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Vaginal Bromocriptine Improves Pain, Menstrual Bleeding and Quality of Life in Women with Adenomyosis; A Pilot study

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Conflicts of interest

Elizabeth A Stewart reports consulting for AbbVie, Allergan, Bayer, and Myovant related to uterine fibroids and Welltwigs related to infertility and has provided paid educational content for UpToDate and the Med Learning Group. Kristina Gemzell Danielsson reports consulting for Bayer AG, Gedeon Richter, HRA-Pharma and Exelgyn related to uterine fibroids, and development of progesterone receptor modulators. J.K. Andersson, Z. Khan, A.L Weaver and L. E. Vaughan have nothing to disclose.

ABSTRACT

Introduction: Adenomyosis is a benign uterine disease where endometrial glands and stroma are found within the myometrium surrounded by an area of hypertrophic myometrium. Symptomatology includes heavy menstrual bleeding and pelvic pain. The pathogenesis of adenomyosis is not known; however, animal models have shown increased uterine concentration of prolactin as a risk factor. Prolactin acts as a smooth muscle cell mitogen. If prolactin is central to adenomyosis pathogenesis, reducing uterine prolactin could be a possible medical treatment option. In this pilot study we aim to evaluate the effect of bromocriptine, a prolactin inhibitor, on menstrual bleeding and pain in women with adenomyosis. **Material and methods**: 23 women with diffuse adenomyosis were enrolled from a university hospital in Sweden and a tertiary care center in the United States. 19 patients completed 6 months of treatment with vaginal bromocriptine at a dose of 5mg daily. Participant completed validated measures at baseline, 3 and 6 months of treatment, and at 9-months (3-months after cessation of bromocriptine). Validated measures utilized included pictorial blood loss assessment chart (PBLAC), Aberdeen Menorrhagia Clinical Outcomes Questionnaire (AMCOQ), visual analog scale for pain (VAS), McGill Pain Questionnaire (MPQ), Endometriosis Health Profile (EHP-30), Female Sexual Function Index (FSFI) and the Fibroid Symptom Quality of Life (UFS-QOL) symptom severity and health related quality of life (HRQL) subscores. Scores were compared between baseline and 9 months using the Wilcoxon signed rank test. **Results:** Mean age of particpants was 44.8 years. 77.8% reported PBLAC scores > 250 and 68.4% reported moderate to severe pain at baseline. Compared to baseline, women had lower 9-month scores (median [interquartile range] for all) on PBLAC (baseline 349[292-645] vs. 9-month 233[149-515], p=0.003),

VAS (5.0[4-8.3] vs. 2.5[0-4.5], p<0.001), EHP Core Pain (15.9[9.1-50.0] vs. 3.4[2.3-34.1], p=0.029), EHP Core Self-image (41.7[16.7-58.3] vs. 25[0-5], p=0.048) and symptom severity score (60[44-72] vs. 44[25-56], p<0.001) and higher HRQL scores (57[37-63] vs. 72[51-85], p<0.001) following bromocriptine treatment. Other EHP core parameters and FSFI were not significantly different.
Conclusions: Significant improvement in menstrual bleeding, pain, and quality of life after vaginal bromocriptine treatment suggests a novel therapeutic agent for adenomyosis.

Key words

bromocriptine, adenomyosis, menstrual bleeding, pain, prolactin

Abbreviations

PRL: prolactin

MRI: magnetic resonance imaging

TVU: transvaginal ultrasound

HMB: heavy menstrual bleeding

PBLAC: pictural blood loss assessment chart

AMCOQ: Aberdeen Menorrhagia Clinical Outcomes Questionnaire

VAS: visual analoge scale
UFS-QOL: Uterine Fibroid Symptom Quality Of Life

HRQL: Health Related Quality of Life
SSS: symptom severity score
EHP30: Endometriosis Health Profile
FSFI: Female Sexual Function Index

JZ junctional zone

MPQ McGill Pain Questionnaire

Key message

Significant improvement in menstrual bleeding, pain, and quality of life after vaginal bromocriptine treatment suggests a novel therapeutic agent for this common disease which has limited uterine-conserving therapies.

INTRODUCTION

Adenomyosis is a benign uterine disease where ectopic endometrial glands and stroma are found within the myometrium surrounded by an area of hypertrophic and hyperplastic myometrium (1). Symptomatology of adenomyosis includes heavy menstrual bleeding (HMB) and pelvic pain (2) resulting in impaired quality of life.

