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The prevalence of adenomyosis in an infertile population; A cross-sectional study

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ABSTRACT:

Research question: Adenomyosis was reported in a high proportion (24.4%) of infertile women which may be over-representative. So, what is the exact prevalence of adenomyosis from an infertility clinic population?

Design: In this cross-sectional study, 320 infertile women ≤ 41 years attending the infertility clinic of a university teaching hospital were screened by two-dimensional transvaginal ultrasound (2D-TVUS) looking for the sonographic markers of adenomyosis with subsequent magnetic resonance imaging (MRI) if suspected. Additionally, the adenomyosis subtype (I-IV) was determined based on MRI geography (Kishi classification). Comparisons between women with and without adenomyosis were done.
Results: Adenomyosis was found in 24 cases (7.5%) and confirmed by MRI in 21 of them (6.6%). The mean age of the studied group was 29.2 ± 4.7 years. Asymmetrical myometrial thickening was observed most frequently (58.3%). The majority of cases (85.7%) had diffuse adenomyosis. A significantly higher prevalence was found in women ≥ 40 compared to women < 40 years old (40% vs. 4.9%, respectively; \( P < 0.0001 \)). Adenomyotic women had significantly increased mean age (32.7 ± 3.0 vs. 28.6 ± 4.4; \( P < 0.0001 \)), body mass index (31.3 ± 2.7 vs. 28.7 ± 3.3; \( P < 0.0001 \)), suffered more dysmenorrhea (38% vs. 17%; \( P = 0.02 \)) and had more ovarian endometriomas (19% vs. 6%; \( P = 0.03 \)) than those without adenomyosis.

Conclusion: The observed prevalence of 7.5% for adenomyosis detected de novo in a population of young infertile women should alert the gynecologists and ultrasonographers to look for the 2D-TVS features of adenomyosis when scanning young infertile women.

Keywords: adenomyosis, infertility, prevalence, transvaginal ultrasound, magnetic resonance imaging.

KEY MESSAGE
The observed prevalence of 7.5% for adenomyosis detected de novo by the two-dimensional transvaginal ultrasound in a population of young infertile women should alert the gynecologists and ultrasonographers to look for the sonographic features of adenomyosis when scanning young infertile women.

INTRODUCTION
Adenomyosis is a benign gynecologic condition classically described by the presence of ectopic foci of endometrial glands and stroma deeply located in the myometrium with subsequent myometrial inflammation and hypertrophy (Bird and McElin, 1972).
Despite having been recognized for over 100 years, adenomyosis still remains a neglected enigmatic disease posing a great challenge to both gynecologists and researchers in the field (Benagiano and Brosens, 2006; Donnez et al., 2018). Currently, there is an accumulating body of evidence about the negative impact of adenomyosis on fertility as well as assisted reproductive technology (ART) outcomes (Younes and Tulandi, 2017; Rocha et al., 2018; Sharma et al., 2019). Disturbed endometrial-myometrium interface or uterine junctional zone (JZ) resulting in disturbed uterine peristalsis and impaired uterotubal transport, as well as implantation failure via altered endometrial function and receptivity, have been reported to explain this negative association. Moreover, iatrogenic uterine contractions mediated by the higher production of prostaglandin in adenomyotic tissues as well as excessive free radical release and nitric oxide exposure, were also proposed (Harada et al., 2016; Vlahos et al., 2017).

Undoubtedly, histopathological diagnosis following hysterectomy is not a feasible option for infertile women. Fortunately, two-dimensional transvaginal ultrasound (2D-TVS) and magnetic resonance imaging (MRI) have been reported as sufficiently accurate techniques for diagnosis of adenomyosis via distinct morphological markers with a sensitivity and specificity up to 92% and 88% for 2D-TVS and 77% and 89%, respectively for MRI (Bazot et al., 2001; Kepkep et al., 2007; Champaneria et al., 2010; Van den Bosch et al., 2015; Andres et al., 2018; Bazot and Daraï, 2018). Adenomyosis has two main forms. The diffuse type in which the ectopic foci of endometrial glands and stroma are evenly scattered in the myometrium, meanwhile the focal type is considered when the ectopic foci aggregate in a circumscribed nodular manner (Van den Bosch et al., 2015).
A systematic review published in 2012 highlighted the lack of studies evaluating the prevalence of adenomyosis among infertile women (Maheshwari et al., 2012). Since then to our knowledge, only one study is currently available in the literature about this topic where adenomyosis was found in a high proportion (24.4%; n=248/1015) of infertile women by three-dimensional (3D)-TVS. However, the authors admitted the possibility of overestimating the prevalence of adenomyosis in the entire infertile population in the light of including a large proportion of cases with repeated ART failures and recurrent miscarriage (36.7%), as well as older women seeking IVF treatment (Puente et al., 2016).

