

# Venous Thromboembolism and Adenomyosis: A Retrospective Review

Eliane Yuting Hong<sup>1\*</sup>, Harvard Zhenjia Lin<sup>1</sup>, Yoke Fai Fong<sup>2</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, National University Hospital, <sup>2</sup>Astra Laparoscopic and Robotic Centre for Women and Fertility, Mount Elizabeth Novena Hospital, Singapore

## Abstract

**Objectives:** The objective of the study was to evaluate the incidence of venous thromboembolism (VTE) in patients who have been admitted for adenomyosis at our institute and describe their clinical characteristics and management.

**Materials and Methods:** A retrospective review of the medical records of all patients who were admitted to the gynecology ward between January 2015 and August 2016 was conducted, and all patients who had adenomyosis were included in this study. Clinical details that were evaluated included age, parity, body mass index, significant comorbidities, size of the uterus on physical examination, the size of the adenomyoma (if present) on pelvic ultrasonography, initial hemoglobin, and hematocrit on admission, whether blood transfusion was required, acute and long-term treatment and whether or not there were any associated VTE and treatment given.

**Results:** Forty-one patients were included in this study. Five (12.2%) out of the 41 patients had associated VTE; all five had pulmonary embolism (PE), while two also had a concurrent left lower limb deep-vein thrombosis. Three out of the five patients had worsening menorrhagia following anticoagulation, which gonadotropin-releasing hormone analogs were effective in controlling. Four of the five patients eventually underwent a hysterectomy for long-term management of adenomyosis.

**Conclusion:** This case series describes a few clinical cases where VTE (particularly PE) has been observed with adenomyosis, the challenges in managing these patients, and effective treatment approaches.

**Keywords:** Adenomyosis, pulmonary embolism, venous thromboembolism

## INTRODUCTION

Adenomyosis is a common benign condition of the uterus, characterized by the presence of endometrial glands and stroma in the myometrium. Similar to fibroids, adenomyosis tends to affect women between 40 and 50 years old and is commonly acknowledged to cause dysmenorrhea and heavy menstrual bleeding.<sup>[1]</sup>

Interestingly, literature search has also yielded isolated case reports describing patients with adenomyosis and thromboembolic events such as cerebral infarcts and deep-vein thrombosis (DVT).<sup>[2-4]</sup> While a definite association between

adenomyosis and venous thromboembolism (VTE) has not been established, several theories have been proposed to explain the potential link between these two conditions.<sup>[1,5]</sup> Treatment of these patients also poses a challenging medical dilemma. The presence of both heavy menstrual bleeding and thromboembolism means that the treatment of one aggravates the other. Anticoagulation would predispose the patient to worsening menorrhagia, while hormonal or antifibrinolytic therapy for menorrhagia is contraindicated if there is an active VTE.

In this case series, we set out to determine the incidence of VTE in patients who were admitted with adenomyosis in

**Address for correspondence:** Dr. Eliane Yuting Hong, Department of Obstetrics and Gynecology, National University Hospital, NUHS Tower Block, Level 12, 1E Kent Ridge Road, 119228, Singapore. E-mail: eliane\_hong@nuhs.edu.sg

### Article History:

Submitted: 21 July 2019

Revised: 11 September 2019

Accepted: 13 November 2019

Published: 28 April 2020

### Access this article online

#### Quick Response Code:



Website:  
www.e-gmit.com

DOI:  
10.4103/GMIT.GMIT\_77\_19

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Hong EY, Lin HZ, Fong YF. Venous thromboembolism and adenomyosis: A retrospective review. Gynecol Minim Invasive Ther 2020;9:64-8.

our institute and to describe their clinical characteristics and management.

## MATERIALS AND METHODS

This study was performed at National University Hospital, a tertiary hospital in Singapore, and ethics board approval was obtained (DSRB 2016/01170, approval date February 9, 2017). Waiver of informed consent was approved by the ethics board. A retrospective review of the medical records of all patients who were admitted to the gynecology ward between January 2015 and August 2016 was conducted and all patients who had adenomyosis were included in this study. Adenomyosis was defined by sonographic findings of an adenomyoma, coarsened echotexture of the myometrium, asymmetrical myometrial thickening, or myometrial or subendometrial cysts.