The pathogenesis of adenomyosis is not known; however, animal models have shown increased uterine concentration of prolactin (PRL) as a risk factor (3-6). PRL is produced in the human endometrium and myometrium as well as the pituitary gland (7, 8) and acts as a smooth muscle cell mitogen *in vitro* (9, 10). In murine uteri minimal serum hyperprolactinemia, such as elevations secondary to pharmacotherapy for affective disorders, is sufficient to cause adenomyosis (11, 12). A retrospective human study observed that a history of depression was the only factor independently associated with adenomyosis (13). Thus, both murine and human studies suggest a link between the action of antidepressants and PRL in the development of adenomyosis. If PRL is central to adenomyosis pathogenesis, reducing uterine PRL could be a possible medical treatment option. The dopamine agonist bromocriptine inhibits pituitary secretion of PRL and is the gold standard of treatment for hyperprolactinemia. Bromocriptine is inexpensive and safe without serious side effects (14). Vaginal administration is well tolerated and effective in reducing circulating PRL levels in women with hyperprolactinemia (15) and has fewer gastrointestinal side effects than is seen with oral administration (16).

In this pilot study, we aim to evaluate the effect of vaginal bromocriptine on disease symptomatology in women with adenomyosis.

MATERIAL AND METHODS

This pilot study included participants from a university hospital in Sweden and a tertiary care hospital in the United States. Women aged 35-50 years with regular heavy menstrual bleeding, pictorial blood loss assessment chart (PBLAC) >100 and diffuse adenomyosis diagnosed with transvaginal ultrasonography (TVU) and magnetic resonance imaging (MRI) were recruited. Patients were considered to have adenomyosis if on MRI the junctional zone (JZ) was ≥12 mm, JZ differential >5mm and ratio JZ/myometrium >40%. Presence of cystic changes in the JZ was also considered. (17, 18). The diagnosis by TVU was based on Morphological Uterus Sonographic Assessment MUSA terms and definitions (19): irregular endometrial myometrial junction, assymetric thickness of myometrial wall, myometrial cysts, absence or presence of fanshaped shadowing in the myometrium. Extent of adenomyotic lesions in the myometrium was classified as < 50% or ≥ 50% and vascularity were measured.

Other inclusion criteria included normal serum PRL, use of barrier contraception, sterilization or sexual abstinence, and being able and willing to read and understand study materials.
Exclusion criteria included women actively pursuing pregnancy, being less than six months postpartum, currently breastfeeding, enlarged uterus over the umbilical level, contraindications to bromocriptine or ergot alkaloids, current use of medications including gonadotropin releasing hormone agonists or antagonists, contraceptive steroids, intrauterine contraceptive device, antidepressants or opioid pain medications. Women with MRI or TVU suggestive of endometriosis, a medical history of prolactinoma, high grade squamous intraepithelial lesion on a Papanicolaou smear or suspected or diagnosed malignant disease of uterus, ovary, or cervix were excluded. All women received written and oral information and gave informed consent prior to inclusion. Women were followed for 9 months, which included a 6-month treatment period followed by 3-month wash-out period after cessation of the study drug. Neither the participants nor study staff was blinded to treatment.

After baseline assessment, vaginal bromocriptine was started. In the original protocol subjects were instructed to start by placing 1 tablet (2.5mg) deep in the vagina once daily and after 1-2 weeks increase to 2 tablets daily. Among the first 7 enrolled women, 3 dropped out due to side effects (fatigue, dizziness, nausea and headache) when increasing dosage. The protocol was therefore modified, to a slower increase. Women started with ½ tablet (1.25 mg) deep in the vagina once daily for one week and then increasing by ½ tablet once a week until a dose of 5 mg was reached. Enrolled subjects received weekly phone calls from the study coordinator during the first month of treatment,

to check compliance and ask for side effects of bromocriptine. The first day the subject successfully took 5 mg bromocriptine was considered study day 1. The medication was then continued for 6 months.

Follow up visits were scheduled in the proliferative phase of the menstrual cycle at 3- and 6- month of medication. The last visit was a 9-month follow up, 3 months after cessation of the study drug.

A variety of self-administered validated questionnaires were utilized to assess changes in symptoms. Questionnaires were filled in by the women at home, close to the last day of the menstrual period, and brought to the clinic.

In addition to the PBLAC (20), the Aberdeen Menorrhagia Clinical Outcomes Questionnaire (AMCOQ) (21) was used to assess menstrual blood loss. The PBLAC is a subjective assessment of the volume of blood loss during each menstrual period, based on the degree of soiling of sanitary pads and tampons. PBLAC scores above 100 are defined as HMB. The AMCOQ consists of 13 questions assessing the amount of bleeding and impact on daily living, where higher scores indicating worse symptoms.