In that domain, this study was conducted to assess the prevalence of adenomyosis in a population of infertile women attending the infertility clinic of a university teaching hospital by using 2D-TVS and confirmed by MRI.

**MATERIALS AND METHODS**

This was an observational cross-sectional study evaluating infertile women ≤ 41 years of age attending the infertility clinic of the gynecology department, Mansoura university hospitals, Mansoura, Egypt from October 2013 to June 2017. All women were complaining of infertility, which was defined as an inability to conceive after one year of unprotected intercourses (Zegers-Hochschild et al., 2017). Exclusion criteria were women not complaining of infertility, women ≥ 42 years of age (a government-funded infertility clinic that only provides treatment for women <42 years age), those complaining of recurrent abortion, those with a previous diagnosis of adenomyosis or those unwilling to participate in the study. The study was approved by the local research ethics committee of our institution (MMREC: Mansoura Medical Research Ethics
Committee - Code No: MS/195/2013) and all participants gave informed consent before inclusion in the study.

For all women, a detailed clinical history was obtained and a physical examination (general, abdominal and local) was performed prior to the 2D-TV scan. The pictorial blood loss assessment chart (PBAC) was used to evaluate the amount of menstrual blood loss. Heavy menstrual bleeding (HMB)/menorrhagia was diagnosed when PBAC score ≥100 (Higham et al., 1990). All investigations previously carried out for infertility such as semen analysis, HSG, hormonal profile, laparoscopy and or hysteroscopy were reviewed. The information obtained was recorded on a data collection sheet.

The 2D-TV assessment was performed using a ClearVue 350 ultrasound machine (Philips, Bothell, WA, USA) with a 4–9 MHz transvaginal probe. All scans were done by the same examiner (H.A.H) during the inter-menstrual phase of the cycle. The uterus was visualized in both longitudinal and transverse planes. The diagnosis of diffuse adenomyosis was made in the presence of one or more morphological sonographic criteria. These criteria were as follows: asymmetrical myometrial thickening, myometrial anechoic cysts, hyperechoic myometrial islands, hyperechoic subendometrial linear striations in the myometrium, fan-shaped shadowing and irregular or ill-defined JZ. Diagnosis of diffuse adenomyosis was made in the presence of one or more its morphological sonographic criteria. Focal adenomyosis was defined as a heterogeneous nodular mass with ill-defined borders (Kepkep et al. 2007; Van den Bosch et al., 2015). Diagnosis of endometriosis was based on a previous laparoscopic report or if an ovarian endometrioma was found during the 2D-TV scan with the following characteristics: ground glass echogenicity of the cyst fluid (i.e. homogeneous
low-level internal echoes) and one to four locules without solid parts (Van Holsbeke et al., 2010).

Subsequently, pelvic MRI examination was done for all cases that showed sonographic markers of adenomyosis. MRI was utilized as a second-line imaging modality for the diagnosis of adenomyosis as well as to differentiate between its subtypes (Bazot and Daraï, 2018). MRI examinations were done by a 1.5 T MRI machine (Philips, Ingenia, Netherlands). The patients were examined in a supine position using a phased-array coil. Patients had an antiperistaltic medication and kept fasting for 4 hours before the examination. The protocol was acquired with a 4mm thick-section and a 1mm gap, field of view of 25x25 cm and a matrix of 512 × 512 pixels. MRI sections included sagittal, coronal and axial fast spin-echo T2-weighted MR imaging. Also, sagittal and axial gradient echo T1-weighted MR imaging, with and without fat suppression was acquired. The following imaging parameters for the T2-weighted spin-echo sequence were utilized: repetition time ms/echo time ms, 4000/120 (effective); echo train length, 35; and two signals were acquired. T1-weighted spin-echo sequences were performed with 320/4 and one signal was acquired.