Clinical details that were evaluated included age, parity, body mass index (BMI), significant comorbidities, size of the uterus on physical examination, size of the adenomyoma (if present) on pelvic ultrasonography, hemoglobin and hematocrit on admission, any associated VTE, and treatment given.

Descriptive statistics were performed with continuous variables being presented as means and standard deviations. Categorical data were compared using *Z*-scores. Between-group means were compared using independent samples *t*-test. Means with multiple groups were compared using the Kruskal–Wallis test. Statistical significance was set at  $P < 0.05$ . All statistical analyses were performed with SPSS version 21 (IBM Inc., Armonk, New York, USA).

## RESULTS

A total of 41 patients were included in this study. The mean age was  $44.1 \pm 5.18$  years old, while the mean BMI was  $27.9 \pm 7.50$  kg/m<sup>2</sup>. Thirty-seven (87.8%) out of the 41 patients had concurrent abnormal uterine bleeding and 5 (12.2%) out of the 41 patients had concurrent VTE. These five patients' clinical characteristics are shown in Table 1.

Interestingly, all five patients had VTE in the form of pulmonary embolism (PE), while two of them also had a concurrent left lower limb DVT. All five patients had an enlarged uterus and abnormal bleeding due to adenomyosis.

All five patients with VTE were referred to a hematologist for management and in all but one patient (patient 4), the VTE was deemed to be provoked by adenomyosis. Patient 4's development of PE was likely related to her underlying condition of chronic thromboembolic pulmonary hypertension, which probably developed as a result of previous undiagnosed PE. This patient did not give a history of a previous acute VTE episode; hence, it was likely to

have been a silent event. However, it would have been most likely precipitated by her enlarged adenomyotic uterus and the use of oral contraceptive pills, as those were her only risk factors.

Anticoagulation was commenced promptly for all five patients; four of them received warfarin and one was given rivaroxaban, a direct factor Xa inhibitor. Three out of the five patients developed worsening menstrual bleeding on starting anticoagulation and were treated with gonadotropin-releasing hormone (GnRH) analogs, which induced a period of amenorrhea during anticoagulant therapy, while also having the additional benefit of reducing uterine volume. This approach was effective for two patients who were both on warfarin. However, the last patient on rivaroxaban had persistent menorrhagia despite GnRH analogs and uterine artery embolization and eventually required a hysterectomy in the same admission.

Four of the five patients eventually underwent a hysterectomy for long-term management of adenomyosis. The remaining patient (patient 4) had opted to return to her home country for further management.

A comparison of the clinical characteristics between patients who had adenomyosis with VTE and patients who had adenomyosis without VTE is shown in Table 2. There were no statistically significant differences between the groups in terms of age, BMI, hemoglobin, hematocrit, or weight of the adenomyotic uterus (for women who had a hysterectomy). There was also no difference in the number of women taking combined oral contraceptive pills or tranexamic acid.

From our results, it can be concluded that VTE in concurrence with adenomyosis is uncommon and there appears to be a greater occurrence of PE than DVT. However, a direct causation cannot be drawn between both conditions as of now.

## DISCUSSION

A direct link between VTE and adenomyosis has not yet been established and it is not known if there is a causal relationship between both conditions. Due to its rare occurrence, literature search has produced only isolated case reports with a wide variety of clinical manifestations, as shown in Table 3. Hence, the estimated incidence is not yet known. From our knowledge, this is the first case series on this topic.

