Possible association between adenomyosis and disseminated intravascular coagulation and thromboembolism: A systematic review

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Abstract. Adenomyosis is an estrogen-dependent gynecologic disease characterized by the presence of endometrial tissue within the myometrium. Adenomyosis presents with abnormal uterine bleeding, pelvic pain and infertility. Recently, patients with adenomyosis with life-threatening disseminated intravascular coagulation (DIC) or thromboembolic events have been reported. The purpose of the present systematic review was to examine the possible associations between adenomyosis and severe complications, and to investigate the clinical characteristics, risk factors and potential mechanisms. A literature search was performed for case reports, reviews of the literature, and preclinical and clinical studies published between January, 2000 and November, 2021 in the PubMed and Google Scholar databases using a combination of specific terms. A total of 20 articles reported these complications. Adenomyosis is characterized by morphologically and functionally abnormal blood vessels, with increased intramural pressure, increased expression of pro-angiogenic markers, excessive angiogenesis and increased microvascular density. Changes in blood coagulation-fibrinolysis markers are encountered even in asymptomatic women during menstruation. Repeated bleeding in larger lesions causes coagulopathy that may result in localized thrombosis or DIC. In addition, elevated levels of mucinous tumor markers, CA125 and CA19-9, induce blood hyperviscosity and hypercoagulability that predispose patients to thromboembolism. On the whole, as demonstrated herein, adenomyosis may cause a wide range of symptoms from asymptomatic to life-threatening DIC and/or thromboembolism.

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Introduction

Adenomyosis is characterized by the presence of ectopic endometrial glands and stroma located within the hypertrophic and hyperplastic myometrium (1). Clinical manifestations are abnormal uterine bleeding (AUB), dysmenorrhea and infertility; however, approximately one third of these cases are completely asymptomatic (2). Adenomyosis often co-exists with endometriosis that causes dysmenorrhea and infertility (3). Researchers have accumulated clinical, histological and genetic, genomic, and proteomic data supporting the pathogenesis of adenomyosis and endometriosis (4). However, it remains inconclusive as to whether adenomyosis and endometriosis are two different diseases (2,5) or different phenotypes of a single disease (3). The clinical manifestations are similar between endometriosis and adenomyosis, although adenomyosis is characterized by AUB (2,6). Recently, some cases of life-threatening disseminated intravascular coagulation (DIC) or thromboembolic events associated with adenomyosis have been reported (7,8). Empirically, giant adenomyosis is considered to cause massive bleeding. On the other hand, such life-threatening events secondary to endometriosis have not been observed to date, at least to the best of the author's knowledge. Adenomyosis and endometriosis are similar diseases; however, studying and elucidating the pathogenic mechanisms of rare complications may provide insight into the pathophysiology and etiology of adenomyosis. The purpose of the present systematic review was to provide evidence of the clinical features and risk factors of DIC or thromboembolism associated with adenomyosis, and to explore the potential mechanisms of this rare complication. The present systematic review is comprised of sections focusing on '*reviews of the existing literature on adenomyosis-associated DIC or thromboembolism*' and '*their underlying mechanisms*'. Finally, future directions on diagnostic and treatment strategies based on the conclusions drawn herein are discussed.

Data and methods

Search strategy and selection criteria. A computerized literature search was performed to identify relevant studies reported in the English language. The study was conducted

in accordance with the PRISMA guidelines updated in 2020 (http://www.prisma-statement.org/) (9). The PubMed and Google Scholar electronic databases were searched for studies published between January, 2000 and November 2021, combining the following key words: Adenomyosis, AUB, DIC and thromboembolism. As a result of the PubMed search, there have been no reports of patients with adenomyosis with DIC or thromboembolism prior to 2000; thus, the search was performed for articles published after January, 2000. The inclusion criteria were as follows: Publications of original studies and review articles, and reference lists of the included studies. The exclusion criteria were letters to the editor, poster presentations, and literature unrelated to the research topic.

A two-step screening process was performed to obtain eligible results. First, the PubMed search was conducted using keywords with the following search combination: Group 1 ('adenomyosis' AND 'abnormal uterine bleeding'), group 2 ('adenomyosis' AND 'disseminated intravascular coagulation') and group 3 ('adenomyosis' AND 'thromboembolism'). Second, the Google Scholar search was performed using keywords with the following search combination: ('adenomyosis', AND 'thromboembolism', OR 'disseminated intravascular coagulation'). Given the heterogeneity in the research theme, data from the studies were synthesized using a descriptive review design with narrative methods. As illustrated in Fig. 1, the first identification phase included records identified through a database search. Terms in the titles and abstracts were focused on in the first screening stage. However, duplicates were removed during the second screening phase, and titles, abstracts and full-text articles were read to remove inappropriate articles. Citation tracking was conducted to identify additional relevant citations. The final eligibility phase included the full-text articles for analysis after excluding those for which detailed data could not be extracted. The last computerized literature search was conducted on January 25, 2022.