The diagnostic criteria for adenomyosis identified on T2-weighted sagittal MR imaging were: (i) maximal JZ thickness ($JZ_{\text{max}}$) ≥ 12 mm (Novellas et al., 2011; Reinhold et al., 1996); (ii) the ratio of the $JZ_{\text{max}}$ to the corresponding overall myometrial thickness at the same level of measurement (ratio$_{\text{max}}$) > 40% (Bazot et al., 2001; Novellas et al., 2011); (iii) high signal intensity myometrial spots (Novellas et al. 2011). Diffuse adenomyosis was diagnosed by at least the association of criteria number (i) and (ii). A low signal intensity mass with ill-defined margins and foci of high signal intensity on T2-weighted images were considered focal adenomyosis (Byun et al., 1999;
Novellas et al., 2011). All MRI findings were evaluated by an experienced radiologist in gynecological MRI (M.E.R) who was blinded to the results from 2D-TVS and the adenomyosis subtype was determined in light of the Kishi classification into four subtypes: (i) subtype I or intrinsic i.e. with direct communication with a thickened JZ, but the outer myometrium and serosa are preserved; (ii) subtype II or extrinsic i.e. originating from the outer uterine layer with intact JZ and the muscle layer in between; (iii) subtype III or focal intramural adenomyosis i.e. solitary lesion with intact JZ and serosa and (iv) subtype IV or indeterminate i.e. did not satisfy any of the aforementioned criteria (Kishi et al., 2012).

**Sample-size calculation**

The sample size of 310 women was established at the study design phase using the following formula:

$$n = \frac{Z^2 \cdot P \cdot (1 - P)}{d^2}$$

Where $n$ is the sample size, $Z = 1.96$ for 95% confidence level, $P$ is the expected prevalence in a proportion of one and $d$ is the precision ($= 0.05$) (Daniel, 1999). $P$ was set at 28% i.e. $P = 0.28$ according to a previous report of a 28% prevalence for adenomyosis (diffuse and focal) by MRI in a control group of young (< 36 years) non-endometriotic women (n=19/67) (Kunz et al., 2005).

**Statistical analyses**

Data were statistically analyzed with the SPSS program (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 16. The normality of data was
tested with the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± SD (standard deviation) for parametric data, and median (range) for non-parametric data. Categorical data were described using number and percent (n, %). The 95% confidence intervals (CI) for proportions and means were calculated when necessary. Comparisons between adenomyotic positive and negative women were carried out using Chi-squared or Fisher’s exact tests for categorical variables; meanwhile, the Student’s t-test was used to compare continuous ones. The results were considered significant when the P-value was < 0.05. Odds ratios (OR) and the mean difference (MD) with 95% CI were calculated for dichotomous and continuous outcomes, respectively.

RESULTS

We approached 355 infertile women to participate in our study; 320 (90.1%) met eligibility criteria and were enrolled in the study. Of these, 264 women (82.5%) had primary infertility and 56 (17.5%) had secondary infertility. Length of infertility ranged from 1 to 15 years with a median of 3 years. Thirty-five women were excluded (Figure 1). Within 320 infertile women screened by 2D-TVS, the adenomyosis prevalence was 7.5 % (95% CI, 4.6-10.4%; n=24/320). The demographic data of the patient population are shown in Table 1. The mean age was 29.2 ± 4.7 years (95% CI, 28.7-29.7 years) and the age range was 19-41 years. The 2D-TVS characteristics for adenomyosis in the 24 cases are shown in Table 2. Asymmetrical myometrial thickening was observed most frequently (58.3%: 95% CI, 38.6-78%). Of note, none of the 24 cases had been previously diagnosed with adenomyosis. The diagnosis was subsequently confirmed by MRI in 21 cases. Two cases with suspected focal adenomyosis by 2D-TVS were found to be fibroids in MRI and a case with ill-defined JZ by 2D-TVS was found to have a thin JZ by MRI. Thereby, the prevalence of adenomyosis by MRI was 6.6% (95% CI,
MRI characters of adenomyosis are shown in Table 2. The majority of cases showed diffuse adenomyosis with the JZ_{max} ≥ 12 mm and ratio_{max} > 40% (85.7%; 95% CI, 70.7-100.7%) (subtype I Kishi), meanwhile focal intramural adenomyosis with an intact thin JZ and serosal coat (subtype III Kishi) was less common (14.3%; 95% CI, -0.7 to 29.3%). No cases of extrinsic adenomyosis (subtype II Kishi) or indeterminate (subtype IV Kishi) were detected by MRI in our study.