Several theories have been proposed to explain a link between adenomyosis and VTE. Conventionally, it was thought that extrinsic pressure on the inferior vena cava caused by an enlarged uterus resulted in venous stasis and, hence, increased risk of lower limb DVT.<sup>[5]</sup> In addition, women with adenomyosis commonly also have menorrhagia, which has

**Table 1: Clinical details of the five patients with venous thromboembolism**

	Age	BMI	Clinical presentation	Ultrasound findings	Clinical size of uterus (weeks)	Hb (g/dL)	Type of VTE	Treatment
Patient 1	44	40.3	Known case of adenomyosis with menorrhagia treated with tranexamic acid. Admitted for symptomatic anemia. Developed dyspnea and desaturation during admission. Imaging showed extensive bilateral PE and left lower limb DVT	Bulky globular uterus with coarse myometrium	20	7.3	Bilateral PE, left lower limb DVT	Warfarin. Developed worsening menorrhagia, which was managed with GnRH analogs and eventually, total hysterectomy and bilateral salpingectomy
Patient 2	38	23	Known case of adenomyosis with menorrhagia treated with tranexamic acid. Presented with pleuritic chest pain and was diagnosed with PE. DVT scan was negative	9 cm posterior adenomyoma	14	4.5	PE	Rivaroxaban. Developed worsening menorrhagia, which did not respond to GnRH analog and UAE. Underwent total laparoscopic hysterectomy and bilateral salpingectomy
Patient 3	50	31.3	Known case of adenomyosis with menorrhagia, Mirena intrauterine system <i>in situ</i> . Had two previous episodes of PE and was on lifelong warfarin. Presented thereafter with symptomatic anaemia. DVT scan was negative	Bulky globular uterus with thick and coarse myometrium in the posterior wall	10	6.2	PE	Warfarin and GnRH analog. Subsequently underwent laparoscopic hysterectomy and bilateral salpingo-oophorectomy
Patient 4	45	26.8	Presented with dyspnea. Known adenomyosis and menorrhagia treated with COCP. Presented with dyspnea and diagnosed with PE and chronic thromboembolic pulmonary hypertension	Bulky globular uterus with thick and coarse myometrium in the posterior wall	22	11.4	PE	Warfarin and GnRH analog. COCP stopped. Returned to home country to continue treatment
Patient 5	51	23.9	Presented with lower limb swelling and respiratory distress, deteriorated to cardiac arrest. Imaging showed massive bilateral PE, enlarged uterus and left lower limb DVT. Has history of menorrhagia over the past year	Globular uterus with 10 cm anterior adenomyoma	18	7.9	Bilateral PE, left lower limb DVT	Thrombolytic therapy, warfarin, IVC filter, GnRH analog. Underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy subsequently

VTE: Venous thromboembolism, PE: Pulmonary embolism, DVT: Deep vein thrombosis, COCP: Combined oral contraceptive pill, GnRH: Gonadotropin-releasing hormone, UAE: Uterine artery embolization, IVC: Inferior vena cava, HB: Hemoglobin

**Table 2: Comparison of clinical characteristics between venous thromboembolism and no venous thromboembolism groups using independent samples *t*-test**

Characteristic	VTE (n=5)	No VTE (n=36)	P
Age	45.6±5.2	43.8±5.2	0.484
BMI (kg/m <sup>2</sup> )	29.1±7.1	27.1±8.9	0.646
Hemoglobin (g/dL)	7.5±2.5	8.5±2.7	0.427
Hematocrit (%)	23.8±7.1	27.6±7.7	0.306
Number of women who underwent hysterectomy	4	20	NA
Weight of uterus, if hysterectomy performed (g)	506.3±216	612±844	0.807

Z-scores were used to compare percentages. Statistical significance is defined by  $P < 0.05$ . BMI: Body mass index, VTE: Venous thromboembolism, NA: Not available

been shown to induce a hypercoagulable state by causing polycythemia and reactive thrombocytosis.<sup>[1]</sup> However, there was no significant difference in terms of the weight of the uterus or hematocrit between the patients in our study who had VTE and those who did not.

Furthermore, it is interesting to note that all five of our patients with adenomyosis and VTE had PE, while only two

of them had DVT. There were otherwise no other risk factors for VTE in these patients. Hence, the development of PE in these patients cannot be sufficiently explained by the theories listed above. Alternative theories have been proposed by other authors.