The visual analog scale (VAS) (22) and the Short form McGill Questionnaire (MPQ) (23) were used for evaluation of pain. VAS is a standard scale for pain assessment (scale of 0-10), and the MPQ uses 20 groups of words to describe three attributes of pain. Higher scores in VAS and MPQ indicate more severe pain.

Since there is no disease-specific quality of life measure for adenomyosis, we elected to use instruments for two related diseases, uterine fibroids and endometriosis. The instrument Uterine Fibroid Symptom Quality Of Life (UFS-QOL), has become the standard instrument in assessing health-related quality of life with fibroids (HRQL)(24). The symptom severity score (SSS) is the primary symptom measure from this instrument; higher score indicates worse symptom severity. Higher UFS-QOL HRQL scores indicate better health-related quality of life.

Similarly, the Endometriosis Health Profile (EHP30) (25) is a standard instrument to assess symptoms of endometriosis. We adapted the EHP30 for this study by substituting the term “adenomyosis” in the

instructions for "endometriosis". The instrument consists of 30 questions in five core measures (pain, control and powerlessness, emotional well-being, social support and self-image), and a modular questionnaire with 23 questions concerning work, sexuality, fertility and medical treatment. Only in the modular questionnaire were women allowed to answer "not applicable." The Female Sexual Function Index (FSFI)(26) consists of 19 questions assessing sexual function, higher score indicates better sexual function.

Subjects were instructed to complete the questionnaires close to their last day of menstrual bleeding during the proliferative phase of the cycle, at baseline and at 3- 6- and 9-month. Participating women were provided with tampons and sanitary pads for standardization of PBLAC reporting. Women were instructed to refrain from the use of any nonsteroidal anti-inflammatory drugs or tranexamic acid therapy during the menstruation for measuring baseline, 3-6-and 9 month, to avoid confounding. Scores obtained from the questionnaires were compared between baseline and, 3-, 6- and 9- months.

Statistical analyses

This is a pilot study and no previously published data exists on which to base a power calculation. Initial plans were to enroll up to 33 patients with plans for an interim analysis. The first enrolled woman at Mayo Clinic was enrolled July 2013 and the first woman at Karolinska Institutet was enrolled January 2014. At time of interim analysis, April 19, 2016, 23 women were enrolled and 11 women had completed the protocol. At that time, decision to halt enrollment was made, due to funding limitations. We had *a priori* set our primary endpoint as an improvement in the UFS-QOL SSS of 10 points since this has been used in prior studies of uterine fibroids as a primary efficacy outcome (27). Data was manually entered into the Research Electronic Data Capture (REDCap, Vanderbilt University) data entry and management program. The entered data were verified by an independent data clerk and discrepancies were resolved. Continuous data with normal distribution are reported as mean ±SD; the median and interquartile range is used for data that is not normally distributed. Categorical data are reported as percentages. Changes in scores from baseline to 3, 6- and 9-months, respectively, were compared using Wilcoxon signed rank test. All statistical analyses were 2 sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using SAS 9.4(SAS Institute, Inc, Cary, NC).

Ethical approval

The study was approved by the regional ethics committee at Karolinska Institutet, Sweden (2013/2060-31/1) and the Institutional Review Board at Mayo Clinic, Rochester, MN, United States and was registered at clinicaltrials.gov (NCT01821001) and Eudract.ema.europa.eu (EudraCT 2013-004409-14) prior to recruitment of patients.

RESULTS

Fifty-five women with suspected adenomyosis were referred to MRI and to an expert in gynecological ultrasound. Thirty-five met eligibility criteria for the study (Figure 1). Major reasons for exclusion included irregular menses (N=8) and current use of antidepressants (N=5). Among those who met eligibility requirements, twenty-three women were enrolled. Reasons for non-participation included time consuming follow-up or desiring an established treatment regimen (Figure 1). Four women dropped out of the study; three in the beginning of the study, due to side effects from bromocriptine and one patient completed the 6 months ultrasound but did not return for the full study visit. Thus, nineteen women completed the study (Figure 1).

Key demographics of study participants are presented in Table 1 and 2. Women enrolled in the study were 44.8±3.5 years, with an average body mass index of 26.5±3.9 (Table1). 84% were parous and 63% had no prior caesarean deliveries (Table 1). At baseline, all women reported HMB, 77.8% reported PBLAC > 250 (Table 2). 78.9% used >10 tampons or pads on their heaviest day of menses, 78.9% reported menses lasting >7 days and 68.4% reported moderate to severe cramps with menses. The history of HMB and pain was long standing; 68.4% reported painful menses and 47.4% reported HMB before age 20. While few women had a history of blood transfusion (5.3%), the majority had previously been on pharmacotherapy for anemia (63.2%). Likewise, the use of medication for painful periods was also reported by 63.2% of women.