The prevalence of adenomyosis was significantly higher in women ≥ 40 years compared to women < 40 years [40% (6/15) vs. 4.9% (n=15/305); OR, 12.9; 95% CI, 4.1-40.9; P < < 0.0001]. Of note, the cut-off of 40 years was chosen for comparison in light of previous reports which showed that approximately 20% of cases of adenomyosis involve women younger than 40 years, meanwhile the vast majority (80%) of them is above 40 years old (Bergeron et al., 2006; Harada et al., 2016; Pontis et al., 2016). The prevalence of adenomyosis within different age subgroups was: < 30 years = 2/151 (1.3%), 30-33 years = 2/76 (2.6%), 34-37 years = 9/69 (13%), and 38-41 years = 8/24 (33.3%), respectively. As shown in Table 3, analysis by the chi-square test for trend revealed a significant association of adenomyosis with female age (Chi-square for linear trend = 31.83; P <0.0000001). The prevalence of adenomyosis was 6.4% (n=17/264) in women with primary infertility and 7.1% (n=4/56) in women with secondary infertility without significant difference (OR, 0.9: 95% CI, 0.3-2.8; P = 0.85).

Adenomyotic women had significantly increased mean age (32.7 ± 3.0 vs. 28.6 ± 4.4 years; MD, 4.0: 95% CI, 2.6-5.4 years; P < 0.000001), body mass index (BMI) (31.3 ± 2.7 vs. 28.7 ± 3.3; MD, 2.6: 95% CI, 1.4-3.8; P < 0.0001) and suffered more dysmenorrhea (38% vs. 17%; OR, 3.0: 95% CI, 1.2-7.6; P = 0.02) than those without
adenomyosis. However, we found no between-group differences in gravidity, parity, HMB, deep dyspareunia and other variables (Table 1).

There was no significant difference in the rates of associated fibroids between groups; however, adenomyotic patients were more likely to have ovarian endometriomas [19% (4/21) vs. 6% (n=18/299); OR, 3.7: 95% CI, 1.1-12.1; \( P = 0.03 \)] (Table 1). Selections from the adenomyotic patients’ MRI scans are shown in Figures 2-4.

**DISCUSSION**

The prevalence of adenomyosis in our study is 7.5% by 2D-TVS. The majority of cases showed diffuse adenomyosis (subtype I Kishi). Adenomyotic women had significantly increased mean age, BMI, suffered more dysmenorrhea and had ovarian endometriomas than those without adenomyosis. The lower prevalence of adenomyosis (7.5%) detected in our study is likely to be explained by the lower mean age of patients (29.2 ± 4.7 years) compared with Puente et al. (2016) (38.3 ± 4.1 and 37.2 ± 4.7 years in positive and negative adenomyotic cases, respectively). Other explanation for their higher prevalence of adenomyosis (24.4%) may be the aforementioned selection biases in 36.7% of cases (Puente et al., 2016), as well as the use of 3D-TVS which has the advantage of evaluating the JZ better than 2D-TVS (Exacoustos et al., 2011; Rasmussen et al., 2019). Our finding of a higher prevalence of adenomyosis in women \( \geq 40 \) years agrees with Puente et al. Furthermore, analysis for linear trend across age subgroups revealed a significant association of adenomyosis with female age which is pretty obvious in women aged \( > 33 \) years (Table 3). This observation corresponds with previous findings by Kunz et al. (2007) who reported a marked increase in the JZ.
thickness indicative of adenomyosis after the age of 34 years in 227 women evaluated by MRI. This could be related to the aging progress of the uterus with more prolonged endogenous estrogen exposure (Garcia and Isaacson, 2011; Kunz et al., 2007, 2005).