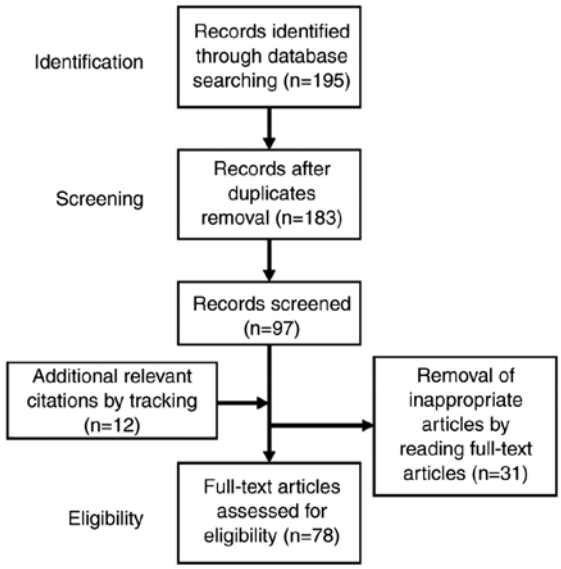
Results

Selection of studies. The search in the PubMed database provided 195 literature citations (n=176 in group 1, n=7 in group 2, and n=12 in group 3). Following the removal of overlaps, 183 records (n=167, n=6 and n=10) were obtained, of which 86 were excluded, and 12 relevant articles (n=5, n=2 and n=5) were cited by the tracking of references, and 78 (n=55, n=8 and n=15) met the inclusion and exclusion criteria (Fig. 1). Following a literature search on PubMed, eight records reporting 8 women with DIC and 13 records reporting 23 women with thromboembolic complications were identified. Second, 64 records met the eligibility criteria by key word searches on Google Scholar. Of the 64 records, 47 records were excluded as their content was not relevant to the study.

Reviews of the literature on adenomyosis-associated massive AUB or DIC. Subsequently, reviews of the literature on patients with adenomyosis with life-threatening massive AUB or DIC were performed. The clinical manifestations, sites of bleeding events, etiology, and risk factors are summarized in Table I. Some case reports on the topic are presented below.

Yamanaka *et al* (10) examined the effects of adenomyosis on the blood coagulation/fibrinolysis system during menstruation. They demonstrated that the blood levels of markers of coagulation and fibrinolysis [thrombin-antithrombin complex (TAT), soluble fibrin (SF), D-dimer and plasmin-alpha 2-plasmin inhibitor complex (PIC)] could increase during menstruation. Patients with extensive adenomyosis may be potentially associated with the risk of activation of coagulation and fibrinolysis during menstruation (10). Yoo *et al* (11) also presented a case of a patient with diffuse adenomyosis with DIC followed by acute renal failure. Massive blood transfusion and hysterectomy were necessary to achieve successful hemostasis (11). Zhang *et al* (12) reported a rare case of adenomyosis with acute DIC following dilation and curettage for missed abortion. Uterine tissue injury following dilation and curettage for missed abortion can lead to the development of DIC through tissue damage, bleeding, degeneration, necrosis, thrombus formation, coagulation system activation, coagulation factor depletion and hyperfibrinolysis (12). It could be managed successfully with tranexamic acid, blood transfusions and subtotal hysterectomy (12). Son *et al* (13) reported a case of acute kidney injury resulting from menstruation-related DIC in a patient with diffuse adenomyosis treated for primary infertility. A 40-year-old woman who had received gonadotropin for ovulation induction therapy developed renal dysfunction and DIC (13). DIC may be triggered by the activation of the coagulation system due to myometrial injury resulting from heavy intra-myometrial menstrual flow by gonadotropins (13). In 2002, Nakamura *et al* (14) also reported that local hemorrhage, blood vessel injury and subsequent thrombosis in the myometrial lesions of diffuse adenomyosis may play a crucial role in the pathophysiology of a rapid progression of DIC. Ohashi *et al* (15) presented a case of a 51-year-old woman with adenomyosis with hemolytic anemia, DIC and acute renal failure after 6 months of gonadotrophin-releasing hormone (GnRH) antagonist treatment. Nishino *et al* (16) presented a case of a 37-year-old woman with nulliparous adenomyosis who developed massive AUB during dienogest therapy. Hemostasis was successfully achieved using balloon tamponade to prevent severe uterine bleeding (16). AUB caused by dienogest may occur from fragile and leaky endometrial vessels (17). Yagi *et al* (18) also presented a case of a 57-year-old woman with hemorrhagic shock and cardiopulmonary arrest caused by massive AUB from diffuse adenomyosis. She had very large adenomyosis with a diameter of 22x20x16 cm and was treated with dienogest therapy (18). Moreover, Takamura *et al* (7) presented a case of a 45-year-old woman who necessitated a surgical management (i.e., emergency hysterectomy) due to refractory hemorrhagic shock occurred during dienogest therapy for adenomyosis. The patient was commenced on dienogest following 6 months of GnRH antagonist. At 9 months after commencing dienogest therapy, it caused a life-threatening massive AUB. Surgical intervention successfully controlled massive AUB (7).

Taken together, eight cases of adenomyosis with DIC have been reported since 2002. Patients with extensive adenomyosis are sometimes at a risk of developing a life-threatening massive AUB or DIC. Surgical procedures (e.g., dilatation and curettage) and pharmacological interventions (e.g., gonadotropins and progestin-only pill) can cause vascular injury,



Key words	Group 1 1+2	Group 2 1+3	Group 3 1+4
Identification	176	7	12
Records after duplicates removal	167	6	10
Records screened	81	6	10
Additional relevant citations by tracking	5	2	5
Removal of inappropriate articles	31	0	0
Eligibility	55	8	15