The radiologic findings at inclusion are presented in table 3 and 4. By MRI, the median JZ was 18.8mm (range 12.1-54.3), median JZdiff 10.6mm (range 4.8-26.3), and median ratio JZ/myom 0.62 (range 0.47-0.82). 83% had diffuse thickening of the JZ and 17% had focal thickening. Cystic changes within the JZ were seen in 53% of the women.

By TVU, asymmetrical myometrium thickness where present in 72 %, irregular JZ in 72%. Fan-shaped shadowing in the myometrium were seen in 94%, lesions >50% of the myometrium in 89% and <50% in 11%. The vascularity was translesional in 100%. Cysts within the myometrium were seen in 33%.

Changes in menstrual bleeding after bromocriptine therapy

There was a significant reduction in scores from both the PBLAC and the AMCOQ questionnaires indicating an improvement in menstrual bleeding severity (Table 5).

For PBLAC questionnaires, a baseline median score of 349 [292-645] decreased to a median score of 242 [76-384] at 6-months ($p<0.001$) while on therapy. These desired effects continued even 3 months after discontinuation of treatment, the median score remained suppressed at 9-months 233 [149-515], ($p=0.003$). Similarly on the AMCOQ, when compared to 51 [40-61] at baseline, scores were significantly suppressed to 35 [21-48] at 6-months ($p<0.001$) and 35 [24-47], ($p<0.001$) at 9 months. (Table 3)

Changes in pain after bromocriptine therapy

Overall, women had a significant improvement of pain scores while on therapy, with the effects of the treatment continuing after the 3-month wash out period (Table 3). For the VAS questionnaire, a baseline median score of 5 [4-8.3] was reduced to 2.2 [0.4-6.3] at 6-months ($p=0.011$). The efficacy of therapy continued at 9-months with a median score of 2.5 [0.4-5], $p<0.001$.

Similar results were seen when using MPQ for assessment of pain. A baseline median score of 10[5-22] was reduced to 6[3-16] at 6 months ($p=0.025$), and the effects lasted 3-months into stopping treatment with 9-months score at 7.5 [3-18], $p=0.021$ (Table 3).

Change in symptoms and quality of life after bromocriptine therapy

Women had decreased symptoms and improved quality of life with treatment. On the SSS, a baseline median score of 60[44-72] was reduced to 44[28-59] at 6 months and remained at that level at 6- and 9- months with similar IQR (p-value <0.001 for all when compared to baseline) (Table 3).

Quality of life as measured by UFS-QOL HRQL improved in women after being on 3- and 6-months of bromocriptine therapy (median change in score from baseline of 10 [4.3-21] ($p<0.001$) at 6-

months). Similar to all other scales, these desired effects on quality of life remained at three months after stopping treatment [median score at 9-months 13 [0, 29], p<0.001] (Table 3).

For EHP30, two core measures showed significant improvement with treatment: pain decreased from baseline levels of 15.9[9.0-9.5] to 3.41[2.3-34.1] (P=0.029) at 9 months and self-image likewise improved with decreasing scores from 41.7[16.7-58.3] at baseline to 25[0,5] at 9 months (p=0.048). For control and powerlessness and emotional well-being core EHP measures, significant improvement was seen at the end of therapy (6 months) but this was no longer significant at 9-months despite similar numerical scores (Table 3). No change at any point was seen in the Social Support core measure. In the modular questionnaire, a substantial number of women indicated these measures to be not applicable and thus these scores are not presented. FSFI did not show any significant changes during the studied period (Table 3).

DISCUSSION

This study demonstrates that vaginal bromocriptine significantly decreases menstrual bleeding and pain while improving quality of life in women with adenomyosis. This suggests that bromocriptine may be a novel medical therapy. Further studies are needed to explore the role of PRL in adenomyosis and the mechanism of action for bromocriptine leading to symptom relief.

While menstrual bleeding improved significantly after treatment, it still remained heavy with PBLAC scores over 100. However, there are known limitations to PBLAC as it has been demonstrated that women assess their use of menstrual protection very differently, with low correlation with true blood loss, especially with increasing scores (28, 29). It has previously been suggested to use a higher limit than 100 to define HMB (28-30). The AMCOQ, which assesses the impact of bleeding on daily life rather than amount of bleeding, may be more reliable and relevant than PBLAC for this study. The AMCOQ results in our study suggest that the measured improvement in bleeding had an impact on daily life and changed women's opinion about their menstruation from "unacceptable" to "acceptable". Although pain was not an inclusion criterion for participation, pain was a common and clinically significant symptom among participants. Pain scores administered independently and as part of the two disease-specific QOL measures decreased significantly during treatment, with some women reporting resolution of their pain at 6 months.