Despite the previously reported increased frequency of adenomyosis in multiparous patients and those with a previous spontaneous abortion (Parazzini et al., 1997; Templeman et al. 2008; Garcia and Isaacson, 2011), we found no difference between the prevalence of adenomyosis in primary and secondary infertility cases. This may be explained by the small number of cases suffering from secondary infertility (17.5%). Our finding of no differences in parity status was reported also by Puente et al.

In our study, asymmetrical myometrial thickening was the most frequently observed sign of adenomyosis on 2D-TVS (58.3%) (Table 2). This finding was reported recently among 53 young nulliparous women with diffuse adenomyosis by 2D-TVS (56.6%) (Pinzauti et al., 2015). The majority of our cases were diffuse adenomyosis (85.7%) confirmed by MRI (Table 2 and Figures 2 and 3A). Our finding confirms that intrinsic adenomyosis (subtype I Kishi) is more common than focal intramural adenomyosis (subtype III Kishi) (Kishi et al., 2012). We found no cases of extrinsic adenomyosis (subtype II Kishi). This could be explained by the current lack of knowledge about the role of TVS in its detection (Bazot and Daraï, 2018). The finding of 3 cases with isolated focal adenomyoma and an intact thin JZ and serosal coat (subtype III Kishi) (Table 2 and Figures 3 C, D and 4) could support the hypothesis concerning metaplasia theory for this subtype (Bergeron et al., 2006; Kishi et al., 2012, García-Solares et al., 2018). Of note, Kishi et al. (2012) highlighted that women in this subtype had the youngest age (34.3 ± 4.7 years).
Unlike Puente et al. (2016), adenomyotic women had a significantly higher mean age than those without adenomyosis in our study (Table 1). This may be related to more duration of estrogen exposure (Garcia and Isaacson, 2011). Increased BMI has been reported as a risk factor for adenomyosis (Templeman et al., 2008). We found such an association in our study (Table 1). Adenomyosis is considered as a cause of abnormal uterine bleeding owing to increased uterine volume, vascularity, improper uterine contractions, and increased estrogen and prostaglandins production (Munro et al., 2011; Abbott, 2017). The observed HMB in 19% of adenomyotic women in our study (Table 1) agrees with that (18.9%) described by others (Pinzauti et al. 2015). Our adenomyotic patients experienced also more dysmenorrhea (Table 1). Of note, Kissler et al. (2008) reported thickening of the JZ suggestive of adenomyosis in 87% (26/30) of infertile patients suffering from severe dysmenorrhea.

We found a significant association between adenomyosis and ovarian endometriomas (Figure 4). This is supported by other investigators who reported that adenomyotic patients were more likely to have other markers of severe endometriosis such as ovarian endometriomas and DIE (Puente et al., 2016). This finding was also reported in patients with MRI diagnosis of adenomyosis (Zacharia et al., 2006; Chapron et al., 2017). This noticeable association warrants rethinking about the contribution of adenomyosis to infertility in this subset of women.

The strength of our study is that we screened a population of young infertile patients without a previous diagnosis of adenomyosis. Adenomyosis was diagnosed by reliable 2D-TVS markers and all scans were performed by a single operator, thereby minimizing inter-observer variability. Additionally, pre-defined peculiar MRI diagnostic criteria were utilized by an experienced radiologist who was blinded to the
results from 2D-TVS. This maximized the accuracy of the diagnosis especially in women who had an associated leiomyoma and when the sonographic diagnosis was uncertain. Moreover, findings were not only interpreted as diffuse or focal adenomyosis, but also differentiation of the adenomyosis subtype based on MRI geography was carried out. This complementary role of MRI could be attributed to the opportunity to examine a volume of tissue in multiple slices and spatial relations.

On the other hand, this study has limitations. First, the sample size (n=320) may be regarded as a relatively small one. However, a priori power calculation was performed in light of a previous study pertinent to this issue (Kunz et al., 2005). The lack of histopathological confirmation for adenomyosis may limit diagnostic accuracy. However, hysterectomy is not a feasible option for infertile women. The lack of 3D-TVS may be regarded as another limitation. Notably, a recent meta-analysis reported no difference in the overall accuracy of 3D-TVS compared with 2D-TVS except in JZ assessment (Andres et al., 2018). However, optimizing JZ details by 3D-TVS could be useful to diagnose adenomyosis (Exacoustos et al., 2011; Rasmussen et al., 2019).