A number of case reports have described the development of disseminated intravascular coagulation in association

**Table 3: Summary of case reports of venous thromboembolism in association with adenomyosis**

Authors	Type of thrombosis	Details
Nishioka <i>et al.</i> <sup>[6]</sup>	Cerebral venous sinus thrombosis	Case report of a patient who developed cerebral venous sinus thrombosis in association with adenomyosis. No recurrence of thrombosis following surgical resection of adenomyosis during 2-year follow-up period
Matsushima <i>et al.</i> <sup>[7]</sup>	Cerebral venous sinus thrombosis	Case report of cerebral venous sinus thrombosis in a patient taking COCP for dysmenorrhea due to adenomyosis. GnRH agonist therapy was administered over 2.5 years, with no recurrence of thrombosis
Akira <i>et al.</i> <sup>[8]</sup>	DVT	Case report of a patient who developed DVT in the left leg in association with adenomyosis. GnRH agonist has been taken as a daily nasal preparation, with no further recurrence of DVT over a 2-year period
Jang <i>et al.</i> <sup>[3]</sup>	DVT	Case report of a patient with DVT in association with adenomyosis
Son <i>et al.</i> <sup>[9]</sup>	Renal	Case report of a patient with adenomyosis who developed DIC during menstruation, resulting in acute kidney injury. She required temporary renal replacement therapy until DIC resolved with cessation of menstruation
Yoo <i>et al.</i> <sup>[10]</sup>	Renal	Case report of acute renal failure induced by DIC in a patient with adenomyosis and menorrhagia
Soeda <i>et al.</i> <sup>[11]</sup>	Cardiac	Case report of nonbacterial thrombotic endocarditis in association with adenomyosis
Kim <i>et al.</i> <sup>[2]</sup>	Cardiac, with emboli to brain	Case report of multiple cerebral embolic infarcts in patient with adenomyosis and nonbacterial thrombotic endocarditis
Yamashiro <i>et al.</i> <sup>[4]</sup>	Brain	Case reports of four patients who developed cerebral infarcts with adenomyosis. Two patients also had systemic emboli in the fingers and kidneys

COCP: Combined oral contraceptive pill, GnRH: Gonadotropin-releasing hormone, DIC: Disseminated intravascular coagulation, DVT: Deep vein thrombosis

with adenomyosis. This manifested as end-organ injury in the form of cerebrovascular thrombosis, acute renal failure, and nonbacterial thrombotic endocarditis in patients with no other thrombotic risk factors.<sup>[10-12]</sup> This combination of disseminated intravascular coagulation with menorrhagia during menstruation in some patients with adenomyosis can be attributed to concurrent dysfunctional coagulation and fibrinolysis. Yamanaka *et al.* described how magnetic resonance imaging detected multiple signal hyperintense spots inside adenomyotic tissues, which likely represented ectopic endometrium or microhemorrhage in the myometrium. They speculated that this then alters the coagulation system through local inflammation and microthrombi formation, which can embolize into the systemic circulation to cause embolic phenomena.<sup>[13]</sup>

The treatment of these patients with concurrent problems of bleeding and thrombosis is also challenging. In the setting of an active VTE, antifibrinolytic therapy and hormonal therapy, common management options for menorrhagia, are usually contraindicated. GnRH analogs were chosen for our patients, as a single dose could achieve a sustained period of amenorrhea, hence, preventing the recurrence of menorrhagia until anticoagulation was established and the thrombus resolved. They were effective in all of our patients except for one (patient 2), who was also the only patient on rivaroxaban. This corresponds with literature, where rivaroxaban has been shown to result in more cases of abnormal bleeding than low-molecular-weight heparin or Vitamin K antagonists.<sup>[14]</sup> An alternative treatment option is the levonorgestrel intrauterine system. However, rates of spontaneous expulsion are higher in women with an enlarged uterus due to adenomyosis or fibroids, and hence, this may not be effective in a significant proportion of patients with adenomyosis.

One of the limitations of this study is the small number of patients included, as we have only included patients with adenomyosis who were admitted, while those managed in the outpatient setting were not included in this study. Hence, although there is no previously quoted figure to compare this to, the incidence of VTE in association with adenomyosis at our institution (12.2%) is likely an overestimation. Further studies are needed to determine if there is an association between VTE and adenomyosis.