Figure 1. Number of articles identified by searching for key word combinations. The figure illustrates the number of articles identified by key word combinations and the number of records identified through database search, records following duplicate removal, records screened, additional relevant citations by tracking, the removal of inappropriate articles by reading full-text articles and full-text articles assessed for eligibility. Key words: 1, adenomyosis; 2, abnormal uterine bleeding; 3, disseminated intravascular coagulation; and 4, thromboembolism.

local microthrombosis, systemic coagulopathy and hemostastic abnormalities, and ultimately, life-threatening DIC and further massive AUB (15,19). Several studies have reported the risk of developing massive AUB in patients with adenomyosis treated with a dienogest-based regimen (7,16-18,20). Of note, even women with diffuse adenomyosis, but without overt clinical manifestations already bear high levels of blood markers reflecting the activation of coagulation and fibrinolysis (10). Abnormal blood vessels in diffuse adenomyosis create a rich uterine vasculature and enter the eutopic endometrium (17). Adenomyosis creates an abnormal vascular structure and a network characterized by fragile and leaky blood vessels (4,17,21). Therefore, some diffuse adenomyosis, consisting of a large number of immature blood vessels, may have a high risk of developing DIC.

Reviews of the literature on adenomyosis-associated thromboembolism. A search of the association between thromboembolic events and adenomyosis was then performed, and the sites of thromboembolic events, etiology and risk factors are reported. The clinical information is summarized in Table II. Some case reports on the topic are presented below.

Hong *et al* (22) reported 5 patients with adenomyosis who developed pulmonary thromboembolism and/or deep venous thrombosis. However, there were no significant differences in the clinicopathological characteristics between VTE and non-VTE patients; thus, it was unclear whether there was a causal association between adenomyosis and thromboembolism (22). Some patients with adenomyosis with a history of cerebral infarction or pulmonary thromboembolism have been shown to have elevated levels of plasma TAT, SF, D-dimer and PIC, suggesting an increased predisposition to thromboembolic events (10). Kimura *et al* (23) also presented a rare case of adenomyosis causing the activation of the coagulation system following a complete loss of the endometrium following microwave endometrial ablation. The authors of that study suggested that the formation of microhemorrhage within adenomyotic lesions ws associated with elevated serum levels of the TAT complex and SF, reflecting a hypercoagulable state (23). Yamashiro *et al* (24) reported four cases of middle-aged women with adenomyosis with concomitant acute cerebral infarction. In addition to cerebral infarction, imaging analyses revealed multiple thromboembolisms in the fingers, kidneys, brachiocephalic trunk and left subclavian artery (24). Increased tissue factor (TF) expression levels, increased mucinous tumor marker levels (e.g., CA125 and CA19-9), and/or menstruation-related coagulopathy were commonly observed in these patients (24). Cancer-associated thrombotic events are well known as Trousseau's syndrome. However, no malignant tumors other than severe adenomyosis were found. Certain benign adenomyotic cells are associated with a hyperviscosity nature and hypercoagulable state due to upregulation of mucinous tumor markers and TF (24). Yamashiro *et al* (25) reported a 42-year-old woman with adenomyosis who presented with acute cerebral infarction in the left frontal lobe and right parietal lobe with motor aphasia. A hyperviscosity nature and hypercoagulable state may be associated with diffuse adenomyosis, accompanied by the production of mucinous tumor marker, such as CA125 (1750 U/ml) (25). Hijikata *et al* (26) presented a case of a 59-year-old woman with adenomyosis with multiple cerebral infarctions. She had long been maintained on combined estrogen-progestin hormone replacement therapy for 10 years for the treatment of menopausal symptoms (26). A laboratory examination revealed an elevated serum CA125 level (334.8 U/ml) (26). Aiura *et al* (27) reported the case of a 48-year-old woman with middle cerebral artery occlusion and recurrent cerebral infarction caused by adenomyosis progression. She was successfully treated with catheter-directed mechanical thrombectomy and by hysterectomy (27). Kim *et al* (28) reported a case of multiple infarctions, including the bilateral cerebellum and the right precentral gyrus associated with non-bacterial

Table I. Reviews of the literature on patients with adenomyosis-related massive abnormal uterine bleeding or DIC.

Authors	Year[a]	Article title	Clinical manifestations	The sites of bleeding events	The etiology and risk factors	(Refs.)
Nakamura *et al*	2002	Acute disseminated intravascular coagulation developed during menstruation in an adenomyosis patient.	A case of adenomyosis with acute DIC during menstruation.	Massive abnormal uterine bleeding	Local hemorrhage, blood vessel injury, and subsequent thrombosis in the adenomyosis lesions may be associated with a rapid progression of DIC.	(14)
Son *et al*	2010	Acute kidney injury due. to menstruation-related disseminated intravascular coagulation in an adenomyosis patient: A case report	A 40-year-old woman. developed renal dysfunction associated with DIC after receiving gonadotropins for ovulation induction therapy	Massive abnormal uterine bleeding and DIC	The authors reported a case of acute kidney injury resulting from menstruation-related disseminated intravascular coagulation (DIC) in a diffuse adenomyosis patients treated for primary infertility. A 40-year-old woman who had received gonadotropin for ovulation induction therapy developed renal dysfunction and DIC. DIC may be triggered by the activation of the coagulation system due to myometrial injury resulting from heavy intra-myometrial menstrual flow by gonadotropins. In 2002, Nakamura *et al* (14) also reported that local hemorrhage, blood vessel injury, and subsequent thrombosis in the myometrial lesions of diffuse adenomyosis may play a crucial role in pathophysiology of a rapid progression of DIC.	(13)
Ohashi *et al*	2011	A case of anemia with schistocytosis, thrombocytopenia, and acute renal failure caused by adenomyosis.	After 6 months of GnRH antagonist treatment for symptomatic adenomyosis, the patient developed hemolytic anemia, DIC, and acute renal failure. DIC was diagnosed by typical blood coagulation tests and clinical information.	Massive abnormal uterine bleeding. DIC was diagnosed by typical blood coagulation tests and clinical information. Renal biopsy revealed DIC and severe acute tubular necrosis.	Intramural bleeding in diffuse adenomyosis lesions can cause vascular injury, TF production, local microthrombosis, and ultimately DIC.	(15)

Table I. Continued.