There is no validated QOL study instrument for adenomyosis and development of such an instrument is a key goal for adenomyosis research. Since symptoms of adenomyosis overlap with those of endometriosis and uterine fibroids, we elected to use the UFS-QOL and EHP30 to evaluate quality of life. Both appeared to show positive response to bromocriptine therapy and utilizing similar domains may be useful in developing an adenomyosis instrument.

Improved bleeding and pain have impact on aspects such as work, family life and physical activity. At baseline, women in our study scored worse on quality of life measures than typical women with fibroids (24). Using bromocriptine improved SSS significantly, although quality of life remained lower compared to healthy women.

We chose to administer bromocriptine vaginally in order to achieve a high uterine concentration of the drug thus maximizing efficacy and lower systemic levels to minimize adverse events. Vaginal administration of bromocriptine has been previously shown to have less gastrointestinal side effects than oral administration (15) and none of the women in our study complained of gastrointestinal side effects once they had reached the prescribed dose. The side effects noted in the present study were mainly headache, dizziness and fatigue at start of treatment, and was more of a problem among the first patients entering the study. However, after changing the protocol to increase the dose by 1.25mg/week instead of 2.5mg/week, few women experienced these side effects. All side effects were transitory, and none of the women reported any adverse effects during the study period.

The strength of the study includes close follow up through phone calls, and standardization of the PBLAC by giving women pads and tampons. There are also several limitations. Most importantly, there was no control group and neither women nor investigators were blinded to treatment, thus raising the possibility of a placebo effect. While this is always a possibility, the fact that not all measures reported improvement argues against this rationale. Our study was also prone to participation bias, which could limit generalizability since the age of the study group was high and many of the participants strongly wished to avoid hysterectomy. Younger women are to a greater degree in need of hormonal contraceptives or IUDs, and therefore not eligible for the study. It is possible that women close to menopause are more willing to try a medical treatment than younger women. Their desire for medical treatment might have had a positive impact on their scoring in the questionnaires. As this is a pilot study, all women were treated with active drug. To evaluate which dose of bromocriptine is needed for optimal symptom relief a randomized, double blinded study with a placebo arm will be needed.

CONCLUSION

Significant improvement in menstrual bleeding, pain and quality of life in women with adenomyosis after bromocriptine treatment suggests a novel therapeutic agent for this common disease with limited alternative therapies. Further studies are needed to explore the role of PRL in adenomyosis and the mechanism of action for bromocriptine leading to symptom relief in women with adenomyosis.

REFERENCES

1. Bird CC, McElin TW, Manalo-Estrella P. The elusive adenomyosis of the uterus--revisited. Am J Obstet Gynecol. 1972;112(5):583-93.

2. Cockerham AZ. Adenomyosis: A Challenge in Clinical Gynecology. J Midwifery Womens Health. 2012;57(3):212-20.

3. Lupicka M, Socha BM, Szczepanska AA, Korzekwa AJ. Prolactin role in the bovine uterus during adenomyosis. Domest Anim Endocrinol. 2017;58:1-13.

4. Mori T, Singtripop T, Kawashima S. Animal model of uterine adenomyosis: is prolactin a potent inducer of adenomyosis in mice? Am J Obstet Gynecol. 1991;165(1):232-4.

5. Singtripop T, Mori T, Park MK, Shiraishi K, Harigaya T, Kawashima S. Prolactin binding-sites in normal uterus and the uterus with adenomyosis in mice. Zoolog Sci. 1993;10(2):353-60.

6. Yamashita M, Matsuda M, Mori T. Increased expression of prolactin receptor mRNA in adenomyotic uterus in mice. Life Sci. 1997;60(17):1437-46.

7. Stewart EA, Jain P, Penglase MD, Friedman AJ, Nowak RA. The myometrium of postmenopausal women produces prolactin in response to human chorionic gonadotropin and alpha-subunit in vitro. Fertil Steril. 1995;64(5):972-6.

8. Gellersen B, Bonhoff A, Hunt N, Bohnet HG. Decidual-type prolactin expression by the human myometrium. Endocrinology. 1991;129(1):158-68.