Nevertheless, as the first case series on this topic, we hope that this collection of cases would help to increase the awareness of a potential link between VTE and adenomyosis, the challenges in managing these patients and also effective treatment approaches.

## CONCLUSION

We conclude that the occurrence of VTE in patients with adenomyosis is uncommon and is not well understood for now; more studies are needed to determine if there is a causal association.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Ramanan S, Chapman-Wardy J, Watson R. Bleeding versus clotting: A complex case of a large fibroid uterus causing menorrhagia and a DVT. *Case Rep Obstet Gynecol* 2016;2016:4169565.
- Kim B, Kim SH, Kim T. Cerebral infarcts by nonbacterial thrombotic endocarditis associated with adenomyosis: A case report. *J Stroke Cerebrovasc Dis* 2018;27:e50-3.
- Jang IS, Kim JH, Im TG, Ahn KH, Lee JH, Lee YS, *et al.* A case of the surgical treatment for deep vein thrombosis in the leg caused by huge uterine adenomyosis. *Korean J Obstet Gynecol* 2001;44:2320-4.

4. Yamashiro K, Tanaka R, Nishioka K, Ueno Y, Shimura H, Okuma Y, *et al.* Cerebral infarcts associated with adenomyosis among middle-aged women. *J Stroke Cerebrovasc Dis* 2012;21:910.e1-5.
5. Riat R, Chowdary P, Mavrides E, Magos A, Gatt A. Is there an association between thrombosis and fibroids? A single centre experience and literature review. *Int J Lab Hematol* 2013;35:e13-6.
6. Nishioka K, Tanaka R, Tsutsumi S, Yamashiro K, Nakahara M, Shimura H, *et al.* Cerebral dural sinus thrombosis associated with adenomyosis: A case report. *J Stroke Cerebrovasc Dis* 2014;23:1985-7.
7. Matsushima T, Akira S, Asakura H, Takeshita T. Low-dose gonadotropin-releasing hormone agonist therapy (draw-back therapy) for successful long-term management of adenomyosis associated with cerebral venous and sinus thrombosis from low-dose oral contraceptive use. *Clin Exp Obstet Gynecol* 2017;44:143-5.
8. Akira S, Iwasaki N, Ichikawa M, Mine K, Kuwabara Y, Takeshita T, *et al.* Successful long-term management of adenomyosis associated with deep thrombosis by low-dose gonadotropin-releasing hormone agonist therapy. *Clin Exp Obstet Gynecol* 2009;36:123-5.
9. Son J, Lee DW, Seong EY, Song SH, Lee SB, Kang J, *et al.* Acute kidney injury due to menstruation-related disseminated intravascular coagulation in an adenomyosis patient: A case report. *J Korean Med Sci* 2010;25:1372-4.
10. Yoo HJ, Chang DS, Lee KH. Acute renal failure induced by disseminated intravascular coagulopathy in a patient with adenomyosis. *J Obstet Gynaecol Res* 2012;38:593-6.
11. Soeda S, Mathuda N, Hashimoto Y, Yamada H, Fujimori K. Non-bacterial thrombotic endocarditis with systemic embolic events caused by adenomyosis. *J Obstet Gynaecol Res* 2011;37:1838-41.
12. Nakamura Y, Kawamura N, Ishiko O, Ogita S. Acute disseminated intravascular coagulation developed during menstruation in an adenomyosis patient. *Arch Gynecol Obstet* 2002;267:110-2.
13. Yamanaka A, Kimura F, Yoshida T, Kita N, Takahashi K, Kushima R, *et al.* Dysfunctional coagulation and fibrinolysis systems due to adenomyosis is a possible cause of thrombosis and menorrhagia. *Eur J Obstet Gynecol Reprod Biol* 2016;204:99-103.
14. De Crem N, Peerlinck K, Vanassche T, Vanheule K, Debaveye B, Middeldorp S, *et al.* Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists. *Thromb Res* 2015;136:749-53.