Authors	Year[a]	Article title	Clinical manifestations	The sites of bleeding events	The etiology and risk factors	(Refs.)
Yoo *et al*	2012	Acute renal failure induced by disseminated intravascular coagulopathy in a patient with adenomyosis.	A case of diffuse adenomyosis patient with DIC followed by acute renal failure.	Massive abnormal uterine bleeding.	DIC is a major contributing factor towards development of acute renal failure. The patient was successfully treated with massive blood transfusion and hysterectomy.	(11)
Zhang *et al*	2013	Acute disseminated intravascular coagulation developed after dilation and curettage in an adenomyosis patient: A case report.	A rare case of adenomyosis with acute DIC after dilation and curettage for missed abortion.	Massive abnormal uterine bleeding and DIC. Histological observation exhibited hemorrhage, degeneration and necrosis in the myometrium of adenomyosis lesions.	Uterus tissue injury after curettage in adenomyosis patients accelerates myometrium bleeding, degeneration, necrosis, microthrombus formation, coagulation system activation, coagulation factor depletion, and hyperfibrinolysis, which leads to severe complications, such as DIC.	(12)
Nishino *et al*	2013	Effective salvage of acute massive uterine bleeding using intrauterine balloon tamponade in a uterine adenomyosis patient on dienogest.	A case of a 37-year-old primigravida adenomyosis woman successfully treated with an intrauterine balloon tamponade device to manage massive uterine bleeding during dienogest therapy.	Massive abnormal uterine bleeding.	The potential risk of massive bleeding from the intramural fragile and permeable vessels during dienogest treatment. Intrauterine balloon tamponade is one of the options in managing severe uterine bleeding, avoiding invasive surgical procedures, and maintaining fertility.	(16)
Yagi *et al*	2016	Cardiac arrest due to massive hemorrhage from uterine adenomyosis with leiomyoma successfully treated with damage control resuscitation.	A case of hemorrhagic shock and cardiopulmonary arrest occurred during dienogest therapy for diffuse adenomyosis.	A life-threatening massive abnormal uterine bleeding and DIC.	Treatment with dienogest for giant adenomyosis resulted in DIC after heavy menstrual bleeding. Surgical management can be recommended over medical management for women with huge adenomyosis.	(18)
Yamanaka *et al*	2016	Dysfunctional coagulation and fibrinolysis systems due to adenomyosis is a possible cause of thrombosis and menorrhagia.	Measurement of specific biomarkers for coagulation and fibrinolysis in peripheral blood of 8 patients with adenomyosis.		Patients with extensive adenomyosis with a uterus volume ≥100 cm^3 are at risk for hemorrhagic and thrombotic events during menstruation.	(10)

Table I. Continued.

Authors	Year[a]	Article title	Clinical manifestations	The sites of bleeding events	The etiology and risk factors	(Refs.)
Takamura *et al*	2020	A case of hemorrhagic shock occurred during dienogest therapy for uterine adenomyosis.	A case of a 45-year-old woman required operative intervention for refractory hemorrhagic shock occurred during dienogest therapy for adenomyosis.	A life-threatening massive abnormal uterine bleeding.	Imaging studies revealed type I adenomyosis measuring 10 cm. The potential risk of late bleeding from the intramural fragile and leaky vessels during dienogest treatment in patients with subtype I adenomyosis.	(7)

[a]Year indicates the year of publication. DIC, disseminated intravascular coagulation.

thrombotic endocarditis (NBTE) in a patient with adenomyosis. NBTE is associated with a hypercoagulable state and an inflammatory response and often accompanies cancer (28). An adenomyosis-related hypercoagulable state can lead to multiple infarctions with NBTE. Yin *et al* (29) summarized three cases with adenomyosis who developed acute ischemic stroke during menstruation. These patients were also accompanied by NBTE (29). Elevated levels of CA125, CA19-9 and D-dimer have been observed only during menstruation (29). Mechanisms, such as mucin protein-related hyperviscosity and hypercoagulability increase the risk of thrombosis formation (29).

Taken together, 18 cases of adenomyosis with thromboembolisms have been reported since 2012. The number of reported cases is limited (24); however, adenomyosis causes serious thromboembolism, including multiple cerebral infarctions. Diffuse adenomyosis, elevated levels of mucinous tumor markers, CA125 and CA19-9, and coexistence of NBTE may be at increased risk of developing thromboembolism (23-32).

