2^**	**7.5±3.1^µ**	**3.0±3.6**
Diffuse Inner Myometrium (JZ) (n=91)	**38.7±7.2**	**249.5±193.5**	**5.9±3.7**	**3.1±3.8**
Score 1 (n=19)	**37.5±7.3**	**208.5±115.1**	**5.6±3.5**	**2.8±3.8**
Score 2 (n=21)	**37.7±8.9**	**233.0±160.9**	**6.4±3.5**	**4±3.6**
Score 3 (n=16)	**40.4±5.9**	**248.0±176.9**	**6.4±3.4**	**2.9±3.6**
Score 4 (n=35)	**39.1±6.7**	**282.4±246.7**	**5.7±4.1**	**2.9±4.0**
Focal Outer Myometrium	**35.5±7.5*§**	**194.7±119.5***	**6.8±2.9§**	**3.5±3.8**

(n=42)				
Score 1 (n=6)	**31.3±6.8 °**	**157.7±82.7**	**5.5±4.4**	**3.3±3.8**
Score 2 (n=23)	**34.2±7.9**	**185.5±133.2**	**6.3±2.9**	**3.9±3.8**
Score 3 (n=12)	**38.8±4.6°**	**232.7±109.9**	**8.4±1.5**	**2.3±3.9**
Score 4 (n=1)	**50**	**256**	**9**	**7**
Focal Inner Myometrium (JZ) (n=30)	**35.2±7.1*§**	**175.4±98.5***	**5.9±3.6**	**3.6±3.9**
Score 1 (n=15)	**33±4.8**	**150.5±68.2**	**6.6±3.0**	**5.0±3.9**
Score 2 (n=12)	**34±4.5**	**239.9±115.1**	**4.7±3.7**	**2.0±3.7**
Score 3 (n=3)	**37.0±4.3**	**156.7±83.3**	**6.7±5.8**	**2.3±2.5**
Score 4 (n=0)				
Adenomyoma (n=21)	**40.8±7.6§**	**243.3±163.7**	**4.5±4.1§**	**2.2±3.3**
Score 1 (n=7)	**39.8±4.8¶**	**170.7±74.2**	**4.4±4.1**	**2.7±3.9**
Score 2 (n=4)	**37.5±8.8**	**239.7±143.8**	**6.7±3.7**	**1.5±1.7**
Score 3 (n=6)	**40.5±10.9**	**339.7±235.0**	**5.5±4.4**	**2.5±3.9**
Score 4 (n=4)	**46.0±2.9¶**	**229.2±153.9**	**1.0±2.0 µ**	**1.7±3.5**

*P<0.05 diffuse vs focal adenomyosis

§P<0.05 adenomyoma vs focal adenomyosis

^ P<0.05 score 1 vs score 4 of diffuse adenomyosis

°P<0.05 score 1 vs score 3 of focal adenomyosis

¶ P<0.05 score 1 vs score 4 of adenomyoma

µ P<0.05 score 4 diffuse adenomyosis vs score 4 adenomyoma

Table 3: Correlation to infertility and at least one miscarriage occured in the last recent 2 years to adenomyosis classified in different types (diffuse, focal and adenomyoma), location inside the myometrium (outer and JZ) and extension inside the uterus scored in 4 points according to our scheme.

Type of Adenomyosis in women who try to conceive Total n= 70	**Infertility n (%)**	**Miscarriage n (%)**

Diffuse Outer Myometrium (n=42)	*22 (52)**	*15 (36) **
Score 1 (n=10)	8 (80)	5 (50)
Score 2 (n=12)	5 (42)	3 (42)
Score 3 (n=6)	2 (33)	2 (33)
Score 4 (n=12)	7 (50)	5 (36)
Diffuse Inner Myometrium (JZ) (n=62)	*33(53)*	*23 (37)*
Score 1 (n=10)	7 (70)	3 (30)
Score 2 (n=13)	7 (54)	5 (38)
Score 3 (n=13)	4 (31)	3 (23)
Score 4 (n=26)	15 (58)	12 (46)
Focal Outer Myometrium (n=22)	*18 (82) **	*9 (43)*
Score 1 (n=2)	2 (100)	1 (100)
Score 2 (n=9)	8 (89)	3 (33)
Score 3 (n=10)	7 (70)	5(50)
Score 4 (n=1)	1 (100)	0 (0)
Focal Inner Myometrium (JZ) (n=16)	*10 (62)*	*11 (69) **
Score 1 (n=4)	3 (75)	2(50)
Score 2 (n=9)	5 (56)	6 (67)
Score 3 (n=3)	2(67)	3 (100)
Score 4 (n=0)		
Adenomyoma (n=19)	*7 (37)*	*4(21)*
Score 1 (n=7)	4 (57)	0
Score 2 (n=4)	2 (50)	1 (25)
Score 3 (n=4)	0	1(25)
Score 4 (n=4)	1 (25)	2(50)

* p<0.005 diffuse vs focal

Table 4: Adenomyosis total score (= sum of the single score of each type) correlation with clinical symptoms and infertility.

Adenomyosis Total Score n=108	Age mean±SD	Menstrual Bleeding PBCA mean ±SD	Dysmenorrhea VAS score mean ±SD	Dyspareunia VAS score mean ±SD	Women try to conceive n=70	Age mean±SD	Infertility n (%)	Miscarriage n (%)
1-3 (mild) n=28	34.9±8.1+	195.7±129.5	5.9±3.6	3.2±3.7	14	38.9±6.3	8 (57)	2 (14)
4-6 (moderate) n=43	36.2±8.0+	263.1±216.6	5.0±3.1	5.0±3.8	24	39±8.3	14 (58)	8 (33)
≥7 (severe) n=37	41.3±5.5 +	270.9±225.5	6.1±3.8	2.4±3.7	32	41.3±5.5	17(53)	14 (44)

+ P<0.05 moderate vs severe and mild vs severe