9. Nowak RA, Rein MS, Heffner LJ, Friedman AJ, Tashjian AH, Jr. Production of prolactin by smooth muscle cells cultured from human uterine fibroid tumors. J Clin Endocrinol Metab. 1993;76(5):1308-13.

10. Nowak RA, Mora S, Diehl T, Rhoades AR, Stewart EA. Prolactin is an autocrine or paracrine growth factor for human myometrial and leiomyoma cells. Gynecol Obstet Invest. 1999;48(2):127-32.

11. Ficicioglu C, Tekin HI, Arioglu PF, Okar I. Effects of fluoxetine-induced hyperprolactinaemia on adenomyosis induction in Wistar Albino rats. Med Sci Res. 1996;24(8):557-9.

12. Singtripop T, Mori T, Park MK, Sakamoto S, Kawashima S. Development of uterine adenomyosis after treatment with dopamine antagonists in mice. Life Sci. 1991;49(3):201-6.

13. Taran FA, Weaver AL, Coddington CC, Stewart EA. Understanding adenomyosis: a case control study. Fertil Steril. 2010;94(4):1223-8.

14. Weil C. The safety of bromocriptine in long-term use: a review of the literature. Curr Med Res Opin. 1986;10(1):25-51.

15. Kletzky OA, Vermesh M. Effectiveness of vaginal bromocriptine in treating women with hyperprolactinemia. Fertil Steril. 1989;51(2):269-72.

16. Vermesh M, Fossum GT, Kletzky OA. Vaginal bromocriptine: pharmacology and effect on serum prolactin in normal women. Obstet Gynecol. 1988;72(5):693-8.

17. Bazot M, Cortez A, Darai E, Rouger J, et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. Hum Reprod. 2001;16(11):2427-33.

18. Dueholm M, Lundorf E, Hansen ES, Sorensen JS, Ledertoug S, Olesen F. Magnetic resonance imaging and transvaginal ultrasonography for the diagnosis of adenomyosis. Fertil Steril. 2001;76(3):588-94.

19. van den Bosch T, Dueholm M, Leone FPG, , et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015;46(3):284-98.

20. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol. 1990;97(8):734-9.

21. Ruta DA, Garratt AM, Chadha YC, Flett GM, Hall MH, Russell IT. Assessment of patients with menorrhagia: how valid is a structured clinical history as a measure of health status? Qual Life Res. 1995;4(1):33-40.

22. Hawker GA, Mian S, Kendzerska T, French M. Measures of Adult Pain Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011;63:S240-S52.

23. Main CJ. Pain assessment in context: a state of the science review of the McGill pain questionnaire 40 years on. Pain. 2016;157(7):1387-99.

24. Spies JB, Coyne K, Guaou NG, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002;99(2):290-300.

25. Jones G, Kennedy S, Barnard A, Wong J, Jenkinson C. Development of an endometriosis quality-of-life instrument: The endometriosis health profile-30. Obstet Gynecol. 2001;98(2):258-64.

26. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191-208.

27. Stewart EA, Rabinovici J, Tempany CM, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril. 2006;85(1):22-9.

28. Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. Br J Obstet Gynaecol. 2000;107(3):320-2.

29. Hald K, Lieng M. Assessment of Periodic Blood Loss: Interindividual and Intraindividual Variations of Pictorial Blood Loss Assessment Chart Registrations. J Minim Invasive Gynecol. 2014;21(4):662-8.

30. Zakherah MS, Sayed GH, El-Nashar SA, Shaaban MM. Pictorial Blood Loss Assessment Chart in the Evaluation of Heavy Menstrual Bleeding: Diagnostic Accuracy Compared to Alkaline Hematin. Gynecol Obstet Invest. 2011;71(4):281-4.

FIGURE LEGEND

Figure 1: Flow Diagram for the Study for the screening, enrollment, and completion of the study by participants in this study in accordance with Consolidated Standards of Reporting Trials (CONSORT) standards.

Table 1. Baseline Characteristics of Study Participants

	N=19
Age at baseline questionnaire, mean(SD)	44.8 (3.5)
Body mass index, mean(SD)	26.5 (3.9)
Gravidity, n(%)	
0	2 (10.5%)
1	1 (5.3%)
≥2	16 (84.2)%)
Parity, n(%)	
0	3 (15.8%)
1	2 (10.5%)
≥2	14 (73.7)%)
History of infertility, n(%)	
No	15 (78.9%)
Yes	2 (10.5%)
No response	2 (10.5%)
Number of cesarean deliveries, n(%)	
0	12 (63.1%)
1	6 (31.6%)
2	1 (5.3%)