In conclusion, our data showed a prevalence of 7.5% of adenomyosis by 2D-TVS detected de novo in a population of young infertile women. It is important for gynecologists and ultrasonographers to keep this observation in mind during their daily practice by looking for the 2D-TVS diagnostic criteria of adenomyosis when scanning young infertile women. Large-scale studies are needed to generate a body of evidence about the prevalence of adenomyosis in other age groups or else define different populations in the same age range who need assessment (e.g. differences based on race, BMI, coexistent diseases). Moreover, in light of the recently published consensus by the International Deep Endometriosis Analysis group (Guerriero et al., 2016), we think that
future studies assessing the prevalence of adenomyosis in infertile women should consider these markers (uterine and adnexa mobility tenderness, sliding sign and deep endometriotic nodules in different compartments) as a complementary step after mapping for sonographic markers of adenomyosis and concomitant endometriomas. This may be of added value for an in-depth evaluation of both entities in infertile women.

Acknowledgments: None.

REFERENCES


### Table 1  Patient characteristics and comparison between cases with and without adenomyosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort(^1) (n=320)</th>
<th>Positive Adenomyosis (n=21)</th>
<th>No Adenomyosis (n=299)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)(^2)</td>
<td>29.2 ± 4.7</td>
<td>32.7 ± 3</td>
<td>28.6 ± 4.4</td>
<td>4 (2.6-5.4)(^1)</td>
<td>&lt;0.00001*</td>
</tr>
<tr>
<td>(BMI)</td>
<td>27.8 ± 2.3</td>
<td>31.3 ± 2.7</td>
<td>28.7 ± 3.3</td>
<td>2.6 (1.4-3.8)(^2)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Age at menarche (y)</td>
<td>12.6 ± 1.0</td>
<td>12.9 ± 0.7</td>
<td>12.6 ± 1.0</td>
<td>0.3 (-0.04, 0.6)(^2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Reguláur cycle</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Regular</td>
<td>243 (75.9)</td>
<td>18 (85.7)</td>
<td>225 (75.2)</td>
<td>2 (0.6-6.9)</td>
<td>0.29</td>
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<tr>
<td>Irregular</td>
<td>77 (24.1)</td>
<td>3 (14.2)</td>
<td>74 (24.7)</td>
<td>0.5 (0.1-1.8)</td>
<td></td>
</tr>
<tr>
<td>HMB (menorrhagia):</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(PBAC ≥ 100)</td>
<td>67 (20.9)</td>
<td>4 (19)</td>
<td>63 (21)</td>
<td>0.9 (0.3-2.7)</td>
<td>0.83</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>59 (18.4)</td>
<td>8 (38)</td>
<td>51 (17)</td>
<td>3 (1.2-7.6)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Gravidity</td>
<td></td>
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<tr>
<td>0</td>
<td>265 (82.8)</td>
<td>17 (80.9)</td>
<td>248 (82.9)</td>
<td>0.9 (0.3-2.7)</td>
<td>0.82</td>
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<td>1</td>
<td>38 (11.9)</td>
<td>2 (9.5)</td>
<td>36 (12.0)</td>
<td>0.8 (0.2-3.4)</td>
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<tr>
<td>&gt;1</td>
<td>17 (5.3)</td>
<td>2 (9.5)</td>
<td>15 (5.0)</td>
<td>2 (0.4-9.4)</td>
<td>0.38</td>
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<tr>
<td>Parity</td>
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<tr>
<td>0</td>
<td>284 (88.8)</td>
<td>19 (90.4)</td>
<td>265 (88.6)</td>
<td>1.2 (0.3-5.5)</td>
<td>0.80</td>
</tr>
<tr>
<td>1</td>
<td>35 (10.9)</td>
<td>2 (9.5)</td>
<td>33 (11)</td>
<td>0.8 (0.2-3.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>&gt;1</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>4.6 (0.2-117.0)</td>
<td>0.35</td>
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<td>Oral Contraceptive use</td>
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<tr>
<td>Previous user</td>
<td>12 (3.8)</td>
<td>2 (9.5)</td>
<td>10 (3.3)</td>
<td>3.0 (0.6-14.9)</td>
<td>0.17</td>
</tr>
<tr>
<td>Never</td>
<td>308 (96.2)</td>
<td>19 (90.4)</td>
<td>289 (96.7)</td>
<td>0.3(0.1-1.6)</td>
<td></td>
</tr>
<tr>
<td>Abortions</td>
<td>26 (8.1)</td>
<td>2 (9.5)</td>
<td>24 (8.0)</td>
<td>1.2 (0.3-5.5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Deep dyspareunia</td>
<td>35 (10.9)</td>
<td>2 (9.5)</td>
<td>33 (11)</td>
<td>0.8 (0.2-3.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Associated fibroids</td>
<td>51 (15.9)</td>
<td>5 (23.8)</td>
<td>46 (15.4)</td>
<td>1.7 (0.6-4.9)</td>
<td>0.31</td>
</tr>
<tr>
<td>Associated Ovarian endometrioma</td>
<td>22 (6.9)</td>
<td>4 (19)</td>
<td>18 (6)</td>
<td>3.7(1.1-12.1)</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; HMB, heavy menstrual bleeding; n, number; OR, Odds ratio; PBAC, pictorial blood loss analysis chart; y, years.
† expressed as: n (%) or mean ± SD.
‡ mean difference (95% CI).
§ Range: 19-41; 27-41 and 19-41 years in total cohort, positive and negative cases respectively.
* significant (P<0.05).
¶ 305 women (95.3%) < 40 years and 15 (4.7%) ≥ 40 years.