Mechanisms underlying the pathogenesis of DIC and thromboembolism in adenomyosis. Heavy menstrual bleeding is one of the most common clinicopathological characteristics of women with adenomyosis (33). Although adenomyosis and endometriosis are both characterized by ectopic endometrial glands and share a similar clinical presentation, patients with adenomyosis have a unique symptom, such as AUB and hypercoagulability. Common patterns of aberrant gene expression, including KRAS mutations, increased estrogen biosynthesis, progesterone resistance and inflammation, have been reported both in adenomyosis and endometriosis (34), suggesting that gene expression profiles are similar in the early stages of disease onset. However, endometrial cells in adenomyosis markedly alter the gene expression patterns during adapting to ever-changing host environments, such as tissue injury, repair, and remodeling. Xiaoyu *et al* (5) identified the patterns of differentially expressed proteins between adenomyosis and endometriosis using a proteomic approach coupled using mass spectrometry. The proteomics analysis revealed that the most significantly enriched protein pathway in adenomyosis was coagulation cascades, while endometriosis was tightly associated with chronic inflammation (5). This indicates that the coagulation system is closely involved in the pathophysiology of established adenomyosis. As evidence, patients with adenomyosis during menstruation may have laboratory abnormalities associated with hypercoagulability and excessive hyperfibrinolysis (10,23). Elevated TAT, SF, D-dimer and PIC levels in patients with adenomyosis reflect a hypercoagulable and hyperfibrinolytic condition (10,23). In addition, patients with adenomyosis had prolonged activated partial thromboplastin time and a shortened thrombin time than those with uterine fibroids, indicating that adenomyosis affects the hemostatic system (19). These hemostasis abnormalities suggest a potential anti- or pro-thrombotic state in this pathology and predispose patients to bleeding and thrombotic complications.

In addition, adenomyosis is a progressive disease involving pathological angiogenesis and, unlike normal uterine vessels, increases uterine vascularity due to the abundant blood vessels penetrating within the myometrium (6,35). Recently, Stratopoulou *et al* (36) reported that the total number of

Table II. Reviews of the literature on patients with adenomyosis-associated thrombosis.

Authors	Year[a]	Article title	Clinical manifestations	The sites of thromboembolic events	The etiology and risk factors	(Refs.)
Yamashiro *et al*	2012	Cerebral infarcts associated with adenomyosis among middle-aged women.	Four cases of adenomyosis women with concomitant acute cerebral infarction.	Multiple thromboembolisms in the cerebral infarction, fingers, kidneys, brachiocephalic trunk, and left subclavian artery.	Risk factors associated with a hyperviscosity and hypercoagulability, including increased tissue factor expression levels, increased mucinous tumor marker levels, and menstruation-related coagulopathy, may be associated with the development of systemic thromboembolism.	(24)
Yamashiro *et al*	2012	Cerebral infarction developing in a patient without cancer with a markedly elevated level of mucinous tumor marker.	The patient developed motor aphasia due to cerebral infarction.	Cerebral infarction in the left frontal lobe and right parietal lobe.	Increased levels of CA125 (1,750 U/ml) and D-dimer (6.0 μg/ml).	(25)
Lee *et al*	2014	Uterine infarction in a patient with uterine adenomyosis following biochemical pregnancy.	Focal uterine infarction after *in vitro* fertilization and embryo transfer (IVF-ET) in a patient with adenomyosis following biochemical pregnancy.	Focal uterine infarction.	Women experiencing biochemical abortion after an IVF-ET procedure.	(45)
Hijikata *et al*	2016	Multiple cerebral infarctions in a patient with adenomyosis on hormone replacement therapy.	A case of multiple cerebral infarctions in a woman with adenomyosis on hormone replacement therapy.	Multiple cerebral infarctions.	Elevated levels of mucinous tumor markers such as CA125 (334.8 U/ml) are associated with a hyperviscosity state.	(26)
Yamanaka *et al*	2016	Dysfunctional coagulation and fibrinolysis systems due to adenomyosis is a possible cause of thrombosis and menorrhagia.	Measurement of fibrinolysis-related proteins in peripheral blood of patients with adenomyosis.	A history of cerebral infarction or pulmonary thromboembolism.	Elevated levels of thrombin-antithrombin complex (TAT), soluble fibrin (SF), D-dimer (DD), and plasmin-alpha 2-plasmin inhibitor complex (PIC). Adenomyosis patients with a uterus volume ≥100 cm^3 are at risk of having an activated coagulation system.	(10)
Kim *et al*	2018	Cerebral infarcts by nonbacterial thrombotic endocarditis associated with adenomyosis.	A rare case of multiple infarctions due to nonbacterial thrombotic endocarditis that occurred in the setting of adenomyosis-related hypercoagulable state.	Bilateral cerebellum and the right precentral gyrus associated with nonbacterial thrombotic endocarditis.	Elevated levels of D-dimer, CA19-9, and CA125.	(28)

Table II. Continued.