Table 2. Symptomatology of Participants at Baseline

	N=19
Pictorial Blood Loss Assessment	
<250	4 (22.2%)
250-500	8 (44.4%)
>500	6 (33.3%)
Missing	1 (5.6%)
Duration of menses, n(%)	
≤6 days	4 (21.1%)
7-10 days	13 (68.4%)
>10 days	2 (10.5%)
Age heavy menstrual bleeding began, n(%)	
<20 years	9 (47.4%)
25-29 years	1 (5.3%)
30-34 years	4 (21.1%)
≥35 years	5 (26.3%)
Pain with menstrual cycles, n(%)	
No pain	1 (5.3%)
Mild cramps	4 (21.1%)
Moderate cramps	10 (52.6%)
Severe cramps	3 (15.8%)
No response	1 (5.3%)
Age painful menses began, n(%)	
No pain	1 (5.3%)
<20 years	13 (68.4%)
25-29 years	1 (5.3%)
30-34 years	2 (10.5%)
≥35 years	2 (10.5%)
Prior medical treatment for anemia, n(%)	
No	5 (26.3%)
Yes	12 (63.2%)

Table 2. Symptomatology of Participants at Baseline

	N=19
No response	2 (10.5%)
History of blood transfusion, n(%)	
No	17 (89.5%)
Yes	1 (5.3%)
No response	1 (5.3%)
Prior medication for heavy or painful menstruation, n(%)	
No	5 (26.3%)
Yes	12 (63.2%)
No response	2 (10.5%)

Table 3: MRI findings at baseline

Subject	Uterus size (mm)			JZ thickness (mm)		JZ diff (mm)	Ratio JZ/myom (%)	Cystic changes in JZ	Leiomyoma (mm)		
	Length	Myom ant	Myom post	max	min			0=no 1=yes	0=no 1=yes	Localization	Size
1	61.0	20.1	26.6	21.0	6.1	14.9	79	0	0		
2	64.6	19.0	23.5	12.8	8.0	4.8	61	1	0		
3	64.0	25.6	26.0	12.2	5.9	6.3	48	0	0		
4	66.6	15.9	26.7	22.0	4.5	17.5	82	1	1	subserosal	6,4
5	69.4	26.3	20.1	12.3	4.6	7.7	47	0	0		
6	58.0	23.3	25.8	17.8	7.8	10.0	69	1	1	subserosal	18,8
7	54.4	23.3	25.3	19.2	9.9	9.3	82	0	0		
8	67.1	23.3	21.7	13.3	7.3	6.0	57	0	0		
9	66.1	21.4	30.3	15.5	8.5	7.0	51	0	0		
10	68.4	18.2	36.4	27.7	6.1	21.6	76	1	1	intramural	16
11	59.6	20.1	17.4	12.3	6.9	5.4	61	1	1	subserosal	12
12	62.9	28.6	31.3	17.8	7.3	10.5	62	1	1	intramural	51
13	64.7	18.6	28.7	15.6	7.6	8.0	54	0	0		
14	76.0	24.8	24.2	15.5	6.5	9.0	63	1	1	intramural	9,3
15	65.0	24.0	26.7	16.3	6.4	9.9	68	0	0		
16	69.0	24.7	29.6	18.9	9.1	9.8	77	1	1	intramural	19
17	66.3	22.7	24.1	12.1	7.1	5.0	50	0	0		
18	59.4	21.7	31.9	20.2	7.2	13.0	63	1	1	Intramural	25
19	174	15.9	59	54.3	28	26.3	*	1	0		

*Indicates missing value.

JZ, junctional zone.

Subject	Uterus size (mm)			JZ		Parallel/ Fan-shaped shadowing 0=no 1=yes	Myometrial cysts 0= no 1= yes	Hyper-echogenic islands 0=no 1=yes	Ill-defined lesions 1=<50% 2=>50%
	Length	Posterior Myo wall	Anterior Myo wall	3D thickness (mm)	Irregular JZ 0=no 1=yes				
1	59	18	20	5.8	1	1	0	0	2
2	55	17	17	8.0	1	0	0	0	1
3	64	14	23	8.1	0	1	0	0	2
4	62	24	14	5.7	0	1	0	0	2
5	5.8	16	21	5,7	1	1	0	0	2
6	61	28	21	12.7	1	1	1	0	2
7	63	25	18	8.2	0	1	0	0	1
8	59	17	20	5.2	1	1	0	0	2
9	68	32	20	*	0	1	0	1	2
10	66	38	18	9.9	1	1	1	0	2
11	53	20	16	8.6	1	1	0	0	2
12	69	25	32	6.1	0	1	0	0	2
13	67	15	23	11.7	1	1	1	0	2
14	65	21	21	8.9	1	1	0	0	2
15	63	20	22	10.3	1	1	1	0	2
16	68	27	25	14.1	1	1	1	1	2
17	71	25	21	8.5	1	1	0	0	2
18	61	28	20	11.9	1	1	1	0	2
19	*	*	*	*	*	*	*	*	*

Table 4: Transvaginal ultrasound findings at baseline

*Indicates missing value

JZ, junctional zone.