Table 2 2D-TVS and MRI characters of adenomyosis

<table>
<thead>
<tr>
<th>2D-TVS findings</th>
<th>n (% , 95% CI)</th>
<th>Number of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric myometrial thickness'</td>
<td>14 (58.3, 38.6 to 78.0)</td>
<td></td>
</tr>
<tr>
<td>Cystic anechoic spaces in the myometrium'</td>
<td>7 (29.1, 10.9 to 47.3)</td>
<td></td>
</tr>
<tr>
<td>Fan-shaped shadowing'</td>
<td>5 (20.8, 4.6 to 37.0)</td>
<td></td>
</tr>
<tr>
<td>Sub endometrial echogenic liner striations'</td>
<td>3 (12.5, -0.7 to 25.7)</td>
<td></td>
</tr>
<tr>
<td>Irregular or ill-defined JZ</td>
<td>2 (8.3, -2.7 to 19.3)</td>
<td></td>
</tr>
<tr>
<td>Intramural mass ?? fibroid ?? focal adenomyosis</td>
<td>5 (20.8, 4.6 to 37.0)</td>
<td></td>
</tr>
</tbody>
</table>

Number of 2D-TVS criteria per 24 women
- 3 criteria                                          1
- 2 criteria                                          10
- 1 criterion                                         8
- ? focal adenomyosis                                 5

MRI characters of adenomyosis

Maximal JZ thickness (JZ\text{max}) ≥ 12 mm             18 (85.7, 70.7 to 100.7)

\text{Ratio}_{\text{max}} (JZ_{\text{max}} / myometrial thickness ) > 40% 18 (85.7, 70.7 to 100.7)

High signal intensity myometrial spots'                10 (47.6, 26.2 to 69)

Focal adenomyosis                                     3 (14.3, -0.7 to 29.3)

Number of MRI criteria of adenomyosis per 21 women
- 3 criteria                                          10
- 2 criteria
- Focal adenomyosis

2D-TVS, two-dimensional transvaginal ultrasound; CI, confidence interval; JZ, junctional zone; max, maximal; MRI, magnetic resonance imaging; n, number.

* Finding associated with others.