Authors	Year[a]	Article title	Clinical manifestations	The sites of thromboembolic events	The etiology and risk factors	(Refs.)
Yin *et al*	2018	Cerebral infarcts associated with adenomyosis: a rare risk factor for stroke in middle-aged women: A case series.	Cases with adenomyosis who developed acute ischemic stroke during menstruation.	Multiple infarctions in the right cerebellum and left temporal lobe.	Mucin protein-related hyperviscosity and hypercoagulability due to increased levels of CA125, CA19-9, and D-dimer.	(29)
Uchino *et al*	2018	Nonbacterial thrombotic endocarditis complicated by cerebral infarction in a patient with adenomyosis with high serum CA125 level.	A 48-year-old adenomyosis woman with multiple cerebral infarctions caused by NBTE.	Multiple cerebral infarctions.	A hyperviscosity nature and hypercoagulable state induced by elevated levels of CA125 (901 U/ml).	(30)
Aso *et al*	2018	Recurrent multiple cerebral infarctions related to the progression of adenomyosis: A case report.	A 44-year-old woman presented with headache, left hand weakness, and gait disturbances during the menstrual phase. Imaging studies revealed multiple thrombotic lesions in cortical and subcortical areas in the cerebrum and cerebellum. She had a history of adenomyosis-related heavy menstrual bleeding and infertility. Hysterectomy prevented recurrence of the multiple cerebral infarctions.	Imaging studies revealed multiple thrombotic lesions in cortical and subcortical areas in the cerebrum and cerebellum.	A history of adenomyosis-related heavy menstrual bleeding and infertility.	(46)
Okazaki *et al*	2018	Cerebral infarction associated with benign mucin-producing adenomyosis: report of two cases.	Women with adenomyosis aged 42 and 50 years old developed right hemiparesis and aphasia caused by cerebral infarctions in the left cerebral hemisphere.	Cerebral infarctions in the left cerebral hemisphere.	Elevated levels of CA125. Mucin-producing malignant and benign tumors such as adenomyosis may cause hypercoagulability and cerebral infarction.	(31)

Table II. Continued.

Authors	Year[a]	Article title	Clinical manifestations	The sites of thromboembolic events	The etiology and risk factors	(Refs.)
Zhao *et al*	2020	Acute cerebral infarction with adenomyosis in a patient with fever: a case report.	A 34-year-old adenomyosis woman presented with headache, fever, and left limb weakness during the menstrual phase. Imaging studies revealed acute cerebral infarction.	Imaging studies revealed acute cerebral infarction in right basal ganglia and subcortical region of right frontotemporal lobe.	Elevated CA125 (937.70 U/ml), elevated D-dimer (27.4 mg/l), anemia, menstruation, and fever.	(32)
Hong *et al*	2020	Venous thromboembolism and adenomyosis: a retrospective review	Adenomyosis with menorrhagia	Case reports of five patients who developed pulmonary thromboembolism and/or deep vein thrombosis with adenomyosis.	There were no clinicopathological differences between VTE and non-VTE patients.	(22)
Aiura *et al*	2021	Systemic thromboembolism including multiple cerebral infarctions with middle cerebral artery occlusion caused by the progression of adenomyosis with benign gynecological tumor.	Adenomyosis woman with heavy uterine bleeding presented with neurological symptoms such as impaired consciousness.	Middle cerebral artery occlusion and recurrent cerebral infarction.	Elevated levels of CA125 and D-dimer. Similar to Trousseau's syndrome, adenomyosis may cause systemic thromboembolism.	(27)
Kimura *et al*	2021	Case of adenomyosis causing the activation of the coagulation system after a complete loss of endometrium following microwave endometrial ablation.	A case of adenomyosis with abnormal coagulation testing after microwave endometrial ablation.	The formation of microhemorrhage within adenomyotic lesions affected coagulation and fibrinolysis function.	Elevated levels of thrombin-antithrombin complex (TAT) and soluble fibrin. Localized microhemorrhage, tissue injury, and necrosis within adenomyotic lesions during menstruation may increase the generation of thrombin, leading to a hypercoagulable state.	(23)
Yasuda *et al*	2021	Recurrent cerebral infarcts associated with uterine adenomyosis: successful prevention by surgical removal.	A 47-year-old Japanese woman with uterine adenomyosis who developed multiple cerebral infarcts during menstruation.	Multiple cerebral infarcts.	Hysterectomy prevented recurrence of cerebral infarct and thrombosis in a patient with adenomyosis.	(8)

[a]Year indicates the year of publication.