Table 5. Changes from Baseline to 3 months, 6 months and 9 months, n=19 women

Measure	Baseline	3 months	Change	P	6 months	Change	P	9 months	Change	P
Assessment of Menstrual Bleeding										
PBLAC[a]	349(292, 645)	264(181, 324)	-103(-295, -24)	0.029	242(76, 384)	-121(-347, -46)	<0.001	233(149, 515)	-133(-229, -44)	0.003
AMCOQ[a]	51(40, 61)	38(25, 52)	-11(-21, -5)	<0.001	35(21, 48)	-15(-21, -6.5)	<0.001	35(24, 47)	-14(-21, -4.1)	<0.001
Assessment of Pain										
VAS[b]	5(4, 8.3)	3(1.6, 4)	-1.3(-5.1, -1)	0.004	2.2(0.4,6.3)	-1.8(-4.3, 0.7)	0.011	2.5(0.4, 5)	-2.5(-4, -0.4)	<0.001
MPQ[b]	10(5, 22)	8(4, 17)	-1.5(-9, 2)	0.09	6(3,16)	-2(-13, 0)	0.025	7.5(3, 18)	-3.5(-5, 1)	0.021
Assessment of Quality of Life										
UFS-QOL										
SSS[c]	60(44, 72)	44(19, 59)	-19(-31, -6.3)	0.001	44(28,59)	-13(-28, -6.3)	<0.001	44(25,56)	-16(-25, -6.3)	<0.001
HRQL[d]	57(37, 63)	72(45, 88)	12(11, 30)	0.001	66(52,85)	10(4.3,21)	<0.001	72(51,85)	13(0, 29)	<0.001
FSFI[e]	24.6(17.2,30.1)	24.3(3.5,31.3)	-0.4(-3.6,2.3)	0.53	21.5(2.4,31)	-0.4(-2.4,3.4)	0.67	22.1(1.2,29.2)	-0.4(-3.2,0.8)	0.34
EHP Core[f]										
Pain	15.9(9.1,50)	15.9(4.6,29.6)	-10.2(-31.8,0)	0.043	3.41(0,47.73)	-6.82(-15.91,0)	0.052	3.41(2.3,34.1)	-9.09(-15.9,0)	0.029
Control and powerlessness	37.5(8.3,70.8)	25(4.17,5)	-14.6(-25,0)	0.028	16.67(0,50)	-8.33(-29.17,0)	0.035	16.7(4.2,45.8)	-8.33(-25,0)	0.08
Emotional well-being	25(12.5,45.8)	25(12.5,33.3)	-4.2(-8.3,4.2)	0.16	20.8(4.2,41.7)	-8.3(-25,0)	0.016	20.8(8.3,37.5)	8.3(-16.7,0)	0.10
Social Support	12.5(0,50)	18.8(0,37.5)	0(-18.8,6.3)	0.21	12.5(0,3.25)	0(-31.3,6.3)	0.17	18.8(0,4.8)		0.37
Self-Image	41.7(16.7,58.3)	33.3(0,50)	-8.3(-25,0)	0.035	20.8(0,4.67)	-8.3(-25,0)	0.08	25(0,5)	-8.3(-25,0)	0.048

Median (interquartile range) values reported.

P-values calculated using the Wilcoxon signed rank test.

[a]Higher AMCOQ and PBLAC scores indicate worse bleeding

[b]Higher MPQ and VAS scores indicate a higher level of pain

[c]Higher UFS-QOL SSS score indicate worse symptom severity

[d]Higher UFS-QOL HRQL scores indicate better health-related quality of life

[e]Higher FSFI score indicates better sexual function

[f]Higher EHP scores indicate worse health status

PBLAC: pictural blood loss assessment chart; AMCOQ: Aberdeen Menorrhagia Clinical Outcomes Questionnaire; VAS: visual analoge scale; MPQ: McGill Pain Questionnaire; UFS-QOL: Uterine Fibroid Symptom Quality Of Life; SSS: symptom severity score; HRQL: Health Related Quality of Life; FSFI: Female Sexual Function Index; EHP30: Endometriosis Health Profile.