**Table 3** Analysis for linear trend of adenomyosis across age subgroups

<table>
<thead>
<tr>
<th>Age subgroup (y)</th>
<th>Score†</th>
<th>Positive Adenomyosis (n=21)</th>
<th>No Adenomyosis (n=299)</th>
<th>Total (n=320)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>0</td>
<td>2</td>
<td>149</td>
<td>151</td>
<td>1.00</td>
</tr>
<tr>
<td>30-33</td>
<td>1</td>
<td>2</td>
<td>74</td>
<td>76</td>
<td>2.01</td>
</tr>
<tr>
<td>34-37</td>
<td>2</td>
<td>9</td>
<td>60</td>
<td>69</td>
<td>11.18</td>
</tr>
<tr>
<td>38-41</td>
<td>3</td>
<td>8</td>
<td>16</td>
<td>24</td>
<td>37.25</td>
</tr>
</tbody>
</table>

Chi-square for linear trend (Extended Mantel-Haenszel) = 31.83

P-value (1 degree of freedom) = <0.0000001

n, number; OR, Odds ratio; y, years.

† A numeric score assigned across the age subgroups starting from number 0 for the subgroup with the lowest prevalence and 3 for the subgroup with the highest prevalence of adenomyosis.

**Figure 1** Study flow diagram

2D-TVS, two-dimensional transvaginal ultrasound; MRI, magnetic resonance imaging

**Figure 2** MRI for diffuse adenomyosis.

(A and B) Sagittal and coronal T2-weighted MRI sections (a 32-year-old woman) showing marked thickening of the junctional zone (JZ) (yellow lines) in both anterior and posterior uterine walls with preserved outer myometrium and serosa (subtype I Kishi) (Kishi et al., 2012) (posterior wall myometrial thickness is marked by the
interrupted red line). (C and D) Sagittal and coronal T2-weighted MRI sections (a 29-year-old woman) showing marked thickening of the JZ (yellow line) of the posterior uterine wall with numerous foci of high signal intensity (interrupted yellow circles) in the posterior myometrium in both sections and in the anterior myometrium in coronal section. The outer myometrium and serosa are kept intact (subtype I Kishi) (Kishi et al., 2012) (posterior wall myometrial thickness is marked by the interrupted red line).

**Figure 3** MRI for diffuse and focal adenomyosis with associated fibroids.

(A) Sagittal T2-weighted MRI section (a 31-year-old woman) showing diffuse adenomyosis with preserved outer myometrium and serosa (subtype I Kishi) (Kishi et al., 2012) (The posterior JZ is marked by yellow line and posterior wall myometrial thickness is marked by interrupted red line). (B) Sagittal T2-weighted MRI section of the same patient in (a) with associated intramural fibroid (yellow star) measuring 4.5 x 4 cm. (C and D) Sagittal and axial T2-weighted MRI sections (a 28-year-old woman) showing focal adenomyosis with numerous foci of high signal intensity located in the posterior myometrium (yellow arrow) with associated anterior intramural fibroid 3.5 x 4.5 cm (yellow star). The JZ (yellow line) and serosa are kept intact (subtype III Kishi) (Kishi et al., 2012).

**Figure 4** MRI for focal adenomyosis with an associated ovarian endometrioma (a 34-year-old woman).

(A) Axial T1-weighted MRI section shows a right bilocular ovarian endometrioma measuring 5 x 4 cm (red stars). (B) Axial T1-weighted MRI section with fat suppression shows very hyperintense blood containing bilocular right ovarian endometrioma (red stars). (C and D) Axial and coronal T2-weighted MRI sections showing localized posterior adenomyosis (subtype III Kishi) (yellow arrows) and right ovarian
endometrioma with shading effect (red arrows). The intact JZ is marked by the yellow line in the axial section.

Fig. 1

Enrollment

Assessed for eligibility (n= 355)

Excluded (n= 35)
- Not meeting inclusion criteria (n=35)
  - Not complaining of infertility (n= 21)
  - Recurrent abortion (n= 11)
  - women ≥ 42 years (n= 2)
  - Previous diagnosis of adenomyosis (n= 1)
- Declined to participate (n= 0)
- Other reasons (n=0)

Allocation

320 met eligibility criteria

320 consented, enrolled & underwent 2D-TVS

Follow-Up

Lost to follow-up (n=0)

Analysis

Analysed
- adenomyosis was found in 24 cases by 2D-TVS.
- adenomyosis was confirmed in 21 cases by MRI.
Fig. 2

Fig. 3
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