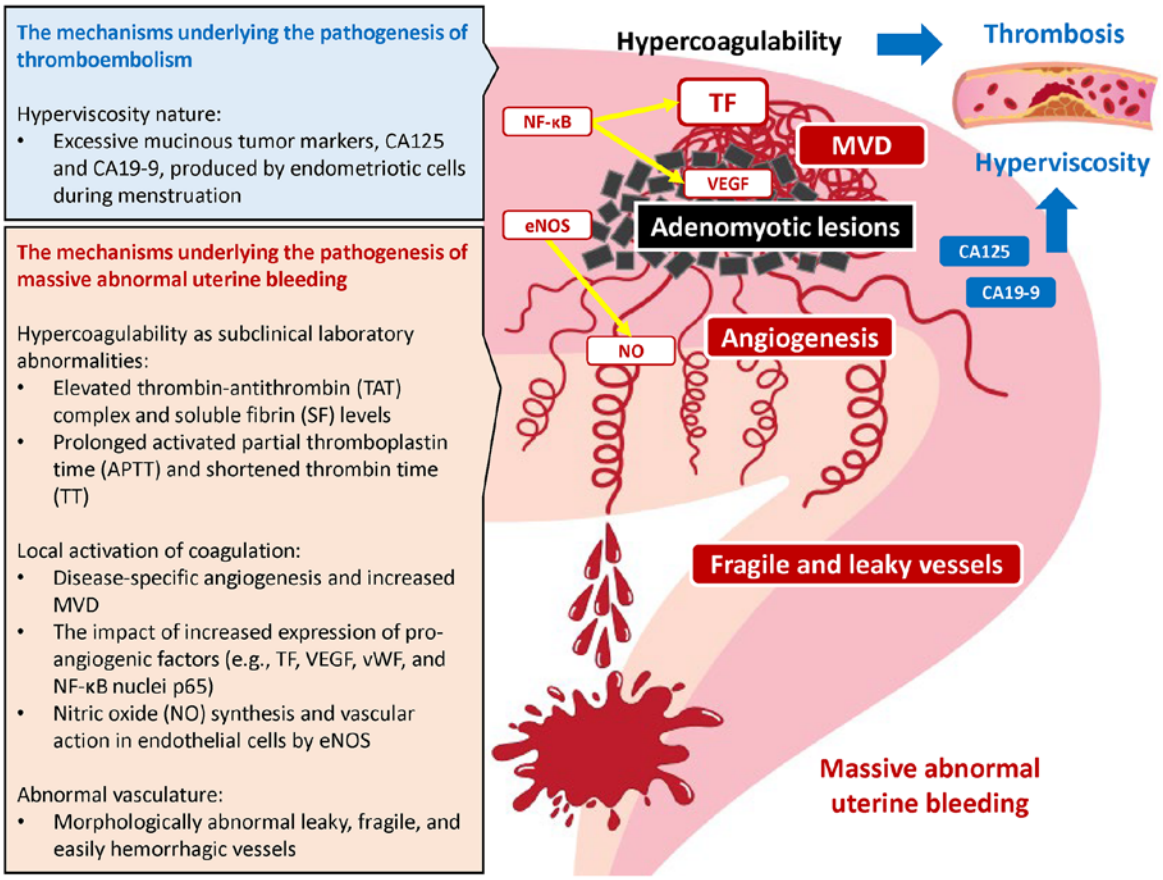


Figure 2. Mechanisms underlying the pathogenesis of disseminated intravascular coagulation and thromboembolism in adenomyosis. MVD, microvascular density; eNOS, endothelial nitric oxide synthase; TF, tissue factor.

adenomyotic vessels was significantly higher in lesions than in the healthy endometrium, and fewer vessels were surrounded by α-smooth muscle actin. This suggests structural abnormalities of the normal vasculature that is composed of endothelial cells, smooth muscle cells and fibroblasts. Therefore, the vasculature of adenomyosis is morphologically abnormal and characterized by the development of leaky, fragile and easily rupturing new vessels (6). Similarly, the tumor vasculature is also characterized by immature, leaky, tortuous, dilated and fragile vessels, and the loss of hierarchical architecture and is known to cause spontaneous hemorrhages (8). These data indicate that the blood vessel formation of adenomyosis may be regulated through a mechanism similar to the carcinogenesis theory, affecting angiogenesis and vasculogenesis (6). Indeed, increased microvascular density (MVD) and higher vascular endothelial growth factor (VEGF) expression have been shown in the endometrium of patients with adenomyosis as compared with the normal endometrium of women without disease (6) (Fig. 2). Pro-angiogenic markers [e.g., TF, VEGF, von Willebrand factor and nuclear factor-κB (NF-κB)] have also been shown to be higher in the adenomyosis than the control group, and to be positively associated with the amount of bleeding (6,37). The angiogenesis-related genes and their multiple signal pathways, such as VEGF, TF, matrix metalloproteinase (MMP)-2, MMP-9 and cyclooxygenase-2 are downstream targets for NF-κB in adenomyosis (6,38). NF-κB regulates the expression of a number of molecules and pathways responsible for angiogenesis, cell invasion, proliferation, anti-apoptosis and impaired cytokine expression (6). The abnormal dysregulation of NF-kB is considered to be a hallmark of adenomyosis (6). Furthermore, endothelial nitric oxide synthase (eNOS) is highly expressed in the endometrial and myometrial tissues of women with adenomyosis-related heavy menstrual bleeding (39,40). Nitric oxide (NO) synthesized in endothelial cells by eNOS may cause AUB possibly through the vascular relaxation and platelet aggregation inhibition (39,40). Therefore, repeated microbleeding episodes from fragile and more permeable vessels within the adenomyosis lesions may trigger activation of the TF and VEGF-dependent coagulation pathways through tissue damage (10,14,29). Furthermore, the persistent activation of the coagulation cascade can lead to massive AUB and life-threatening DIC.

On the other hand, endometriotic cells that are abundant in diffuse adenomyosis produce excessive CA125 and CA19-9 during menstruation (10,25,29). Indeed, markedly elevated levels of CA125 and CA19-9 hare detected most often in patients with adenomyosis who develop multiple thromboembolisms during menstruation (10,25,29). Members of the mucin family glycoproteins, CA125 and CA19-9, are relatively large molecules that can increase blood viscosity. The entry of CA125 and CA19-9 into the systemic circulation leads to blood hyperviscosity (10,25,29). The hyperviscosity is a risk factor for hypercoagulability and predisposes patients to thrombosis. Therefore, elevated levels of these tumor markers may be associated with an increased risk of the development of thrombosis. Furthermore, the hypercoagulable state and the

Table III. The clinical characteristics and risk factors for adenomyosis-associated DIC and thromboembolism.

Clinical characteristics	Risk factors and pathophysiology
Adenomyosis-associated DIC	
Massive AUB (from heavy menstrual bleeding to life-threatening DIC)	Diffuse adenomyosis or subtype I adenomyosis Treatment with dienogest or gonadotropins Dilation and curettage for missed abortion Elevated pro-angiogenic markers (e.g., TF, VEGF, vWF, and NF-κB) Leaky, fragile, and easily hemorrhagic vessels
Adenomyosis-associated thromboembolism	
Similar to Trousseau's syndrome More often associated with multiple cerebral infarctions	Diffuse adenomyosis A hyperviscosity nature due to elevated levels of mucinous tumor markers, CA125 and CA19-9 Local hemorrhage in the adenomyosis lesions followed by a hypercoagulable state through activation of the TF and VEGF-dependent coagulation pathways The coexistence of non-bacterial thrombotic endocarditis (NBTE)

TF, tissue factor; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor; NF-κB, nuclear factor κB.

hyperviscosity nature are likely to be associated with a risk of the development of NBTE (41). The ability of diagnosis and management of adenomyosis-related hemostasis abnormalities is important in reducing life-threatening complications, such as DIC and thromboembolism.

Discussion

The present systematic review summarizes the clinical features, risk factors and potential mechanisms of severe hemorrhagic and thrombotic events associated with adenomyosis. DIC and thromboembolism are rare, yet life-threatening complications in adenomyosis. The clinical characteristics and risk factors for adenomyosis-associated DIC and thromboembolism are summarized in Table III. That is, clinical features, such as adenomyosis phenotypes (e.g., diffuse or type 1) may increase the risk of developing severe hemorrhagic events, while a marked increase in mucinous tumor markers may confer the risk of developing severe thrombotic events. In addition, adenomyosis-specific abnormal blood vessels can cause thrombo-hemorrhagic events, but they are clinically undetectable until surgical procedures are performed. More specifically, the pathophysiology of adenomyosis-associated thrombo-hemorrhagic events could be related to disease-specific endogenous risk factors and exogenous factors such as current therapeutic strategies. Examples of the former include changes in the gene and protein expression patterns related to the coagulation and fibrinolysis systems, abnormal vascular distribution and network formation, a marked elevation in serum mucinous tumor markers, and subtypes of adenomyosis, while examples of the latter include treatment with progestin-only pill or dilation and curettage for abortion. In particular, the extent and subtype of adenomyosis lesions are the most clinically influential factors in predicting the onset. Adenomyosis is composed of multiple heterogeneous subtypes. Types I (intrinsic) and II (extrinsic) consist of adenomyosis that occurs in the uterine inner and outer layer, respectively (42). Immature and fragile blood vessels penetrate the endometrial-myometrial barrier in type I adenomyosis (17). Moreover, Turner *et al* (43) suggested that 'impaired venous drainage and endometrial vascular ectasia, secondary to increased intramural pressure' can cause AUB in diffuse adenomyosis. Therefore, adenomyosis-specific angiogenesis, increased MVD and morphologically abnormal blood vessels with leaky and fragile features are considered to cause vascular damage, leading to the extravasation of blood, damage to surrounding tissue, and subsequently, to thrombo-hemorrhagic events (43). In patients with diffuse or type I adenomyosis, surgical procedures, such as dilatation and curettage for abortion and pharmacological interventions, such as gonadotropins and progestin-only pill, may be a potential risk factor for massive hemorrhage and life-threatening DIC. Additionally, markedly elevated levels of mucinous tumor markers, CA125 and CA19-9 during menstruation may pose as risk factors for thromboembolism. The fragile blood vessels in adenomyosis can lead to massive uterine bleeding during menstruation, while locally produced pro-angiogenic factors, coagulation-related factors and mucins may cause hypercoagulability and hyperviscosity, leading to thrombosis. The clinical manifestations are secondary to different conditions, such as structural vascular abnormality, a hyperviscosity state, or a hypercoagulable state, and range from asymptomatic and sub-clinical illness to severe, life-threatening DIC and thromboembolism.

Finally, based on the present systematic review, future directions of diagnostic and therapeutic strategies for the

field are explored. As a first step towards clinical diagnosis, it is crucial to distinguish focal and diffuse adenomyosis or type I and type II adenomyosis through the assessment of transvaginal ultrasound. In patients with type I adenomyosis, the damaged microvessels are contiguous with endometrial stromal cells at the inner myometrium and endometrium (17). Blood vessels in patients with diffuse adenomyosis demonstrate a morphologically and functionally abnormal phenotype that includes leaky, fragile and easily rupturing vessels (6). Therefore, type I and diffuse adenomyosis may be associated with severe unpredictable bleeding (17). Microvascular damage induced by surgical procedures or hormonal treatment in these patients can contribute to excessive bleeding. Moreover, CA125 and CA19-9 are mucin glycoproteins produced by endometrial cells. Diffuse adenomyosis is particularly rich in endometrial cells and is considered to be more likely to produce these mucins. Elevated levels of mucin protein (CA125 and CA19-9)-related hyperviscosity and hypercoagulability increases the risk of thromboembolism in women affected by extensive adenomyosis (24,29). Additionally, estrogen is generally considered to induce the activation of coagulation (e.g., factors II, VII, IX, X and XII, and protein C) and fibrinolysis (e.g., plasminogen) genes that play roles in coagulation, fibrinolysis and inflammation (44). However, it is currently unknown when and how these genes and proteins are regulated in adenomyosis lesions. Collectively, patients with diffuse or type I adenomyosis may develop AUB/DIC or thromboembolism; thus, specific attention should be paid to surgical and hormonal therapy.

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Author's contributions

HK performed all of the following regarding the preparation of this manuscript: Conception and design, acquisition of data, analysis and interpretation of data, and writing the manuscript. HK confirms the authenticity of all the raw data. The author has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The author declares that he has no competing interests.

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